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

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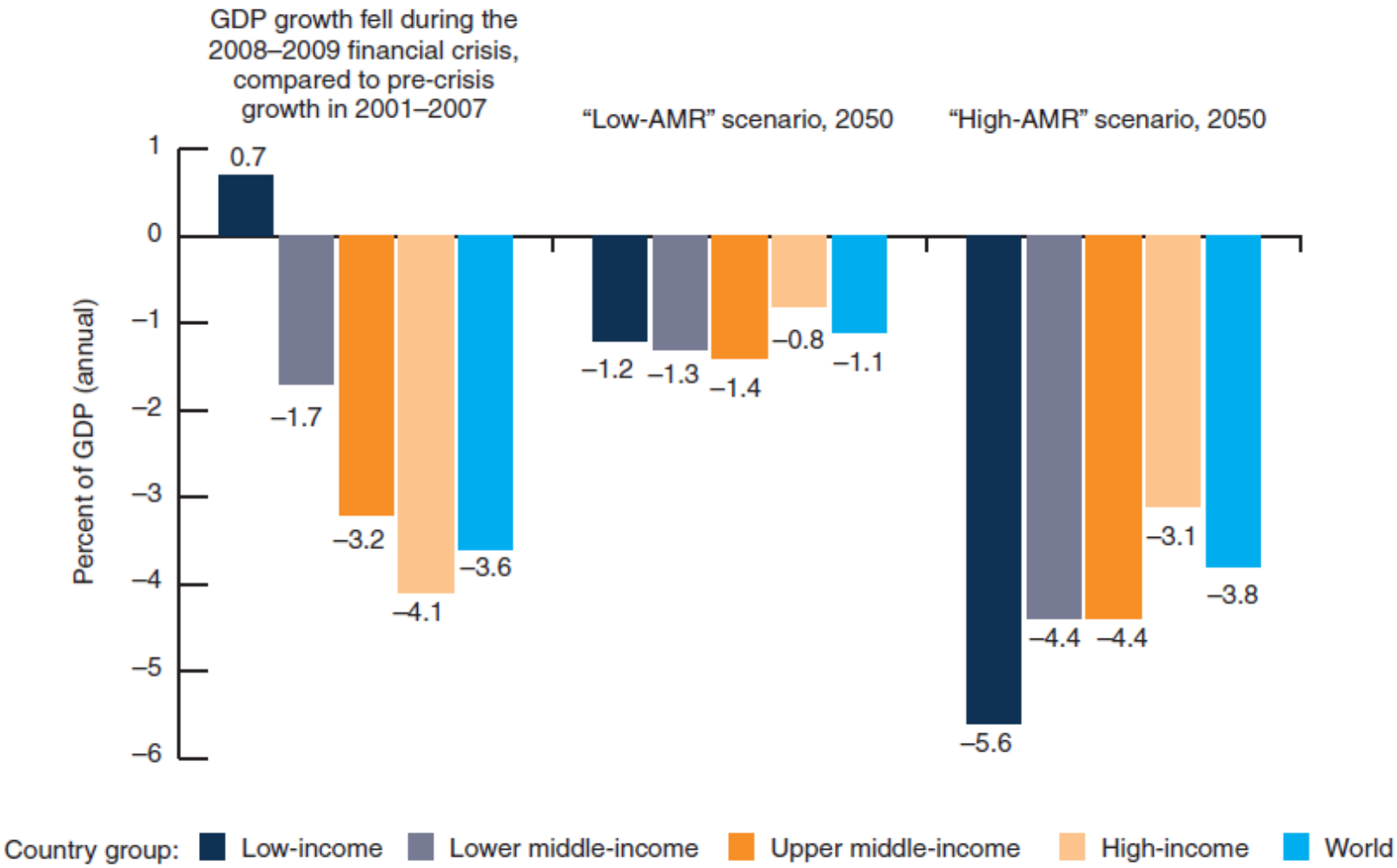
Disclosures

