Challenges in Studying Rapid Diagnostic Tests in Outpatient Respiratory Tract Infections

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Antibacterial Resistance Leadership Group (ARLG)

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Outline

- Outpatient Antibiotic Use and Resistance
- Need for Rapid Diagnostic Tests
- ARLG's TRAP-LRTI Study
- DOOR / RADAR Methods

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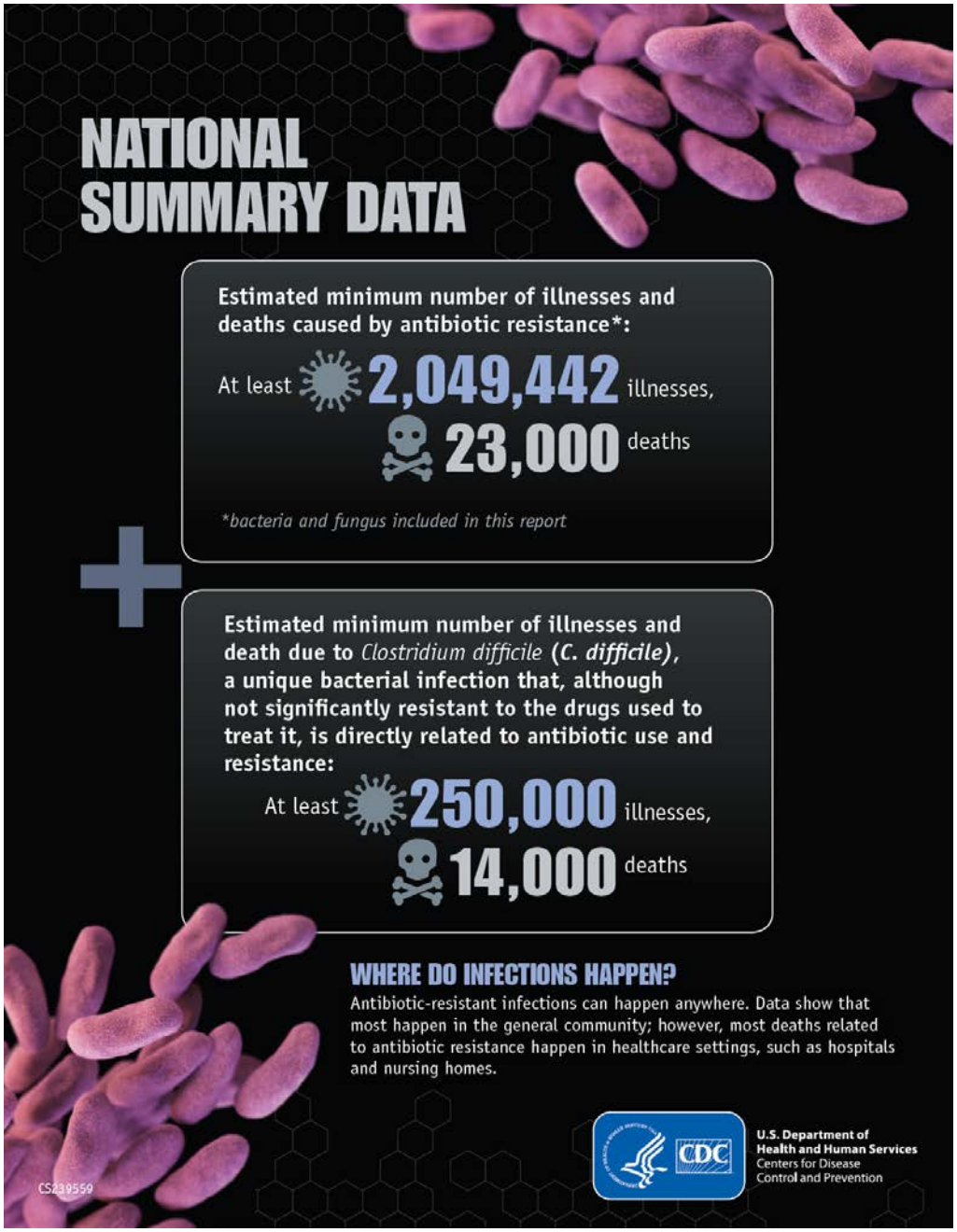
Landscape of Antibiotic Resistance

