Combating the Real Threat of Antibiotic Resistance

Carol A. Rauch, MD, PhD, FCAP

Adjunct Associate Professor of
Pathology, Microbiology, & Immunology

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Disclosures

- I have no financial conflicts of interest to disclose.
- Opinions expressed are my own and do not necessarily reflect those of the federal government.

Why am I here?

- Clinical Microbiologist with strong interest in relationship with Public Health
  - Bioterrorism/emergency preparedness & management
  - Healthcare-associated infections
  - Stewardship, patient safety, other initiatives
- Technical laboratory liaison, AR Lab Network with CDC Antibiotic Resistance Coordination & Strategy Unit (ARX) 2019 - 2021
  - Work with CDC & APHL included “clinical laboratory engagement”

I love the WCLN model !!

- Y’all have got it right!
- This is the ultimate in clinical laboratory engagement
- Facilitated partnership coordinated by WSLH

Let me count the ways …

- Clinical lab representation on LabTAG not just a token
  - number/mix of members from regions/roles
  - service is rotated
- Bidirectional communication
- Broadly inclusive across the state with 138 participants, designed for sustained inclusion to promote:
  - desired laboratory practices (homogeneous)
  - readiness for threats, trusted communication
  - collegiality

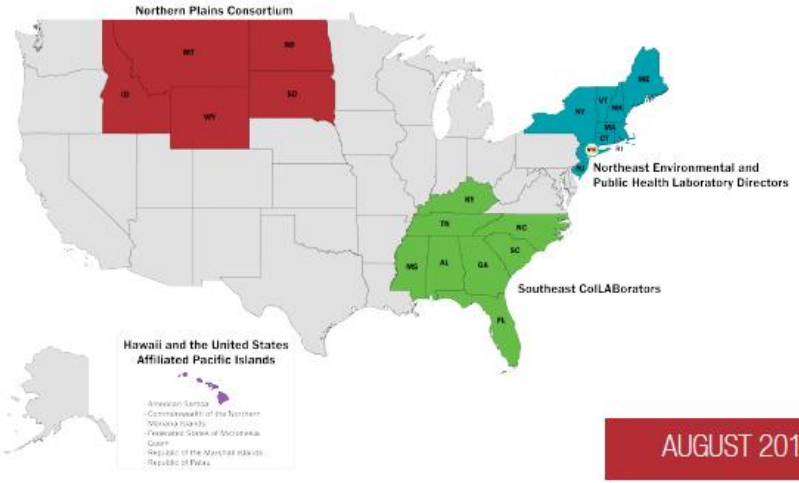
Bateman, *et al*. Public Health Reports 2019; vol 134 (supplement 2): 6S – 10S.
Kirk CJ, Shult PA. Public Health Reports 2010 Supp 2; vol 125: 102-109.

Let me count the ways …

- Predictable value for clinical laboratory to support
  - PACE credit
  - relationships with peers and partners
  - curated information from trusted sources
  - annual meeting, newsletter, listserve, webinars
- Leadership is not top-down, also bottom-up and side-to-side with focus on coordination

Bateman, *et al*. Public Health Reports 2019; vol 134 (supplement 2): 6S – 10S.
Kirk CJ, Shult PA. Public Health Reports 2010 Supp 2; vol 125: 102-109.

The Status of State-Driven Regional Networks in the Public Health Laboratory Community



AUGUST 2017

APHL ASSOCIATION OF PUBLIC HEALTH LABORATORIES

Advice and Moving Forward

Respondents outlined various areas of need to help strengthen regional networks, including increased funding for informatics, training and workforce development, and travel. Areas where CDC or APHL could assist networks were also identified.

Existing consortia members also shared eight tips for ensuring successful and effective networks, as they believe that these collaborative partnerships need to be sustained.

To conclude, the interviews supported the idea that state-driven networks, and the deliberations and outcomes of these networks, provide a sound foundation for the evolution and continued sustainability of the public health laboratory system.

> "I would like to see a whole nation of networks, each state and local in a regional network so all could experience the value and importance of these collaborations."
>
> --Mike Pentella, former director, MA PHL

Vision for the Future

"State-driven networks, and the deliberations and outcomes of these networks, provide a sound foundation for the evolution and continued sustainability of the public health laboratory system."

https://www.aphl.org/aboutAPHL/publications/Documents/QS-2017Aug-Regional-Network-Update.pdf

Learning objectives

Participants will be able to:

1. List important issues related to antibiotic/antimicrobial resistance
2. Identify important variables critical to patient care as well as to public health efforts
3. Critically evaluate opportunities for practice improvement

Antibiotic Resistance Threats in the United States 2019

- Report updated from first version in 2013 with revised death and infection estimates
- AR threat overall greater, deaths decreased
- Bottom line:
  - efforts to prevent infections and transmission are working
  - more effort is needed

www.cdc.gov/DrugResistance/Biggest-Threats.html
https://www.cdc.gov/drugresistance/pdf/threats-report/2019-ar-threats-report-508.pdf

CDC Leads the Public Health Fight Against Antibiotic Resistance (AR)