- **Grant Recipient**: MeMed diagnostics, Merck and Entasis Pharmaceuticals

Objectives

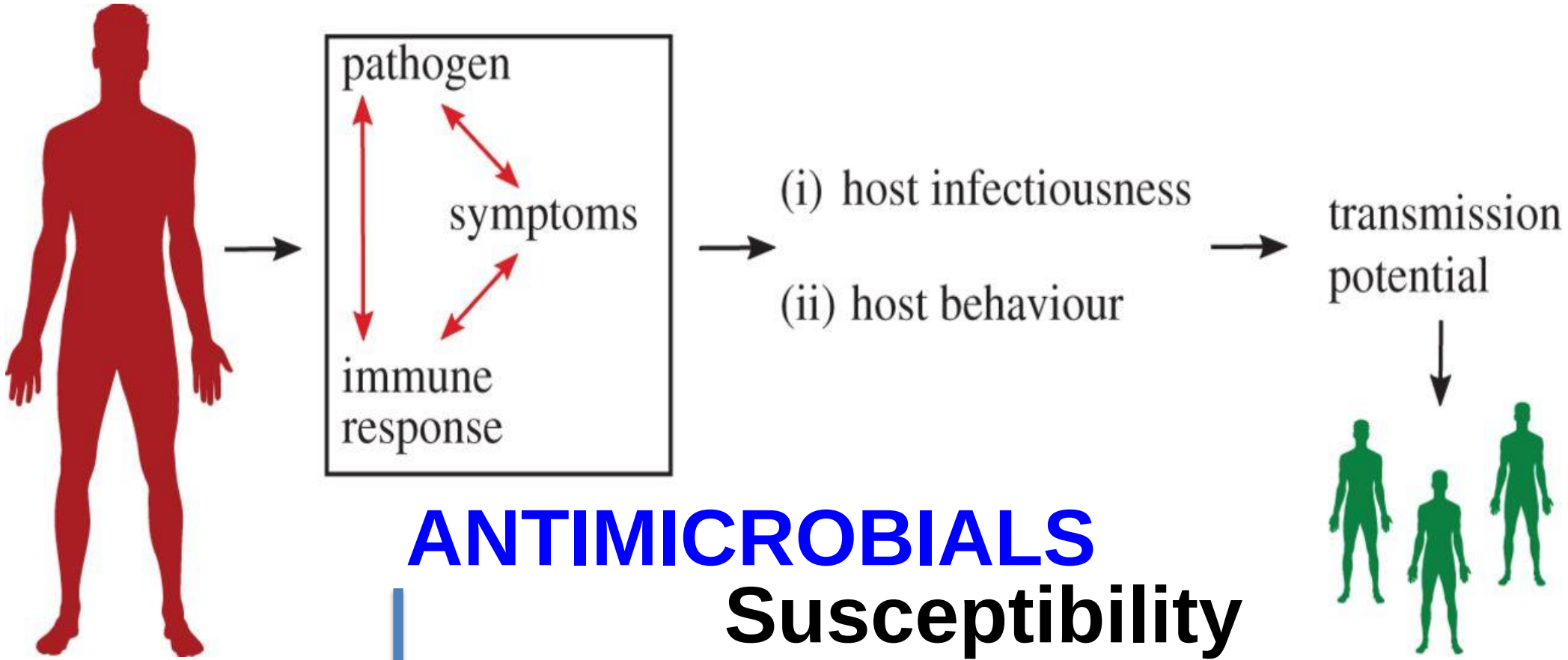
- Strengthening knowledge and evidence-based data for AMR
  - Conceptual framework
  - Diagnosis
  - Surveillance
  - Clinical data