- ~10% of hospitalizations are complicated by healthcare associated infections (HAIs)
  - 60-70% HAIs are resistant to first line therapy
- Antibiotic-resistant infections
  - $20 billion annual healthcare costs
  - 8 million additional hospital days
  - $35 billion in societal costs
- Loss of confidence in our health care system
- Many states now require screening for certain multidrug-resistant organisms

Roberts R, *Clin Infect Dis* 2009;49:1175-84
Cosgrove SE, *Clin Infect Dis* 2006;42(Supp):S82
Harrison P, IOM, 1998



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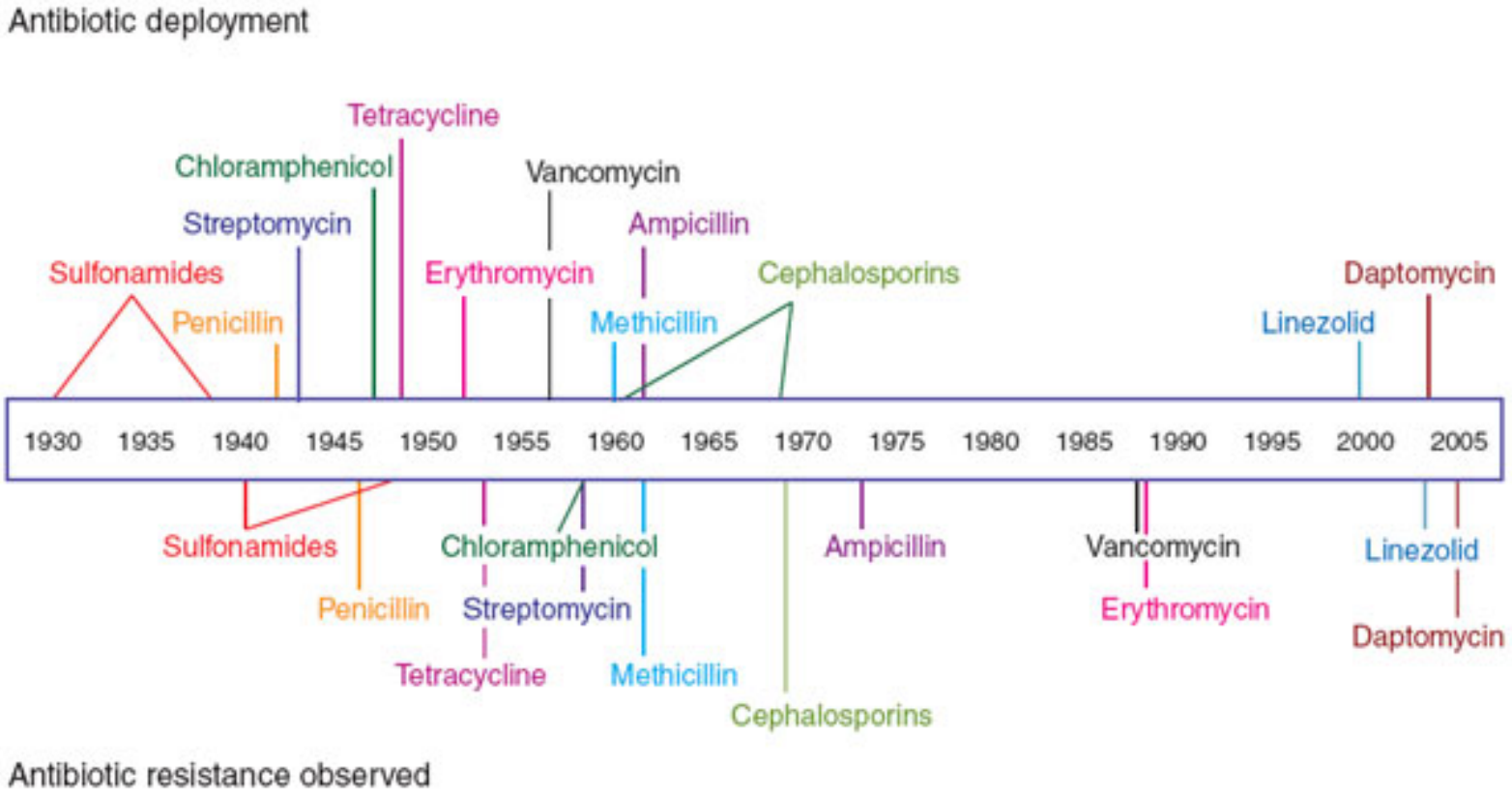
Primary Driver of Resistance is Antibiotic Use



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Clatworthy AE,*Nature Chemical Biology 2007;*3:541-8