2013
CDC releases *Antibiotic Resistance Threats in the United States, 2013*

2014
CDC publishes *Core Elements of Hospital Antibiotic Stewardship Programs*, other settings followed

White House Executive Order 13676 establishes *National Strategy for CARB*[1] and Presidential Advisory Council

2015
U.S. government releases *National Action Plan for CARB*

CONGRESS APPROPRIATES $160 MILLION for AR Solutions Initiative*
(CDC's initial request was $264M)

CDC launches CDC & FDA AR Isolate Bank

ARLABnetwork

2016
CDC establishes AR Lab Network and funds local AR experts in every state, some major cities, and Puerto Rico

CDC awards first innovation funding ($40M) to academic, industry, and healthcare investigators, including CDC's Prevention Epicenters Program

CDC launches the Antibiotic Use and Antibiotic Resistance tracking modules through the National Healthcare Safety Network

United Nations (UN) General Assembly holds high-level meeting on AR

2017
CDC begins supporting innovation to combat AR globally

*as part of funding across the U.S. government to implement CARB
1 Combating Antibiotic-Resistant Bacteria

CDC Leads the Public Health Fight Against Antibiotic Resistance (AR)

2017
CDC adds National Tuberculosis Molecular Surveillance Center to AR Lab Network

FDA[2] releases Veterinary Feed Directive to help ensure antibiotics only used to treat and prevent infections in food animals

2018
CDC co-hosts forum to publish report, *Initiatives for Addressing Antimicrobial Resistance in the Environment*

CDC RELEASES CONTAINMENT STRATEGY to stop the spread of new or emerging resistance

CDC co-hosts AMR[3] Challenge, a global one-year initiative to drive meaningful action worldwide

2019
PulseNet laboratories transition to whole genome sequencing for foodborne germs, enabling routine surveillance to predict resistance

CDC and HHS[4] conclude AMR Challenge Year with 300+ PARTNER COMMITMENTS WORLDWIDE

UN Interagency Coordination Group on AR calls for urgent action

CDC publishes second *Antibiotic Resistance Threats in the United States, 2019*

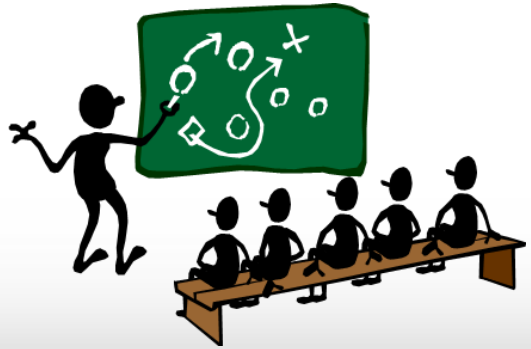
[2] Food and Drug Administration
[3] Antimicrobial resistance
[4] U.S. Department of Health & Human Services

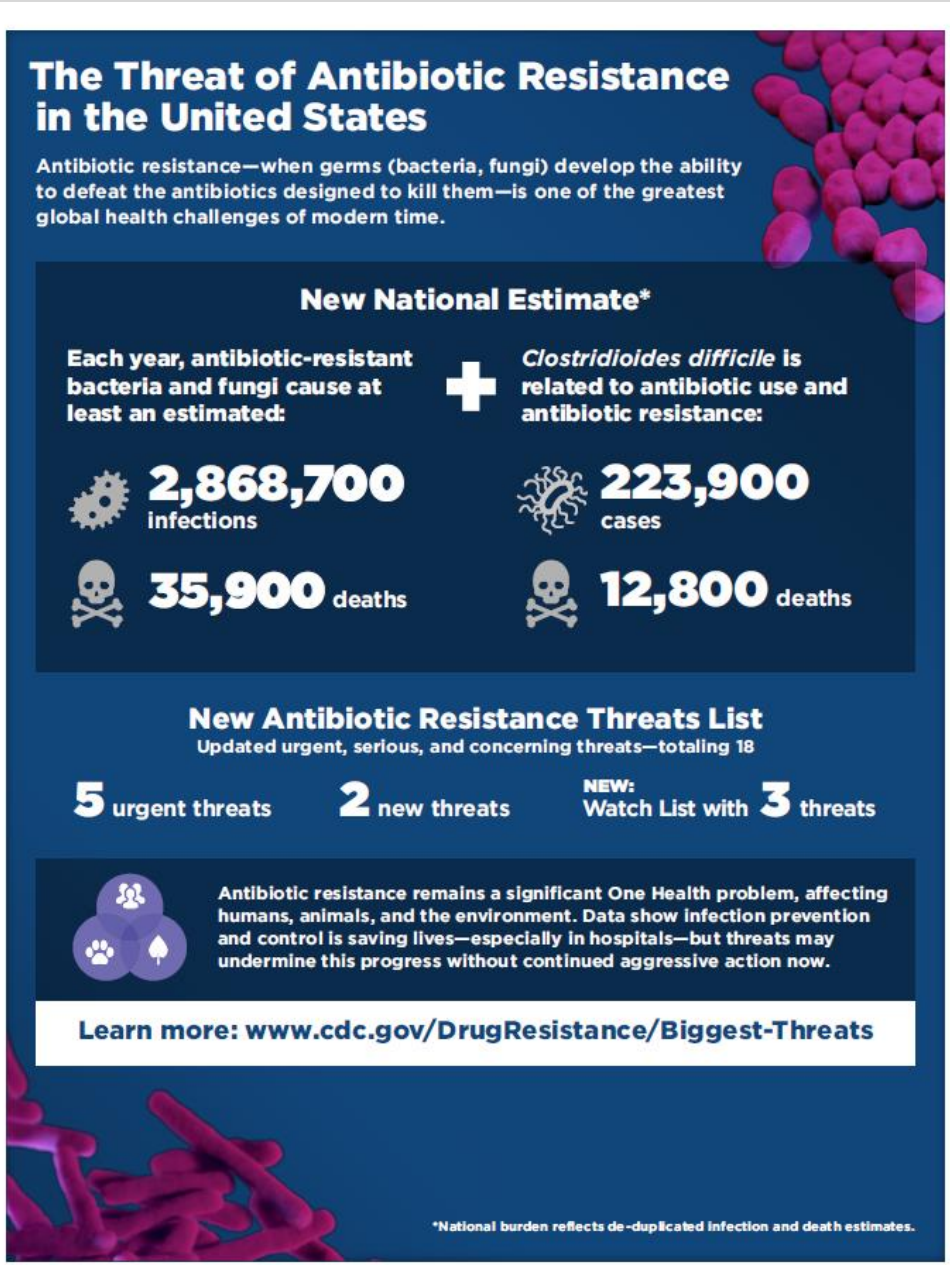
CDC Antibiotic Resistance Threats in the United States, 2019. Atlanta, GA: U.S. Department of Health and Human Services, CDC; 2019.