Costs of The “Silent” Pandemic of AMR



World Bank Group, September 2016

Conceptual Framework



ANTIMICROBIALS

OUTCOME

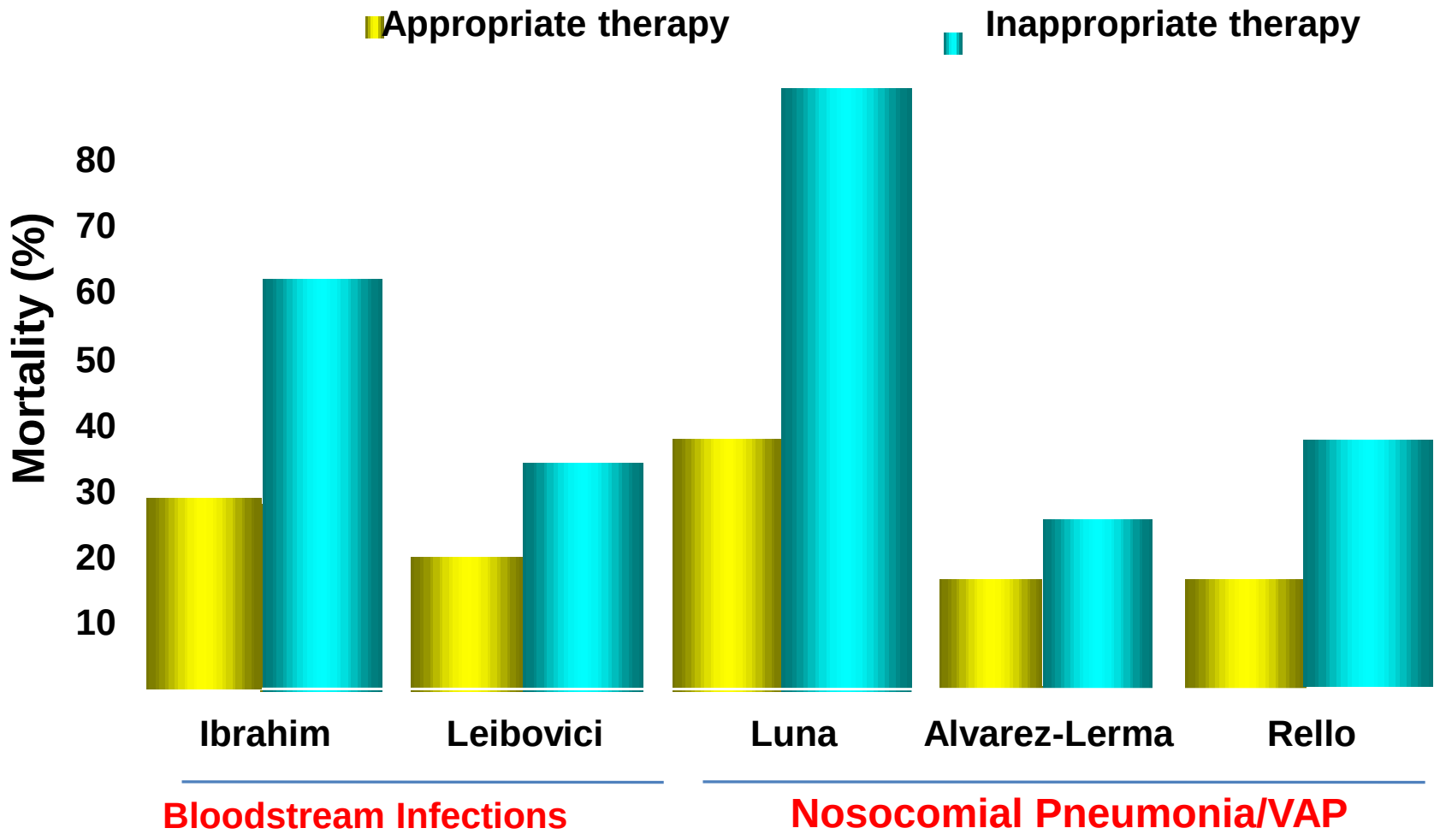
Susceptibility

R= Failure

S= Success

Adapted from Handel & Rohani, Philosophical Transactions of the Royal Society, 2016

Appropriate Use of Antibiotics Saves Lives



1. Ibrahim, et al. *Chest.*2000;118:146–155. 2. Leibovici, et al. *J Intern Med.*1998;244:379–386. 3. Luna, et al. *Chest.*1997;111:676–685. 4. Alvarez-Lerma, et al. *Intensive Care Med.*1996;22:387–394. 5. Rello, et al. *AJRCCM.*1997;156:196–200.