Antimicrobial Stewardship

Infectious Diseases Society of America and the Society for Healthcare Epidemiology of America Guidelines for Developing an Institutional Program to Enhance Antimicrobial Stewardship

Timothy H. Dellit,[1] Robert C. Owens,[2] John E. McGowan, Jr.,[3] Dale N. Gerding,[4] Robert A. Weinstein,[5] John P. Burke,[6] W. Charles Huskins,[7] David L. Paterson,[8] Neil O. Fishman,[9] Christopher F. Carpenter,[10] P. J. Brennan,[9] Marianne Billeter,[11] and Thomas M. Hooton[12]

- Antimicrobial Stewardship Programs recommended for hospitals
- Most antibiotic use occurs in the outpatient setting
- is outpatient “stewardship” achievable?

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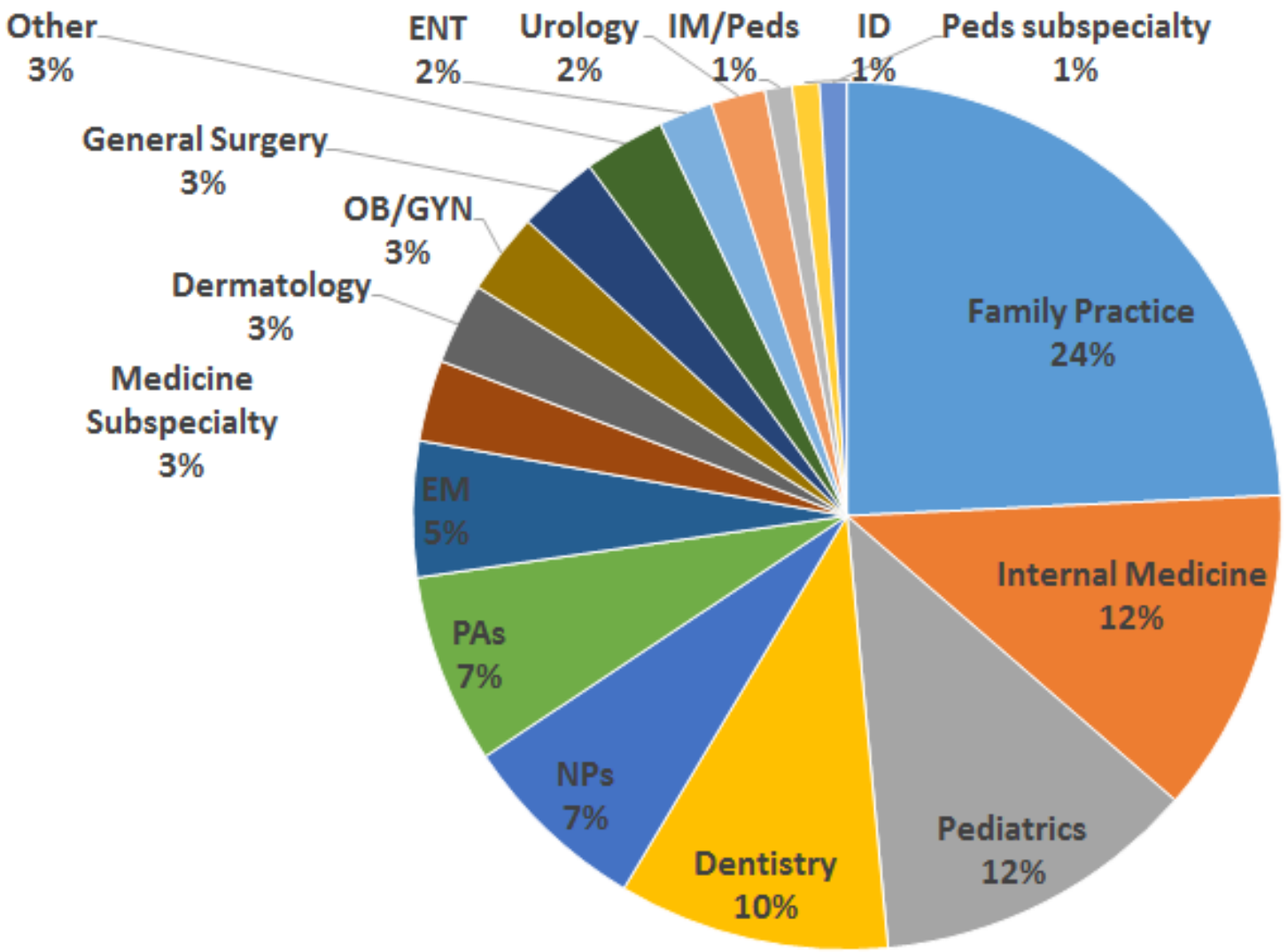
Schumock, *Am J Health-Syst Pharm*. 2014; 71:482-99