The AR Threat in United States

- More than 2,800,000 AR infections per year
- More than 35,000 deaths per year
- *Clostridioides difficile* infections (related to antibiotic use) account for additional 223,900 cases and 12,800 deaths (2017)
- I will not belabor quantitative comparisons (such as to influenza), can be devastating for individual patient or facility

You are the team that defends us!





CDC Antibiotic Resistance Threats in the United States, 2019. Atlanta, GA: U.S. Department of Health and Human Services, CDC; 2019.

AR Threats in US: the pathogens

- Threats classified according to:
  - Clinical and economic impact
  - Incidence and 10-year projection of incidence
  - Transmissibility
  - Availability of effective antibiotics
  - Barriers to prevention

CDC Antibiotic Resistance Threats in the United States, 2019. Atlanta, GA: U.S. Department of Health and Human Services, CDC; 2019.

DRUG-RESISTANT
SHIGELLA

Urgent Threats

- Carbapenem-resistant *Acinetobacter*
- *Candida auris (C. auris)*
- *Clostridioides difficile (C. difficile)*
- Carbapenem-resistant Enterobacteriaceae (CRE)
- Drug-resistant *Neisseria gonorrhoeae (N. gonorrhoeae)*

Serious Threats

- Drug-resistant *Campylobacter*
- Drug-resistant *Candida*
- Extended-spectrum beta-lactamase (ESBL)-producing Enterobacteriaceae
- Vancomycin-resistant *Enterococci* (VRE)
- Multidrug-resistant *Pseudomonas aeruginosa (P. aeruginosa)*
- Drug-resistant nontyphoidal *Salmonella*
- Drug-resistant *Salmonella* serotype Typhi
- Drug-resistant *Shigella*
- Methicillin-resistant *Staphylococcus aureus* (MRSA)
- Drug-resistant *Streptococcus pneumoniae (S. pneumoniae)*
- Drug-resistant Tuberculosis (TB)

Concerning Threats

- Erythromycin-resistant group A *Streptococcus*
- Clindamycin-resistant group B *Streptococcus*

Watch List

- Azole-resistant *Aspergillus fumigatus (A. fumigatus)*
- Drug-resistant *Mycoplasma genitalium (M. genitalium)*
- Drug-resistant *Bordetella pertussis (B. pertussis)*

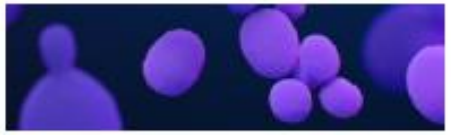
These are the ones to watch!

CDC Antibiotic Resistance Threats in the United States, 2019. Atlanta, GA: U.S. Department of Health and Human Services, CDC; 2019.

Urgent Threats

These germs are public health threats that require urgent and aggressive action:

CARBAPENEM-RESISTANT
ACINETOBACTER



CANDIDA AURIS

CLOSTRIDIOIDES DIFFICILE

CARBAPENEM-RESISTANT
ENTEROBACTERIACEAE

DRUG-RESISTANT
NEISSERIA GONORRHOEAE

Serious Threats

These germs are public health threats that require prompt and sustained action:

DRUG-RESISTANT
CAMPYLOBACTER

DRUG-RESISTANT
CANDIDA

ESBL-PRODUCING
ENTEROBACTERIACEAE

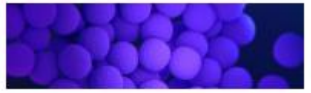
VANCOMYCIN-RESISTANT
ENTEROCOCCI

MULTIDRUG-RESISTANT
PSEUDOMONAS AERUGINOSA

DRUG-RESISTANT
NONTYPHOIDAL *SALMONELLA*

DRUG-RESISTANT
***SALMONELLA* SEROTYPE TYPHI**

DRUG-RESISTANT
SHIGELLA



METHICILLIN-RESISTANT
STAPHYLOCOCCUS AUREUS

DRUG-RESISTANT
STREPTOCOCCUS PNEUMONIAE

DRUG-RESISTANT
TUBERCULOSIS

Concerning Threats

These germs are public health threats that require careful monitoring and prevention action:

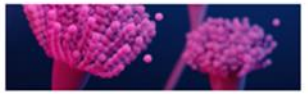
ERYTHROMYCIN-RESISTANT
GROUP A *STREPTOCOCCUS*

CLINDAMYCIN-RESISTANT
GROUP B *STREPTOCOCCUS*

The landscape is always changing … stay tuned!

Watch List

CDC's Watch List includes three threats that are uncommon, or the full burden of these germs is not yet understood in the United States. There is the potential for these resistant germs to spread across borders and cause significant morbidity and mortality. CDC and other public health experts are closely monitoring these germs, which have the potential to be included as listed threats in the future. Early detection of resistant germs within the United States, followed by implementation of prevention strategies, could reduce spread and public health impact.



AZOLE-RESISTANT
ASPERGILLUS FUMIGATUS

Aspergillus fumigatus is a fungus that can cause life-threatening infections in people with weakened immune systems. These infections are treated with antifungals called azoles. Azoles are also increasingly used in agriculture to prevent and treat fungal diseases in crops. Azole use in human medicine and agriculture can contribute to resistance to antifungal medicines. Although few infections caused by azole-resistant *A. fumigatus* have been identified in the United States, many more infections have been reported in other countries. *A. fumigatus* is challenging to detect because symptoms are similar to many other respiratory infections. When *A. fumigatus* is identified as the cause of an infection, most U.S. laboratories do not have the capability to test for resistance. CDC currently has limited tracking for *A. fumigatus* infections, but CDC is working to better understand how common these infections are and identify the best prevention strategies.

DRUG-RESISTANT
MYCOPLASMA GENITALIUM

M. genitalium bacteria are sexually transmitted and can cause urethritis in men (inflammation of the urethra) and may cause cervicitis in women (inflammation of the cervix). If left untreated, *M. genitalium* may also cause pelvic inflammatory disease in women, leading to chronic pelvic pain, ectopic pregnancy, and infertility. Few antibiotics are available to treat *M. genitalium* infections. Resistance to azithromycin, which has been recommended for treatment, is high across the globe. CDC is collaborating with partners, including STD clinics and other Federal agencies, on research to better understand the prevalence of *M. genitalium* in the United States and how resistance develops in this germ.

DRUG-RESISTANT
BORDETELLA PERTUSSIS

Pertussis, a respiratory illness commonly known as whooping cough, is a very contagious disease caused by a type of bacteria called *Bordetella pertussis*. It can cause serious and sometimes deadly complications, especially in babies. The best way to prevent this infection is to get vaccinated. Azithromycin and erythromycin are the recommended antibiotics to treat whooping cough. While antibiotic-resistant pertussis is rarely reported in the United States, resistance has been documented in other countries. CDC is monitoring resistance in the United States by testing isolates received through CDC's Emerging Infections Program.

"Global burden of bacterial antimicrobial resistance in 2019: a systematic analysis"

- Authors: "Antimicrobial Resistance Collaborators" (many!)
- Funding: Bill and Melinda Gates Foundation, Wellcome Trust, UK Dept Health and Social Care
- Data: systematic literature reviews, hospital systems, surveillance systems, other
- Comprehensive assessment: used predictive statistical modeling to estimate deaths and disability-adjusted life-years for all regions

Lancet. 2022; 399: 629-655. Feb 12, 2022

"Global burden of bacterial antimicrobial resistance in 2019: a systematic analysis"

- Estimates: ~4.95M deaths associated with bacterial AMR, including ~1.27M deaths directly attributable
- Highest region: Western sub-Saharan Africa
- Lowest region: Australasia
- Highest AMR-associated syndrome: Lower respiratory tract infection (other dominant syndromes bloodstream and intra-abdominal infections)
- Highest AMR-associated death pathogens (6): *E. coli, S. aureus, K. pneumoniae, S. pneumoniae, A. baumannii, P. aeruginosa*

Lancet. 2022; 399: 629-655. Feb 12, 2022

"Global burden of bacterial antimicrobial resistance in 2019: a systematic analysis"

- AMR is a leading cause of death around the world
  - Highest burden in low-resource settings
  - Need to expand microbiology lab capacity and data collection systems
  - In high-income super-region (including U.S.), roughly half of fatal AMR burden due to *S. aureus* and *E. coli*
- Global Burden of Diseases 2019 ranking leading causes of death
  - "Counterfactual" no infection – AMR is 3rd (after ischemic heart dz, stroke)
  - "Counterfactual" susceptible infection – AMR is 12th (ahead of HIV, malaria)

Lancet. 2022; 399: 629-655. Feb 12, 2022

World Health Organization priorities for AMR

- Stepping up leadership for AMR response
- Driving public health impact in every country to address AMR
- Research and development for better access to quality prevention and care measures for AMR
- Monitoring the AMR burden and global AMR response

WHO Strategic Priorities on Antimicrobial Resistance.
https://www.who.int/health-topics/antimicrobial-resistance
Accessed 4/19/2022

What does this mean?