Diagnosis of Antimicrobial Resistance

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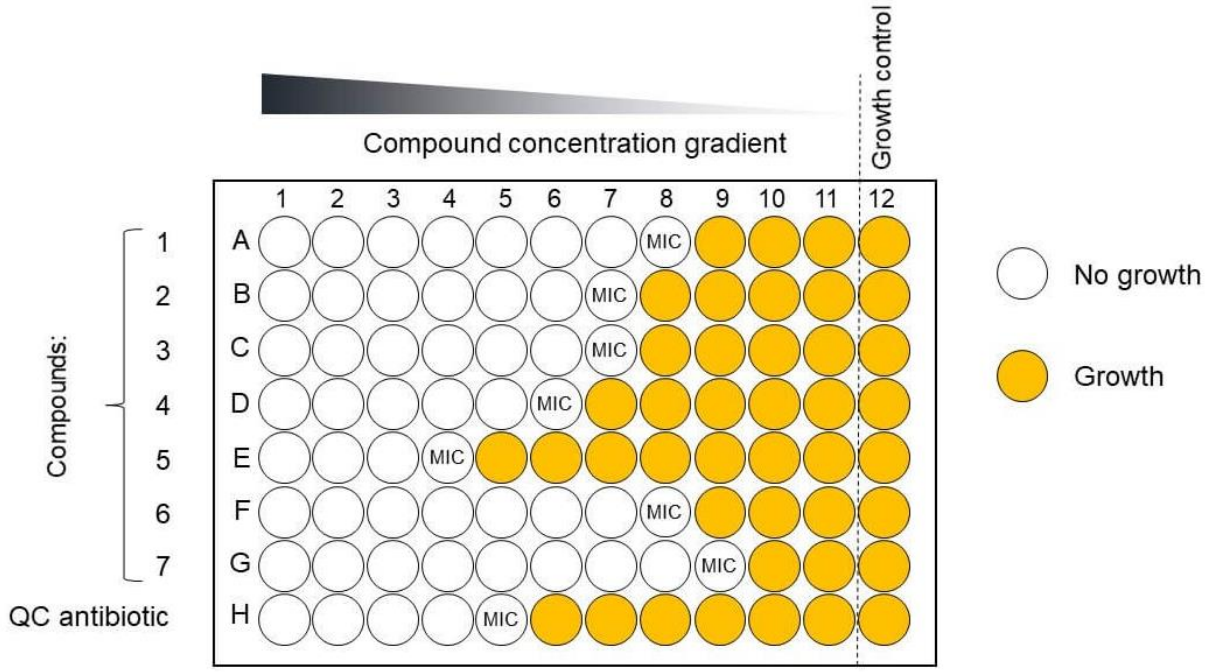
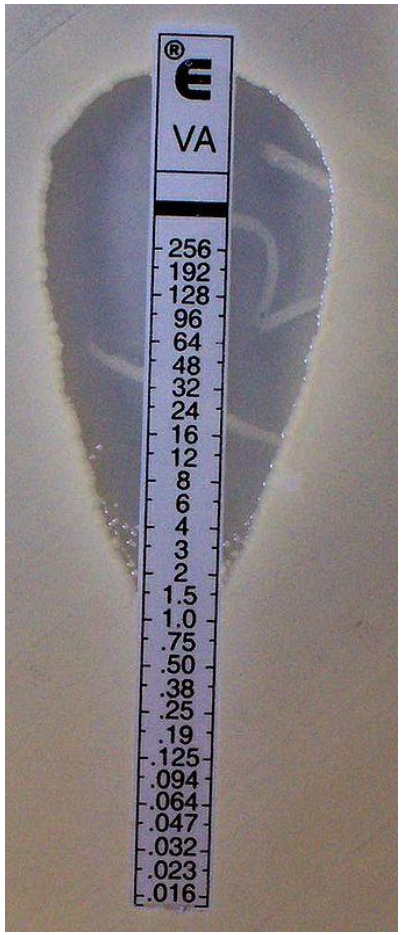
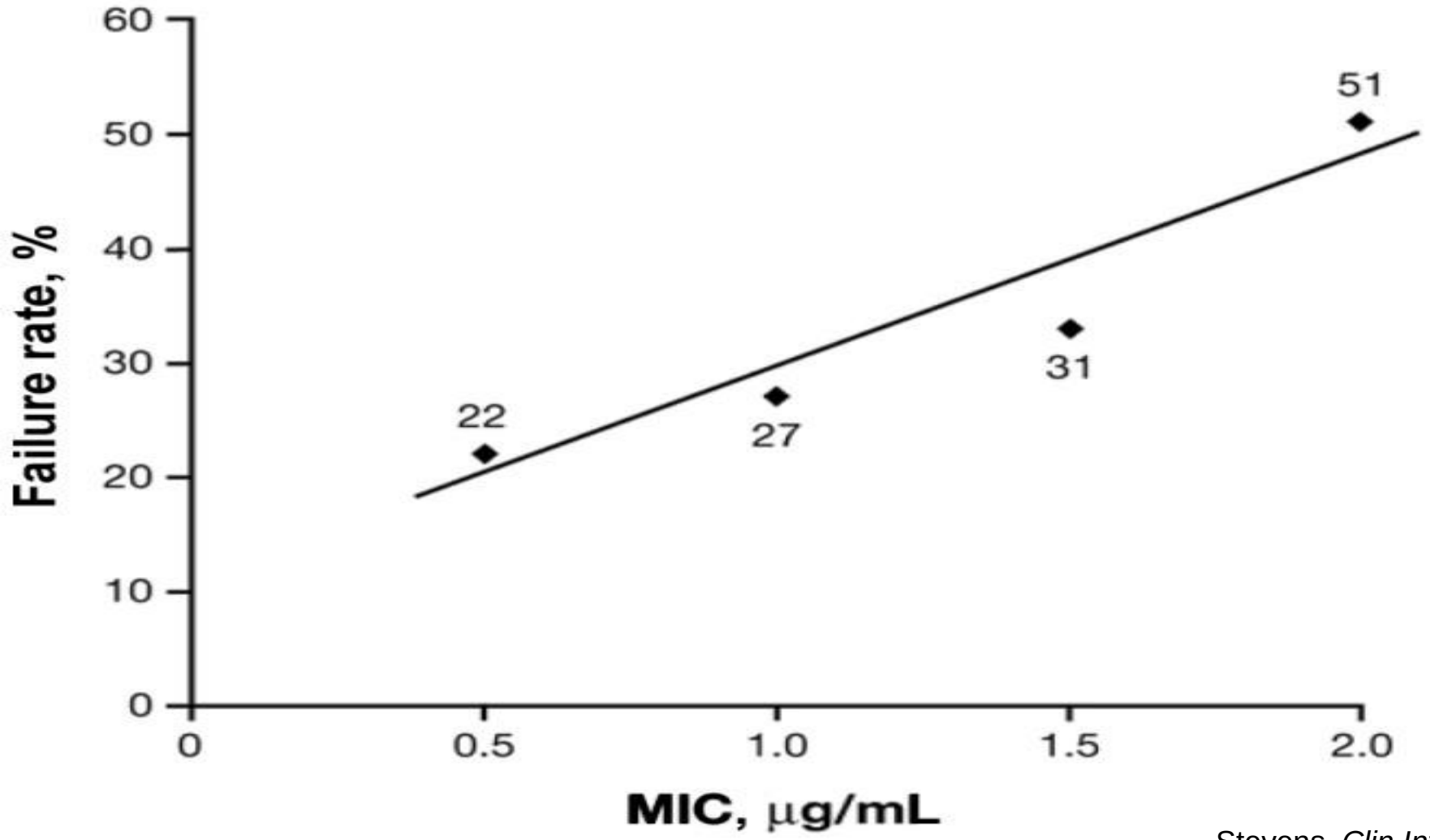
Diagnostic approaches to identify resistance are grossly inaccurate