Ambulatory Antimicrobial Stewardship

- 262.5 million courses of outpatient antibiotics in 2011
  - 789 prescriptions per 1000 adults
  - 889 prescriptions per 1000 children
- 50% of all outpatient antibiotics prescribed are unnecessary
- Most inappropriate use is for acute respiratory infections (ARI)
  - Antibiotics prescribed for 71% of acute bronchitis cases
  - Antibiotics are prescribed for 80% of cases of acute sinusitis, despite most cases being viral in origin
  - Prescribing rate increasing in some settings
- Substantial variation among prescribers
  - Highest decile prescribes for 95% of ARIs
  - Highest quartile prescribes for 38% of tier 3 visits (diagnoses in which antibiotics are almost never indicated)

Suda KJ, et al. J Antimicrob Chemother 2013.
Hicks LA, et al. Clin Infect Dis 2015.
Dantes R, et al. Open Forum Infect Dis 2015.
Barnett ML, Linder JA. JAMA 2014.
Jones BE, et al. Ann Intern Med 2015.
Caplow J, et al. IDWeek 2016

Ambulatory Antimicrobials by Specialty



Hicks LA, et al. Clin Infect Dis 2015.

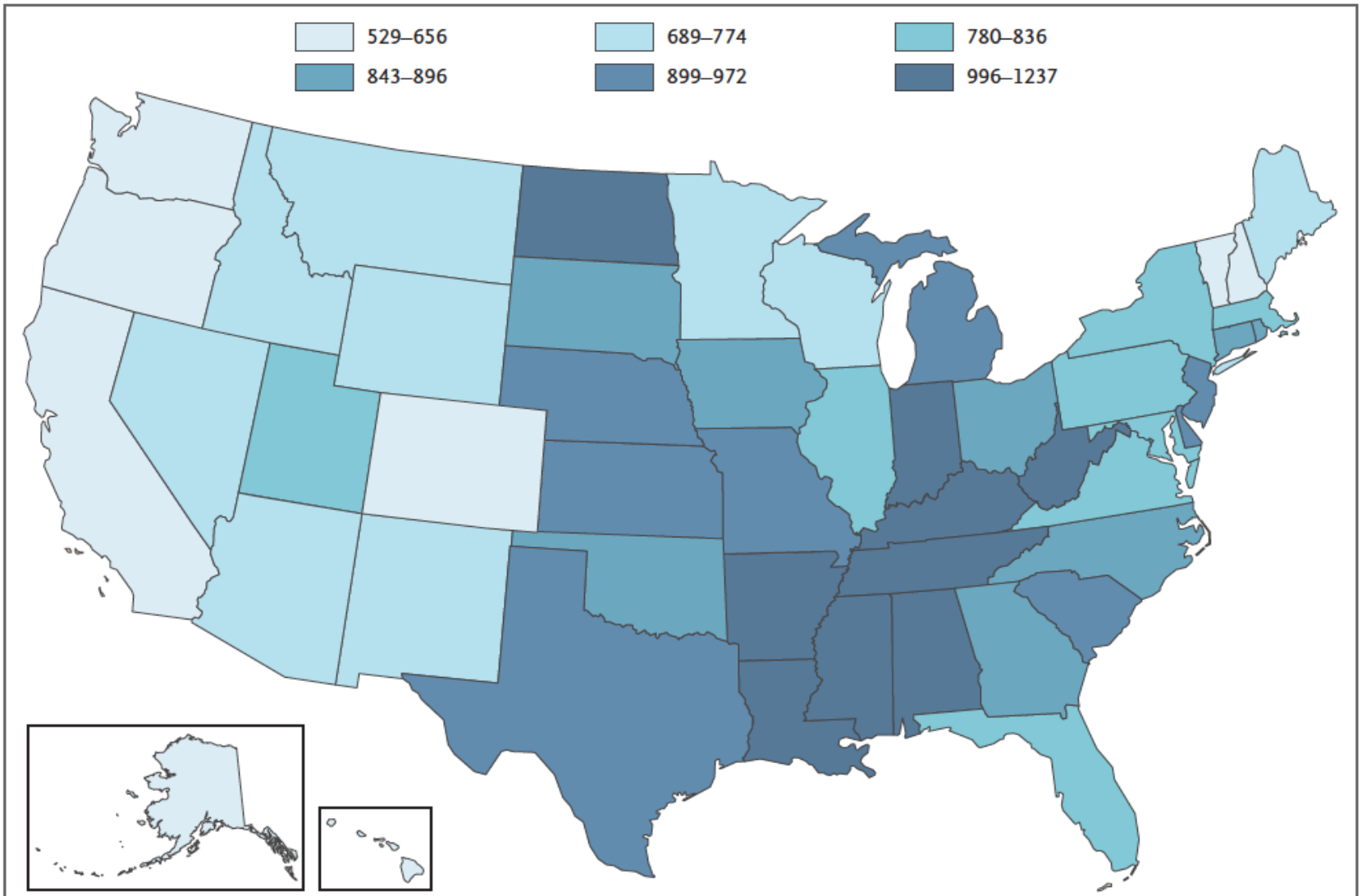


Figure 1. Antibiotic Prescriptions per 1000 Persons of All Ages According to State, 2010.

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Hicks L et. Al. *NEJM* April 11, 2013

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Inappropriate Use in Ambulatory Settings

- 72% of patients that present with an upper respiratory tract infection expect to receive a prescription for an antibiotic
- Antibiotics are prescribed in 21% of acute pediatric ambulatory visits (>70% are for URIs, representing 10 million antibiotic prescriptions per year)