We need you!

Roles and Responsibilities for AR infections

- The clinical laboratory supports patient care and public health
  - organism identification and susceptibility test results inform clinician's management of the patient
  - results and isolates are needed for further analysis in public health laboratories and health departments
- Many partners are critical to response, mitigation
  - infection preventionists, epidemiologists
  - PHLs, AR Lab Network regional labs, CDC, APHL, other
- Regardless of what position you play, the whole team is needed!

Public Health Laboratories:
Eleven Core Functions

- Disease Prevention, Control, Surveillance
- Integrated Data Management
- Reference and Specialized Testing
- Environmental Health and Protection
- Food Safety
- Laboratory Improvement and Regulation
- Policy Development
- Public Health Preparedness and Response
- Public Health Related Research
- Training and Education
- Partnerships and Communication

https://www.aphl.org/aboutAPHL/publications/Documents/APHLCoreFunctionsandCapabilities_2014.pdf

Do we have a problem on the front line?

- College of American Pathologists Microbiology Committee members had increasing concerns about breakpoints used in clinical laboratories
- Variability in PT results indicated that some laboratories may be using obsolete breakpoints
  - Labs commonly use FDA-cleared cAST devices, isn't that enough?
  - An organism with a certain minimum inhibitory concentration (MIC) is evaluated in many laboratories; some interpret as susceptible and others as resistant
  - What is going on here? Does this impact patient safety?
- Interest in understanding this issue further

Revised breakpoints, obsolete breakpoints

- When revised breakpoints are published, issues arise
  - Does the panel used for cAST in a laboratory include dilutions needed to assess organisms according to new breakpoints? Change panels?
  - Is there software update from manufacturer?
- Is it clear that when a revised breakpoint is published (*e.g.* by CLSI), old breakpoints are or may be considered obsolete?
- How do you know what to do next?
  - Unfortunately, complicated but necessary if we are all included as part of the response to the AR threat
  - Shouldn't AR be assessed with the same criteria? (apples to apples)

Response to AR includes breakpoint revisions

- For example, carbapenem breakpoints lowered in 2010 for Enterobacterales after carbapenemases were detected
- This resistance highly significant for infected patient and prevention of transmission
- We needed more reliable detection than phenotypic tests
- CLSI M100 had extra revisions in 2010

However, …

… not all the parts are synchronized or keeping up.

Changing roles and processes in U.S.

- Food and Drug Administration (FDA) and Clinical Laboratory Standards Institute (CLSI) both have important impact on AST performance and interpretation of results in the clinical laboratory
- FDA breakpoints found on “FDA STIC” website (Antibacterial Susceptibility Test Interpretive Criteria) after 21st Century Cures Act of 2016
- CLSI breakpoints for bacteria found in M100, updated annually and a free version is available online

Excellent overview of the story of these relationships: CLSI / CAP webinar Jan 2022 (R. Humphries, J. Patel)

CAP Participant Summary Report Bacteriology (D) survey

"Clinical and Laboratory Standards Institute (CLSI) has been updating breakpoints since 2010 and a listing of the revisions can be found in the front of CLSI M100-Ed31 "Performance Standards for Antimicrobial Susceptibility Testing (AST)" (January 2021). FDA has been updating breakpoints as well; however, not all CLSI and FDA breakpoints are identical at this time. FDA breakpoints are now available on the Antibacterial Susceptibility Test Interpretive Criteria Website, https://www.fda.gov/drugs/developmentresources/antibacterial-susceptibility-test-interpretive-criteria. Federal regulations require manufacturers of AST devices to use the FDA (and not CLSI) breakpoints. For those antimicrobial agent-organism combinations that have been updated by the FDA, manufacturers are in the process of updating their system's breakpoints. Clinical laboratories should check with technical services to determine when the updated breakpoints will be available on their system's software. If the breakpoints have not been updated on their system, the laboratory can implement them following a verification study. Currently, clinical laboratories have the option to use either CLSI or FDA breakpoints and either will be acceptable to CAP."

College of American Pathologists investigation: supplemental questionnaire with DB-2019 PT survey

- Assessed seven drug/bug combinations where breakpoints had changed, asked participant laboratories to respond whether they were using current breakpoints
- If they answered that they were not, they were asked why
- Relatively large data set of responses (roughly 1,000 each)

Simner, *et al*. Open Forum Infectious Diseases. Published online Feb 7, 2022

Open Forum Infectious Diseases

MAJOR ARTICLE

Raising the Bar: Improving Antimicrobial Resistance Detection by Clinical Laboratories by Ensuring Use of Current Breakpoints

Patricia J. Simner,[1] Carol A. Rauch,[2] Isabella W. Martin,[3] Kaede V. Sullivan,[4] Daniel Rhoads,[5] Robin Rolf,[6] Rosemary She,[7] Rhona J. Souers,[6] Christina Wojewoda,[8] and Romney M. Humphries[9]