“Susceptible” or “Resistant” does not often translate into therapeutic success or failure



Stevens, *Clin Infect Dis* 2006;42:S51
Moise-Broder et al., *Clin Infect Dis* 2004;38:1700-5

Genomics and the Conundrum of identifying resistance

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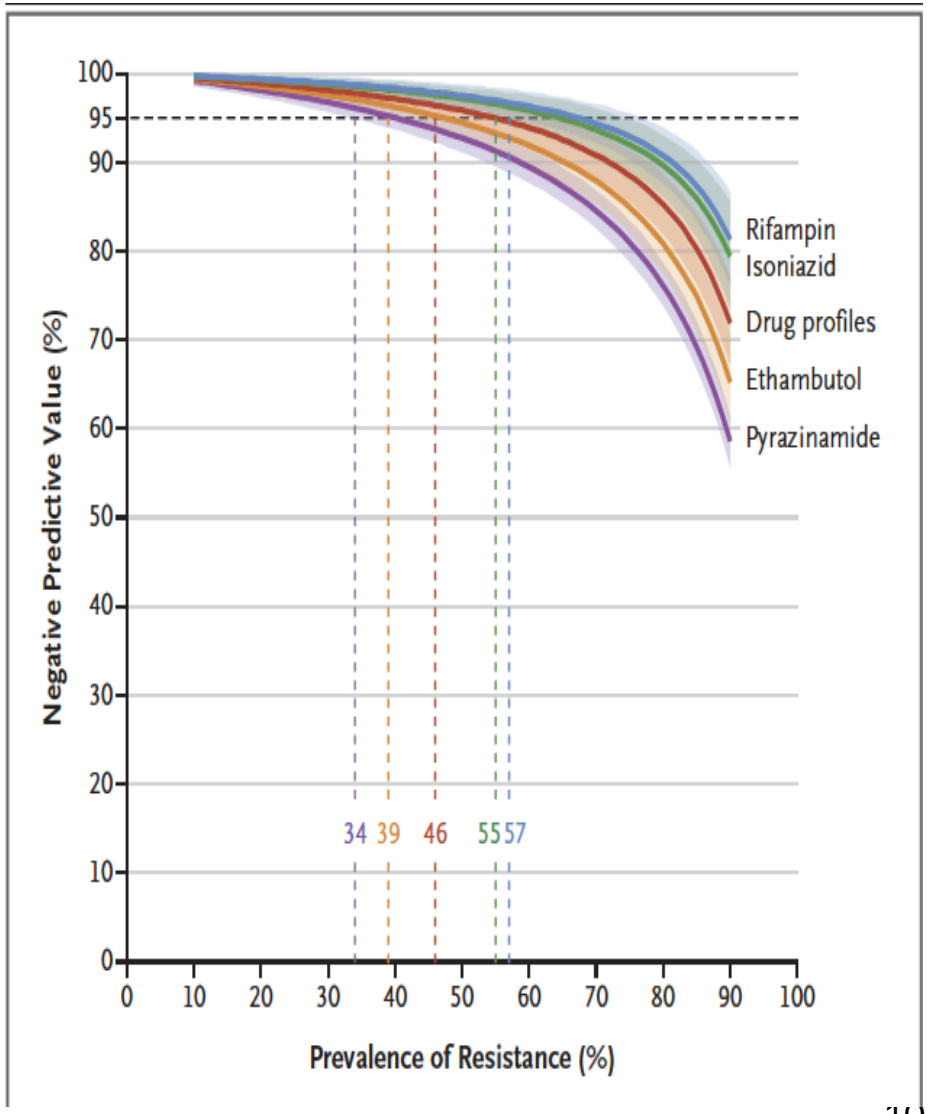
The NEW ENGLAND JOURNAL of MEDICINE