- Of the providers who gave a prescription for antibiotic, 20% felt the antibiotic was clinically indicated
- Impractical to change antibiotics after prescription

Hicks, Clin Infect Dis, 2015.
Cooper, Ann Intern Med, 2001.
Bisno, Clin Infect Dis, 2002.
Hersh, Pediatrics, 2011.
Macfarlane, BMJ, 2007.

Limited Effect of Current Strategies

- Benchmarking overall prescribing and prescribing of broad-spectrum antibiotics has shown modest improvement in antimicrobial prescribing
  - Unclear role of academic detailing
- RCT of education coupled with periodic feedback decreased broad-spectrum antibiotic prescribing but did not affect prescribing for viral infections
- Mixed results of studies using other methods to improve prescribing: delayed prescriptions, communication skills training, and clinical decision support

Naughton C, et al. J Eval Clin Pract 2009.
Gerber JS, et al. JAMA 2013.
Drekonja DM, et al. Infect Control Hosp Epidemiol 2015.
Schuetz P, et al. Cochrane Database Syst Rev 2012.
Meeker D, et al. JAMA Intern Med 2014.

Potential Role of Rapid Diagnostics

- Changing attitudes and behaviors of clinicians (and patients) challenging
- Rapid diagnostic offer promise in providing objective data to inform treatment
  - Some rapid diagnostics (e.g. streptococcal antigen) have demonstrated decreased antibiotic prescribing
- Time required to develop/test new diagnostics prohibitive
- Development of novel diagnostics challenging given frequent lack of clear microbiologic diagnosis

