Public Health Implications of Antimicrobial Resistance Surveillance

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From a Central Microbiology Laboratory Perspective:

How could the resources, capabilities and information gained through global *antimicrobial resistance surveillance* be used to expedite development and approval of new susceptibility testing diagnostic technologies?

- **Quicker dissemination to clinical labs for:**
  - **New drugs on current platforms**
  - **New platforms and technologies**

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About Antimicrobial Resistance Surveillance

- An ongoing requirement of any sponsor in late stages of antimicrobial drug development that continues for years beyond regulatory approval for human use
- Maintains ongoing up-to-date status of any new agents activity and relevant comparators to assist in early discovery of changing or developing trends, including underlying molecular mechanisms
- Often done in concert with Phase II and III clinical trials focused on the clinical safety and efficacy of new agents
- *Therefore, data and organisms are focused on those agents that are also in the "diagnostic pipeline" and in need of access to testing for clinical laboratories*
- Focuses on same drugs and clinically relevant organisms of concern to clinical microbiologists, infectious disease specialists and the medical environment overall
- Antimicrobial testing is performed centrally (Central Microbiology Laboratory) using standard methodologies and organisms are stored and available for further analysis
- The resources generated by Antimicrobial Resistance Surveillance could provide collateral support of industry needs for:
  - New drugs on current platforms
  - New platforms and technologies for susceptibility testing

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Overview of the Central Microbiology Laboratory

- Many of the robust *Antimicrobial Resistance Surveillance* initiatives are conducted by a Central Microbiology Laboratory
- Summary of Capabilities:
  - Ongoing production of current and robust data and collection of target organisms
  - Broad catchment of organisms from a wide variety of geographic and demographic backgrounds
  - Regular and ongoing interactions with clinical microbiology laboratories throughout the world
  - High throughput antimicrobial susceptibility testing capabilities following strict guidelines (CLSI; EUCAST)
  - Efficient and high volume molecular characterization and sequencing of strains of interest
  - Strong scientific and clinical expertise in general and on most drugs in development specifically
  - Strong data management and project management infrastructure
- Other Key Factors
  - Strong business and collegial working relationship already in place with most drug sponsors for their human clinical trials and surveillance needs
  - Strong business and collegial working relationship with several diagnostic manufacturers and the FDA that could be easily expanded

Data Production from Global Surveillance (IHMA)

2013 – 2016

- **> 290,000 target organisms collected and susceptibility tested**
- **Profiled against all key available antimicrobials and several products under development**
- **From all regions:**
  - **North America**
  - **Latin America**
  - **Europe**
  - **Asia Pacific**
  - **Middle East/Africa**
- **Of the strains collected > 36,000 had resistance mechanisms molecular characterized**
  - **All key beta-lactamases (ESBL, MBL, KPC, AmpC, etc.)**
  - **Porins**
  - **Efflux**
- **All strains catalogued according to species, demographics, resistance profiles, and molecular mechanisms and can be made available for further analysis**

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mcr Occurance Among *Enterobacteriaceae*

- 2014-2015, 24,987 isolates of *Enterobacteriaceae* were collected from 82 medical centers worldwide
- Of these 587 isolates were colistin-resistant and were screened for the presence of the plasmid-borne *mcr*-1 and *mcr*-2 genes

Results: *mcr* was detected in 21 isolates (3.6%). The remainder presumably have a chromosomal mechanism of resistance. Frequency of global *mcr* carriage is in accordance with previously published data (4.9%)[a]

Year	Country	Organism	mcr gene product
2014	Spain	Escherichia coli	MCR-1
2014	Malaysia	Escherichia coli	MCR-1
2014	Portugal	Enterobacter cloacae	MCR-1
2014	Italy	Escherichia coli	MCR-1
2014	Italy	Escherichia coli	MCR-1.2
2014	South Africa	Escherichia coli	MCR-1
2014	Germany	Escherichia coli	MCR-1
2014	Russia	Escherichia coli	MCR-1
2014	Taiwan	Escherichia coli	MCR-1
2014	Spain	Escherichia coli	MCR-1
2014	Hong Kong	Escherichia coli	MCR-1
2014	Malaysia	Escherichia coli	MCR-1
2015	Argentina	Escherichia coli	MCR-1.5
2015	Venezuela	Escherichia coli	MCR-1
2015	Spain	Escherichia coli	MCR-1
2015	Thailand	Escherichia coli	MCR-1
2015	Malaysia	Escherichia coli	MCR-1
2015	Malaysia	Escherichia coli	MCR-1
2015	Argentina	Escherichia coli	MCR-1
2015	Malaysia	Escherichia coli	MCR-1
2015	Colombia	Escherichia coli	MCR-1