ESTABLISHED IN 1812 OCTOBER 11, 2018 VOL. 379 NO. 15

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

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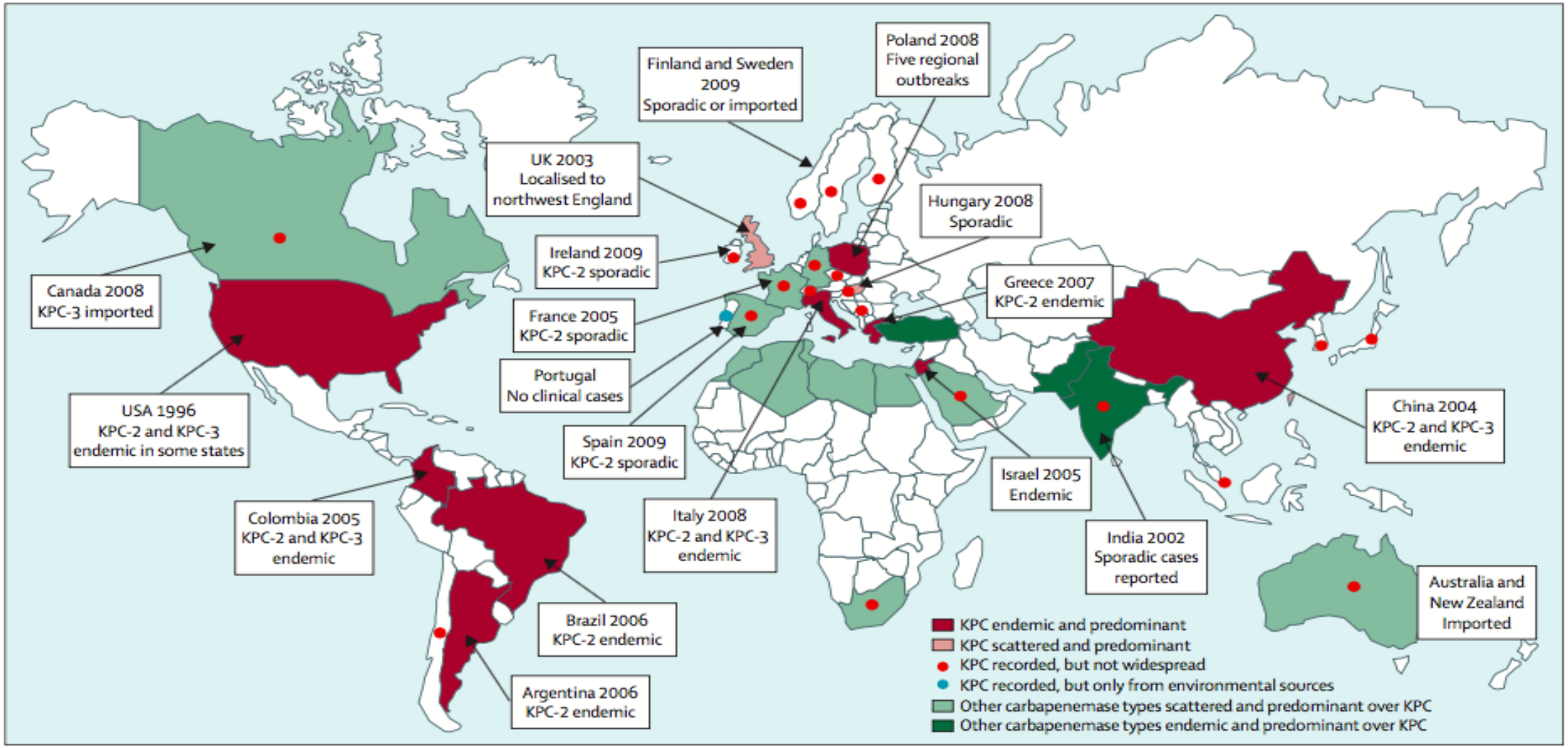