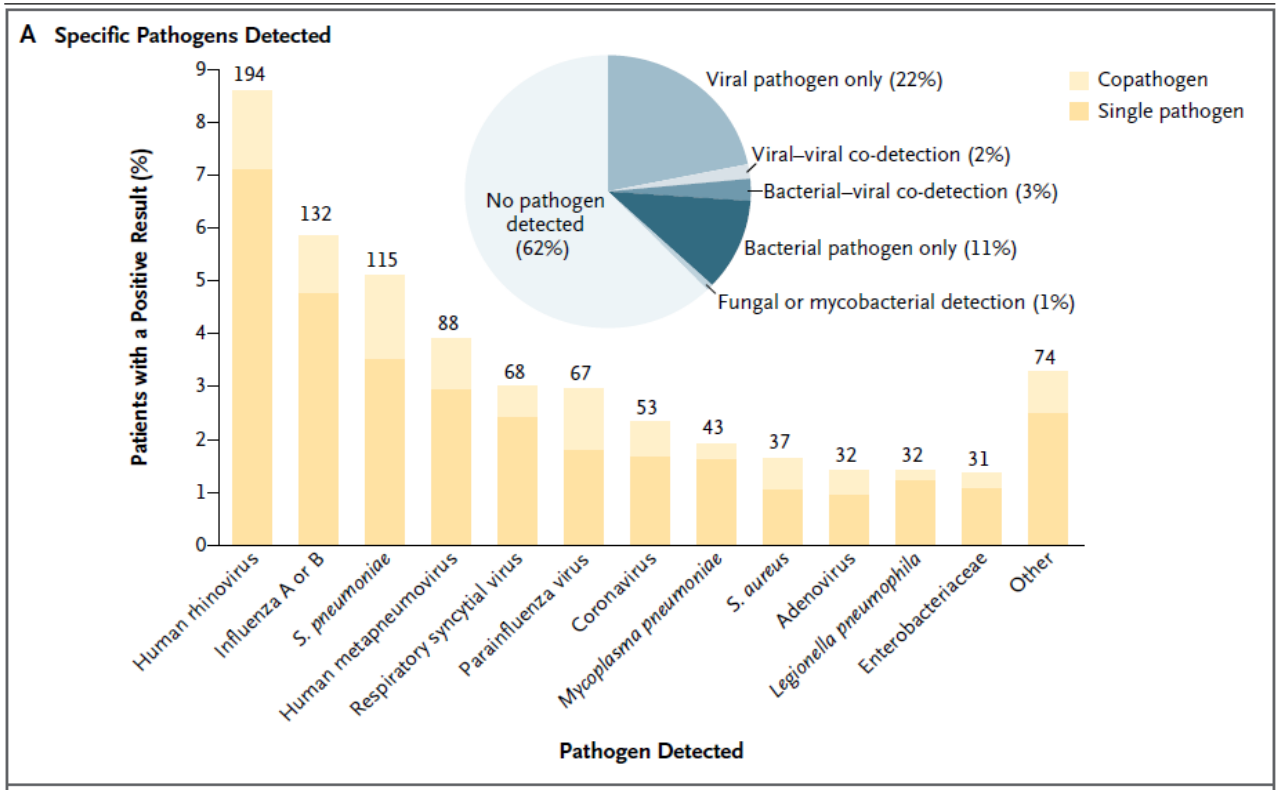
Potential Role of Rapid Diagnostics

- Two potential strategies:
  - #1) inform initiation of therapy (start: yes/no)
  - #2) decrease duration of therapy
  - Focus should be based on population under study
    - #1 should be priority for ARIs
- Two potential targets:
  - #1) bacterial vs non-bacterial/non-infectious
  - #2) identification of organism
- Given most ARIs are viral and the goal is reducing overall antibiotic use, should prioritize focus on #1

Diagnostic Uncertainty

- Etiology of Pneumonia in the Community (EPIC) Study (2010-2012)
- Population-based surveillance for community-acquired pneumonia Blood, urine, respiratory samples
  - Culture, serologic testing, antigen detection, molecular diagnostics
- 2259 patients with radiographic CAP and specimens for diagnosis

- Pathogen identified in 853 (38%)



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Jain S, NEJM 2015;30:415-27

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Antibacterial Resistance Leadership Group (ARLG)

Mission Statement: To prioritize, design, and execute clinical research that will reduce the public health threat of antibacterial resistance

https://arlg.org/

NIH National Institute of Allergy and Infectious Diseases
Leading research to understand, treat, and prevent infectious, immunologic, and allergic diseases.

U.S. Department of Health and Human Services
NIH News
National Institutes of Health

NIH to Fund Clinical Research Network on Antibacterial Resistance
Researchers at Duke University Will Lead the Initiative

National Institute of Allergy and Infectious Diseases (NIAID)
http://www.niaid.nih.gov

FOR IMMEDIATE RELEASE
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Additional Information From NIAID

Media Contact Info
News Releases by Topic
Health & Research Topics

Duke University, Durham, N.C., has been awarded $2 million to initiate a new clinical research network focused on antibacterial resistance. Total funding for the leadership group cooperative agreement award could reach up to $62 million through 2019. Funding is provided by the National Institute of Allergy and Infectious Diseases (NIAID), part of the National Institutes of Health.

"Antibacterial resistance is a serious and growing public health threat that is endangering the global medical community's ability to effectively treat conditions ranging from simple skin infections to tuberculosis," said NIAID Director Anthony S. Fauci, M.D. "Through this new clinical research network, we will strengthen our existing research capacity and address the most pressing scientific priorities related to antibacterial resistance."