[1]Johns Hopkins Medical Institute, Baltimore, Maryland, USA, [2]Vanderbilt University, Nashville, Tennessee, USA, [3]Dartmouth-Hitchcock Medical Center, Lebanon, New Hampshire, USA, [4]Temple University Hospital, Philadelphia, Pennsylvania, USA, [5]Cleveland Clinic, Cleveland, Ohio, USA, [6]College of American Pathologists, Chicago, Illinois, USA, [7]University of Southern California, Los Angeles, California, USA, [8]University of Vermont Medical Center, Burlington, Vermont, USA, and [9]Vanderbilt University Medical Center, Nashville, Tennessee, USA

Background. Antimicrobial resistance (AMR) is a pressing global challenge detected by antimicrobial susceptibility testing (AST) performed by clinical laboratories. AST results are interpreted using clinical breakpoints, which are updated to enable accurate detection of new and emerging AMR. Laboratories that do not apply up-to-date breakpoints impede global efforts to address the AMR crisis, but the extent of this practice is poorly understood.

Methods. A total of 1490 clinical laboratories participating in a College of American Pathologists proficiency testing survey for bacterial cultures were queried to determine use of obsolete breakpoints.

Results. Between 37.9% and 70.5% of US laboratories reported using obsolete breakpoints for the antimicrobials that were queried. In contrast, only 17.7%–43.7% of international laboratories reported using obsolete breakpoints ($P < .001$ for all comparisons). Use of current breakpoints varied by AST system, with more laboratories reporting use of current breakpoints in the US if the system had achieved US Food and Drug Administration clearance with current breakpoints. Among laboratories that indicated use of obsolete breakpoints, 55.9% had no plans to update to current standards. The most common reason cited was manufacturer-related issues (51.3%) and lack of internal resources to perform analytical validation studies to make the update (23.4%). Thirteen percent of laboratories indicated they were unaware of breakpoint changes or the need to update breakpoints.

Conclusions. These data demonstrate a significant gap in the ability to detect AMR in the US, and to a lesser extent internationally. Improved application of current breakpoints by clinical laboratories will require combined action from regulatory agencies, laboratory accreditation groups, and device manufacturers.

Keywords. antimicrobial resistance; breakpoints; laboratory testing; susceptibility testing.

Many laboratories are using obsolete breakpoints, often thinking that use of FDA-cleared device is sufficient.

Some laboratories reported being unaware of changes in breakpoints.

Table 1. Clinical Breakpoints Evaluated by the College of American Pathologists Survey to Laboratories Participating in Bacteriology Proficiency Testing Program

Organism	Antimicrobial	Year BP Updated by CLSI[a]	Rationale for BP Update [4]	Obsolete Susceptible BP	Current Susceptible BP
Enterobacterales	Ceftazidime	2010	A public health need was identified due to the spread of AMR (ie, ESBL producers) Revised BPs simplified testing and eliminated the need for additional tests to detect AMR	≤8 µg/mL	≤4 µg/mL
Enterobacterales	Ceftriaxone	2010		≤8 µg/mL	≤1 µg/mL
Enterobacterales	Ciprofloxacin	2019	New PK/PD data indicated the previous breakpoints were set too high	≤1 µg/mL	≤0.25 µg/mL
Enterobacterales	Levofloxacin	2019	Revised BPs allowed harmonization across SDOs	≤2 µg/mL	≤0.5 µg/mL
Enterobacterales	Meropenem	2010	A public health need was identified related to recognition of a new AMR mechanism (ie, carbapenemase genes) Revised BPs simplified testing and eliminated the need for additional tests to detect AMR	≤4 µg/mL	≤1 µg/mL
Pseudomonas aeruginosa	Piperacillin-tazobactam	2012	New data demonstrated poor prediction of clinical response using existing breakpoints	≤64/4 µg/mL	≤16/4 µg/mL
Acinetobacter baumannii	Imipenem	2014	New data demonstrated poor prediction of clinical response using existing breakpoints	≤4 µg/mL	≤2 µg/mL

Abbreviations: AMR, antimicrobial resistance; BP, breakpoint; CLSI, Clinical and Laboratory Standards Institute; ESBL, extended-spectrum β-lactamase; PK/PD, pharmacokinetic/pharmacodynamic; SDO, standards development organization.

[a]US Food and Drug Administration recognition of the CLSI breakpoints was generally 1–3 years after publication by CLSI, although exact dates prior to 2018 are unavailable.