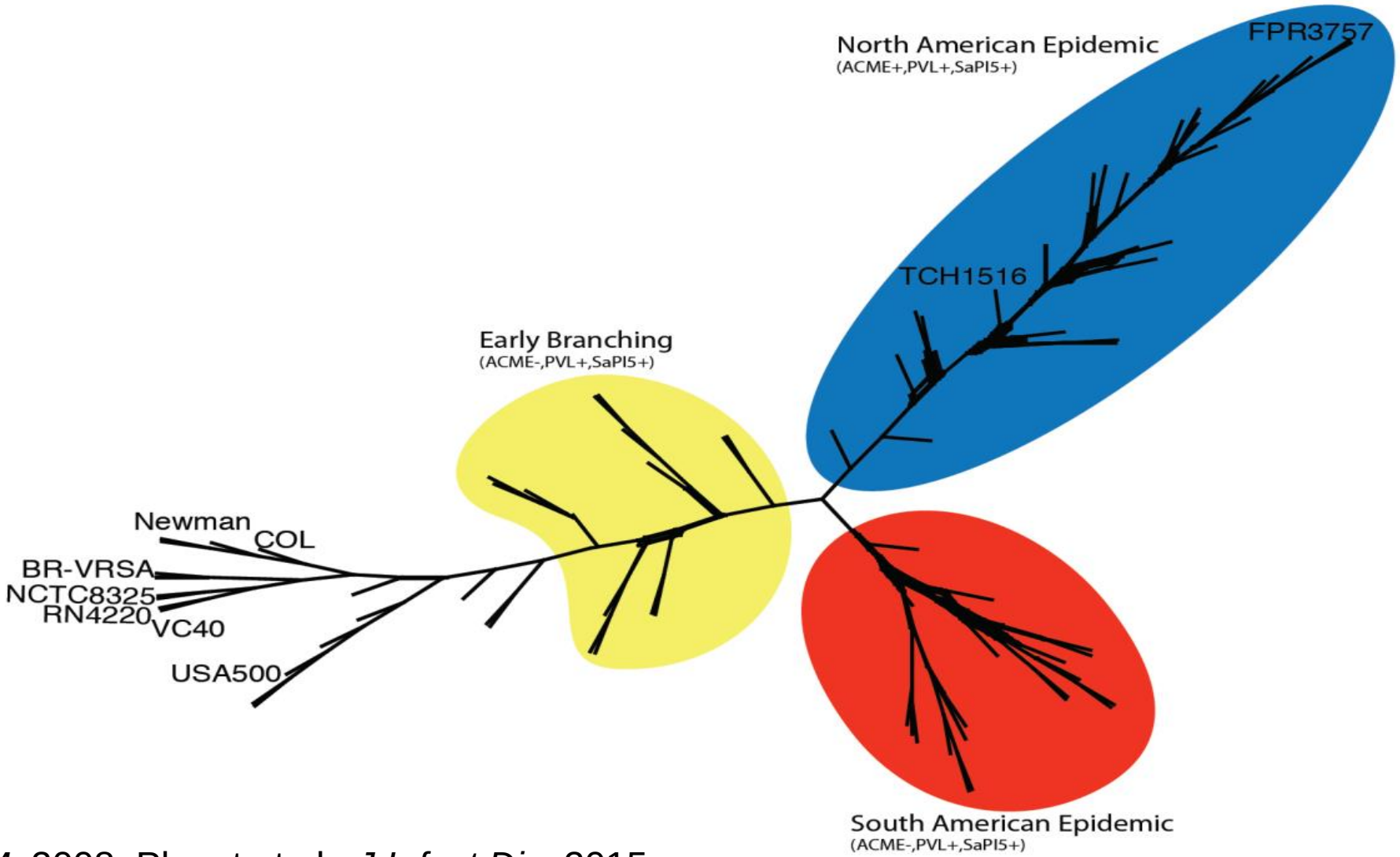
“Gene” Dissemination



Munoz-Price LS, et.al. 2013. Clinical epidemiology of the global expansion of Klebsiella pneumoniae carbapenemases. The Lancet Infectious Diseases **13:**785-796.