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Chambers HF, *Clin Infect Dis* 2014;58:1571-6

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Scientific Committees: Research Agenda Priorities

Significance	Long-Term Objectives
MDR Gram-negative Bacilli	Identify and design clinical trials to improve outcomes of MDR-GNB infections and minimize opportunities for further resistance
Antimicrobial Stewardship and Infection Prevention	Identify and develop institutional and provider-based strategies to reduce the use and environmental impact of antibacterials, and thus selective pressure for antibacterial resistance
MDR Gram-positive Bacteria	Design and develop innovative observational and interventional projects to determine safety and effectiveness of directed therapy and to improve outcomes of Gram-positive infections
Diagnostics and Devices	Studies to validate diagnostics toenable early identification of MDROs in clinical trials to improve outcomes and lower cost

Special Emphasis Panels (SEPs)

- Pediatrics
- Pharmacokinetics
- Special Populations

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Chambers HF, *Clin Infect Dis* 2014;58:1571-6

Targeted Reduction of Antibiotics using Procalcitonin in outpatient adults with suspect lower respiratory tract infection (TRAP-LRTI)

DMID Funding Mechanism: Vaccine and Treatment Evaluation Unit
IND Sponsor: NIH/NIAID/DMID

VTEU Principal Investigators:
Geeta K. Swamy, MD and Christopher W. Woods, MD, MPH
ARLG Principal Investigators:
Ebbing Lautenbach, MD, MPH, MSCE, Vance Fowler, MD, MHS, and Henry “Chip” Chambers, MD

Industrial Support Provided by: bioMérieux

DMID Scientific Lead: Jane Knisely, PhD
DMID Medical Officer: Richard Gorman, MD
DMID Clinical Project Manager: Marina Lee, PhD
DMID Medical Monitor: Venus Shahamatdar, MD

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TRAP-LRTI

Overall Goal:

To demonstrate the ability of a biomarker test to identify a patient population in which antibacterial treatment provides no clear benefit.

TRAP-LRTI: Study Methods

- **Design:** Randomized, placebo-controlled, double-blinded, non-inferiority clinical trial of azithromycin v placebo
- **Population:** adults presenting as outpatients with suspect LRTI and a PCT level of <0.1 ng/mL,
- **Sites:** Duke Univ/Durham VA Medical Center (Coord Site); Baylor University/ Michael E. DeBakey VA Medical Center; and Emory University/Atlanta VA Medical Center
- **Screening**: Suspect LRTI defined as the new onset or worsening of at least two of the following symptoms or at least one symptom and one vital sign abnormality:
  - 1) *symptoms*: cough, sputum production, chest pain, and difficulty breathing
  - 2) *vital sign abnormalities*: temp >38°C, tachycardia of >90 beats/minute, and tachypnea of >20 breaths/minute

TRAP-LRTI: Study Methods

- **Enrollment**
  - Individuals fulfilling inclusion criteria will be approached to provide informed consent
  - Blood will be collected for PCT testing and banking
  - Nasopharyngeal swab will be obtained for testing and banking
- **Randomization**
  - If the PCT value is <0.1 ng/mL, the participant will be randomized 1:1 to receive oral azithromycin or placebo
  - Initiation of study drug will occur within 12 hours of enrollment and randomization and must be initiated prior to administration of any antibiotic

TRAP-LRTI: Study Methods

- **Follow-up and Assessment of Endpoints**
- **Day 1:** day of enrollment and first day of study drug administration
- **Day 3:** Subjects evaluated via telephone. Only presenting symptoms will be assessed
- **Day 5:** Outcome assessment will represent primary outcome; assessment of presenting signs and symptoms
  - Blood sample will also be collected for repeat PCT sampling
  - All clinical parameters will be ascertained at this time.
- **Day 11: S**ubjects evaluated via telephone
  - Secondary outcome measures : 1) all antibiotic use from enrollment through study day 11; 2) return visits to a physician's office; 3) emergency department visits; and 4) improvement in presenting symptoms.
- **Day 28:** Subjects evaluated via telephone
  - Secondary outcome measures same as day 11 visit

TRAP-LRTI

Primary Study Objective

To compare the efficacy of azithromycin versus placebo on study day 5 (i.e., at 4 days of treatment) in subjects with suspect LRTI and PCT levels of <0.1 ng/mL using a non-inferiority approach.