Simner, *et al*. Open Forum Infectious Diseases. Published online Feb 7, 2022

Table 3. Current Breakpoint Usage by Laboratory Location (United States Versus International)

Organism	Antimicrobial Agent	United States		International		*P* Value, Difference Between US and International
		Total No. of Laboratories	Current Breakpoints, No. (%)	Total No. of Laboratories	Current Breakpoints, No. (%)	
Enterobacterales	Ceftazidime	1046	620 (59.3)	201	164 (81.6)	<.001
Enterobacterales	Ceftriaxone	1124	694 (61.7)	186	153 (82.3)	<.001
Enterobacterales	Ciprofloxacin	1058	312 (29.5)	206	122 (59.2)	<.001
Enterobacterales	Levofloxacin	1019	306 (30.0)	160	90 (56.3)	<.001
Enterobacterales	Meropenem	982	610 (62.1)	187	149 (79.7)	<.001
Pseudomonas aeruginosa	Piperacillin-tazobactam	1064	559 (52.5)	197	150 (761)	<.001
Acinetobacter baumannii	Imipenem	784	367 (46.8)	182	139 (76.4)	<.001

- International laboratories more likely to use current breakpoints (some relationship with FDA)
- Use of current breakpoints is variable

Simner, *et al*. Open Forum Infectious Diseases. Published online Feb 7, 2022

Table 5. Comment Summary for Laboratories Unsure of the Breakpoints They Applied or if They Used Obsolete Breakpoints by Location

Reason	All (N = 918)	United States (n = 835)	International (n = 83)
Efforts to use or implement current breakpoints underway	405 (44.1)	372 (44.6)	33 (39.8)
Plan to update, in progress	188 (46.4)	181 (48.7)	7 (21.2)
Not applicable because do not report, use alternate method, or send to reference laboratory	128 (31.6)	102 (27.4)	26 (78.8)
Changing panels or instruments	55 (13.6)	55 (14.8)	0 (0.0)
Validation testing not completed but underway	34 (8.4)	34 (9.1)	0 (0.0)
Ongoing use of obsolete breakpoints, no current revisions in progress	513 (55.9)	463 (55.4)	50 (60.2)
Manufacturer-related issues	263 (51.3)	232 (50.1)	31 (62.0)
Resource limitations of staff, time, organisms, guidance, laboratory information system issues, cost	120 (23.4)	112 (24.2)	8 (16.0)
Overlooked or unaware of breakpoint change or need to update	68 (13.3)	57 (12.3)	11 (22.0)
Facility does not support	30 (5.8)	30 (6.5)	0 (0.0)
Not done, under review for a variety of concerns	28 (5.4)	28 (6.0)	0 (0.0)
Do not want or intend to update	4 (0.8)	4 (0.8)	0 (0.0)

Data are presented as No. (%).

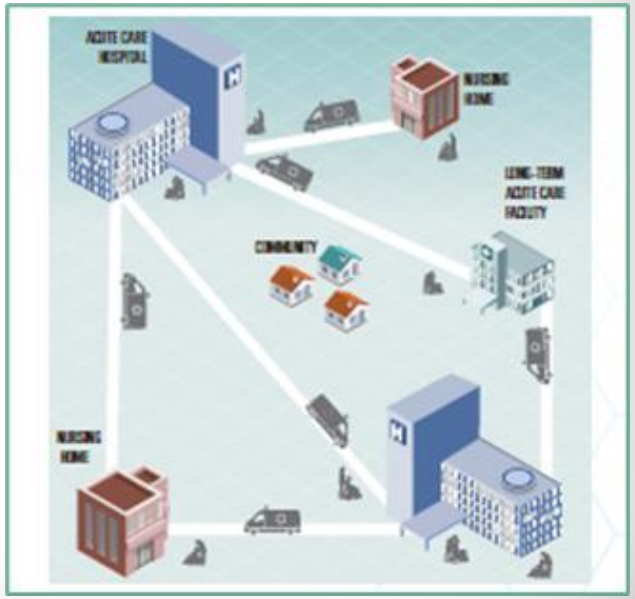
- For those using obsolete breakpoints, comments most often reliance on manufacturer and some were unaware of need

Simner, *et al*. Open Forum Infectious Diseases. Published online Feb 7, 2022

We have some housecleaning to do!

Combating the threat of AR requires accurate initial test results

- Do not want to misclassify a patient's isolate as susceptible using obsolete breakpoints when the isolate is considered resistant by current guidance
  - Bad for patient care
  - Bad for programs that monitor and respond to clusters of resistant organisms
    - within individual facility or healthcare system
    - public health systems that monitor across facilities, systems, and beyond



AR Threats Report 2019

CAP Laboratory Accreditation Program requirements for microbiology labs

***REVISED** 09/22/2021*

MIC.11380 Antimicrobial Susceptibility Test Interpretation Criteria **Phase II**

For antimicrobial susceptibility testing systems, there are written criteria for determining and interpreting minimal inhibitory concentration (MIC) or zone diameter sizes as susceptible, intermediate, resistant, non-susceptible, or susceptible dose-dependent. These criteria are reviewed annually.

Evidence of Compliance:

- ✓ Listing of antimicrobial susceptibility test interpretive criteria applied to test results and the specific source document for these **AND**
- ✓ Patient reports with reporting of antimicrobial agents following written protocol **AND**
- ✓ Records of annual breakpoint review **AND**
- ✓ Proficiency testing susceptibility results following written policy

- Includes AST performed on bacteria, fungi, and mycobacteria
- Lab can use CLSI, FDA, EUCAST (or even institutionally-derived breakpoints with appropriate documentation)
- Must be reviewed annually

CAP Microbiology Checklist 09/22/2021

CAP Laboratory Accreditation Program requirements for microbiology labs

***NEW** 09/22/2021*

MIC.11385 Current Antimicrobial Susceptibility Test Interpretation Breakpoints Phase I

Effective January 1, 2024, the laboratory uses current breakpoints for interpretation of antimicrobial minimum inhibitory concentration (MIC) and disk diffusion test results, and implements new breakpoints within three years of the date of official publication by the FDA or other standards development organization (SDO) used by the laboratory.