Clone Dissemination: MRSA USA300 Lineage



Arias et al, *NEJM*; 2008; Planet et al., *J Infect Dis*. 2015

Strengthening The Knowledge and Evidence-Base in AMR Surveillance

- 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

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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)

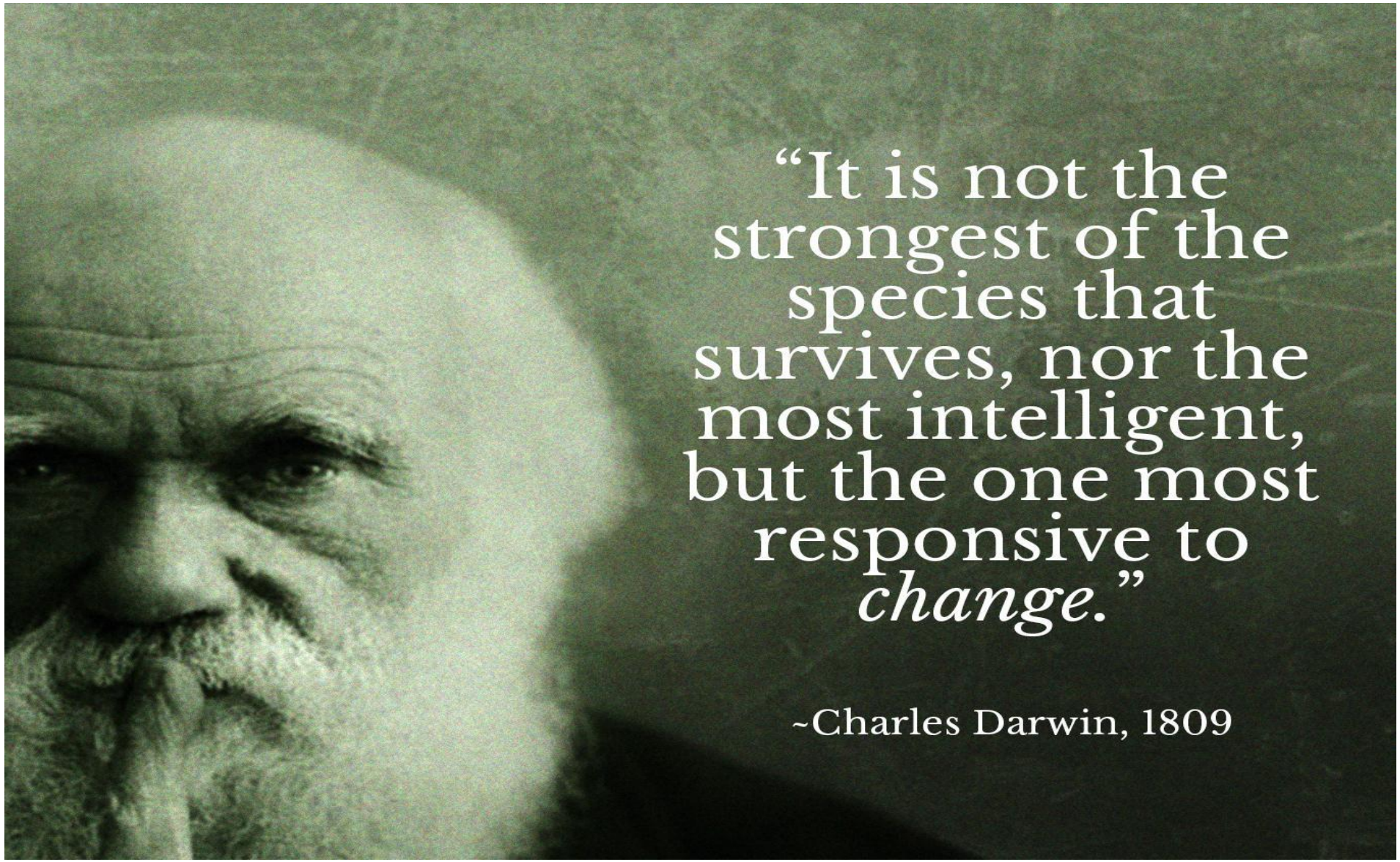
Evans et al. Clin Infect Dis, 2015

Strengthening The Knowledge and Evidence in Clinical Outcomes

- 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