Strengthening The Knowledge and Evidence-Based Data for Anti-Microbial Resistance

Cesar A. Arias MD PhD
@SuperBugDoc
Disclosures

• **Grant Recipient**: MeMed diagnostics, Merck and Entasis Pharmaceuticals
Objectives

• Strengthening knowledge and evidence-based data for AMR
  – Conceptual framework
  – Diagnosis
  – Surveillance
  – Clinical data
Costs of The “Silent” Pandemic of AMR


Country group: Low-income Lower middle-income Upper middle-income High-income World

World Bank Group, September 2016
Conceptual Framework

ANTIMICROBIALS

Susceptibility

R = Failure

S = Success

Outcome

(i) Host infectiousness

(ii) Host behaviour

Transmission potential

Adapted from Handel & Rohani, Philosophical Transactions of the Royal Society, 2016
Appropriate Use of Antibiotics Saves Lives

![Bar chart showing mortality rates for appropriate and inappropriate therapy in bloodstream infections and nosocomial pneumonia/VAP.]

- **Bloodstream Infections**
  - Ibrahim: 20%
  - Leibovici: 30%
  - Luna: 70%
  - Alvarez-Lerma: 50%
  - Rello: 40%

- **Nosocomial Pneumonia/VAP**
  - Ibrahim: 10%
  - Leibovici: 20%
  - Luna: 80%
  - Alvarez-Lerma: 30%
  - Rello: 60%

Diagnosis of Antimicrobial Resistance
Diagnostic approaches to identify resistance are grossly inaccurate.
“Susceptible” or “Resistant” does not often translate into therapeutic success or failure

Moise-Broder et al., Clin Infect Dis 2004;38:1700-5

Stevens, Clin Infect Dis 2006;42:S51
Genomics and the Conundrum of identifying resistance

Prediction of Susceptibility to First-Line Tuberculosis Drugs by DNA Sequencing

The CRyPTIC Consortium and the 100,000 Genomes Project
Strengthening The Knowledge and Evidence in AMR Diagnosis

• Breakpoint interpretation to be universal
• Moving from a phenotypic to genotypic interpretation and, likely, a mixed approach
• Free and widespread access to genomic information and tools for resistance interpretation
• “Real-time” tools to identify emerging patterns of resistance with genotypic and mechanistic basis
• Genomic diagnostic platform development for each AMR priority pathogen
Surveillance of Antimicrobial Resistance
Clone Dissemination: MRSA USA300 Lineage

• Sustained and real-time global data sharing of information that permits identification of emerging mechanisms of resistance in priority pathogens
• Deployment of targeted genomic tools with a coordinated system that allows real-time understanding of changes in epidemiology of AMR organisms
• Bug-specific typing systems that need to be facile and flexible to identify emerging genetic lineages carrying particular resistance determinants
• Strengthening bioinformatic capabilities for the developing world
Clinical Outcomes of AMR Infections
Measuring patient-centered outcomes in AMR infections is not trivial

• Studies typically measure hospital days, intensive care unit days, and antibiotic use (a surrogate for future antimicrobial resistance). This outcomes could be misleading

• Non-inferiority trial design with respect to clinical outcome (eg, cure) does not address the relevant question regarding whether one approach is better than another

• The null hypothesis is that the experimental strategy is inferior, viewed by some as a violation of the equipoise necessary for randomization.

• Trial results show that some patients may benefit while some may experience harm (adverse effects)
• Clinical trial platforms with a global reach that can continually enroll patients infected with priority pathogens
• Pragmatic clinical trials that can pivot once new agents become available in latest stages of development
• Prioritization of efficacy, safety, and quality of life
• Global clinical trial network that allows access to enrollment in both developed and developing world.
• Innovative trial designs are critically needed. DOOR and other modalities may need to be explored at large scale
Conclusions

• Strengthening knowledge and evidence-based data in AMR should focus in three major domains: diagnosis, surveillance and measurement of clinical outcomes

• Deployment of genomics tools holds promise to develop a truly global network of data and interpretation to help dealing with recalcitrant cases

• These strategies need to be coordinated with efforts in drug development and in the understanding of the mechanistic basis of resistance

• Innovations in clinical trial design derived form the COVID-19 pandemic can be used to tackle the AMR crisis.
“It is not the strongest of the species that survives, nor the most intelligent, but the one most responsive to change.”

~Charles Darwin, 1809