Evidence of Compliance:

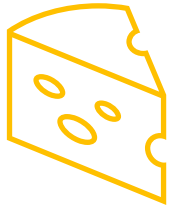
- ✓ Written policy for updating breakpoints used for antimicrobial susceptibility test interpretations **AND**
- ✓ Records of validation reports for breakpoints that differ from those included in the FDA-clearance of an instrument **AND**
- ✓ Records of the interpretive criteria used for antimicrobial susceptibility testing **AND**
- ✓ Source document (including year of publication) from which the interpretive criteria were derived **AND**
- ✓ Patient or LIS reports with interpretations matching the source document

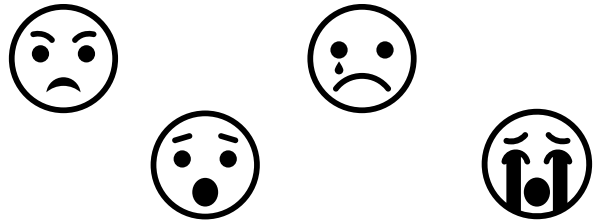
- There is advanced warning; first step is to identify bp's used in your laboratory
- Contact manufacturer as needed
- Unacceptable to use breakpoint no longer recognized by CLSI, EUCAST, FDA
  (unless alternative is justified and documented)

CAP Microbiology Checklist 09/22/2021

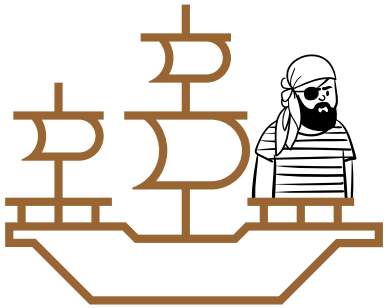
What's next?

Who moved my cheese?!





Mutiny?!



Getting all onto the same page …

Where we need to be

- We are here to focus on AR/AMR, which affects all of us and which needs all of us to combat this threat
- We need to be more standardized in AST reporting, all measuring resistance the same way with current breakpoints
- We have identified problems and **why** they need to be addressed

Help is on the way for guidance in **how** to do this!

APHL, ASM, CAP, and more

My dream …

- Print copies of CLSI M100
  - every clinical lab
  - every year
  - free (or cheap)
- Secret wish to find funding
  - negotiate price discount from CLSI for large bulk order?
  - Michigan does this, I am not currently aware of other states

Wisconsin?

Why?

- I suspect that M100 is most frequently accessed for finding or confirming a particular breakpoint within Table 2 sections
- Important information in other sections may be overlooked
  - Front matter (overview of changes, CLSI breakpoint additions/revisions since 2010)
  - Warning statements (such as agents not to report for CSF isolates)
  - Glossaries needed to implement warnings

Resources: front matter in CLSI M100 31st ed.

- CLSI additions/revisions since 2010 (page *xxiii*)

  (new bp) (changed bp or applicable organisms)

- CLSI Reference Methods vs Commercial Methods and CLSI vs US Food and Drug Administration Breakpoints (page *xxx*)
  - In the US, acceptable with FDA-cleared cAST devices to use existing FDA bp's
  - If device includes sufficient concentrations, could be used by a lab after appropriate verification studies to report with CLSI bps for interpretation

Combating the Real Threat of Antibiotic Resistance

- Doom & gloom is not always a great space for action
  - crowded by pandemic, war, climate change, politics

- Playing active role in a strong network is a great space
  - surveillance targets
  - identify microbes and resistance using best methods
  - report to PH (data +/- isolates)
  - WCLN → WSLH ARLN regional laboratory, beyond

Learning objectives

1. List important issues related to antibiotic/antimicrobial resistance
   (global disease burden related to AMR is significant, including U.S.)
   (domestic threats classified, with 18 pathogens urgent or serious)
2. Identify important variables critical to patient care as well as to public health efforts
   (AST result interpretation must use correct breakpoints for management of individual patients and for quality of data shared with public health)
   (breakpoints should reflect current evidence and what is needed for circulating organisms)
3. Critically evaluate opportunities for practice improvement
   (have a critical look at your lab's breakpoints and go from there)

Take-home

- Prepare to review and document source of AST breakpoints
  - Identify breakpoints used and specific source (*e.g.* which year of M100)
  - Determine whether any are obsolete
- Consider how/when to update breakpoints, especially if laboratory is CAP-accredited
  - Contact manufacturer as needed to understand status and plans
  - Identify guidance resources … help is available, more on the way!
  - If implementing revised bp's, discuss with relevant laboratory partners the potential for clinical impact as well as rates (local and downstream)

Thank you for your attention!

Questions? Comments? Enjoy your day!

Contact: carol.a.rauch@vanderbilt.edu