Hypothesis: Clinical outcomes in enrollees who do not receive antibiotic therapy will be comparable, or non-inferior, to those who do receive antibiotic therapy

TRAP-LRTI

Secondary Study Objectives

To compare azithromycin versus placebo with regard to antibiotic use through study days 11 and 28

To compare azithromycin versus placebo with regard to return visits to a physician's office by study days 11 and 28

To compare azithromycin versus placebo with regard to emergency department visits by study days 11 and 28

To compare azithromycin versus placebo with regard to improvement in presenting symptoms by study days 11 and 28

To compare the efficacy of azithromycin versus placebo in subjects with suspected LRTI and PCT levels of <0.1 ng/mL at study day 5 using a superiority approach, employing the "Response Adjusted for Days of Antibiotic Risk (RADAR)" methodology

TRAP-LRTI

Analysis / Sample Size

- Primary analysis: intention-to-treat estimation of the difference in proportions improved at study day 5 in the antibiotic and placebo arms
- Per-protocol analysis conducted as a sensitivity analysis
- Trial designed to evaluate if there is a lack of clinically meaningful superiority of azithromycin over placebo
- 420 people (210 per arm) in study
- 80% probability to rule out a 12.5% increase in improvement rate with antibiotic therapy

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Challenges in Antibiotic Use / Antibiotic Resistance Research

- **<u>Competing Risks</u>**
  - Primary endpoint of interest is measure(s) of antibiotic use
  - Other important outcomes: repeat provider visit, emergency department visit, length of stay, mortality
  - Significant distortion issues due to competing risks when considered as outcomes separately
  - Outcomes must be interpreted in context of each other

Evans SR, *Clin Infect Dis* 2015;61:800-6

Challenges in Antibiotic Use / Antibiotic Resistance Research

- **<u>Issues with Non-Inferiority Designs</u>**
  - Doesn't address whether one approach is better
  - More susceptible to biases and manipulation
    - Lower scientific integrity
  - Implies preservation of previously demonstrate effect (i.e., vs placebo)
  - Effectiveness of the "control" may change over time
  - Acceptance of non-inferiority margin

Evans SR, *Clin Infect Dis* 2015;61:800-6

Challenges in Antibiotic Use / Antibiotic Resistance Research

- **Individual vs Group Assessment**
  - Some patients experience benefit while some patients experience harm
    - Degree of overlap of these two groups often unclear
  - If little overlap: focus intervention on those who experience benefit but not harm
  - If great overlap: determine net effect (benefits vs risks)
  - Traditional analytic approaches treat these benefit and harm outcomes separately
  - Need novel approaches to evaluate net effect in individuals

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Evans SR, *Clin Infect Dis* 2015;61:800-6

Desirability of Outcome Ranking (DOOR)

- Ranking of trial participants by their overall outcome
- "Outcomes used to analyze patients rather than using patients to analyze outcomes"
- Define ordinal overall clinical outcome: Example
  - Clinical benefit (symptoms/function) without adverse effects (AEs)
  - Clinical benefit with some AEs
  - Survival without clinical benefit or AEs
  - Survival without clinical benefit but with AEs
  - Death
- Number of definition of categories tailored to disease
- Consensus regarding the definition is key

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Evans SR, *Clin Infect Dis* 2015;61:800-6

Response Adjusted for Duration of Antibiotic Risk (RADAR)

- Version of DOOR tailored for studies comparing antibiotic use strategies
- Subjects assigned a DOOR ranking using 2-step process
  - Better overall clinical outcome receives a higher rank
  - When two patients have the same overall clinical outcome, the patient with the shorter duration of antibiotic use receives a high rank
- Clinical outcome trumps duration of antibiotic use
- Adherence incorporated into the DOOR ranking
- Duration of antibiotic use most common measures
  - Others: broad vs narrow spectrum; oral vs IV

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Evans SR, *Clin Infect Dis* 2015;61:800-6

DOOR/RADAR Analysis

- Distributions of DOORs compared between strategies
  - Non-parametric testing – Wilcoxon Rank Sum test
- Sample size based on superiority testing
  - Null hypothesis: no difference in DOOR between groups
  - Alternative: new strategy has higher DOOR (i.e., >50%)
    - Magnitude of superiority based on minimum clinical importance
- Sample sizes lower than comparable non-inferiority studies

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Evans SR, *Clin Infect Dis* 2015;61:800-6

Conclusions

- Antibiotic use is the primary driver of resistance
- Given antibiotic use trends, efforts to curtail antibiotic use should focus on the outpatient setting
- Great potential for impact of rapid diagnostics to differentiate bacterial from non-bacterial/non-infectious etiologies
- TRAP-LRTI study will use rapid diagnostic to identify target population in which antibiotics not needed
- Need for continued development of novel methods to assess the impact of antibiotic use strategies