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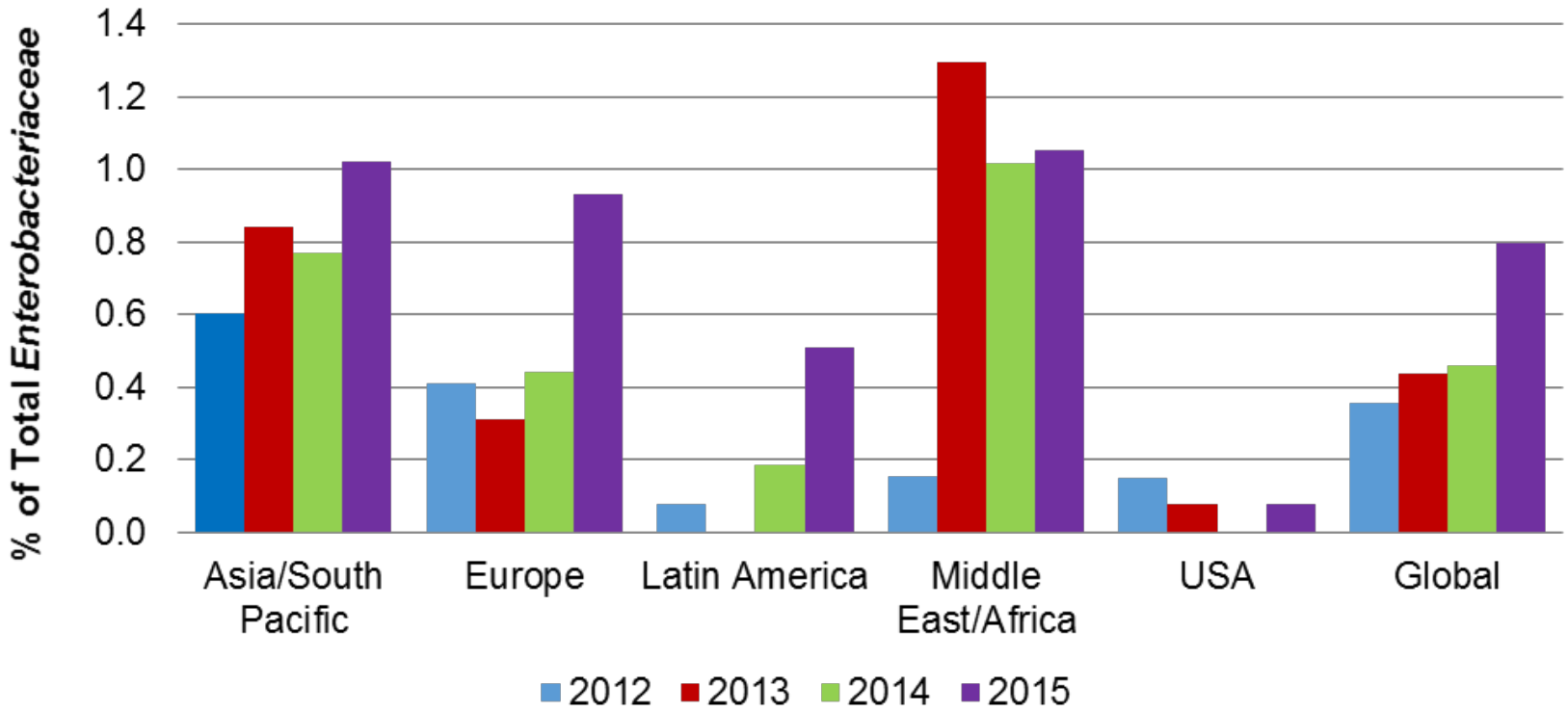
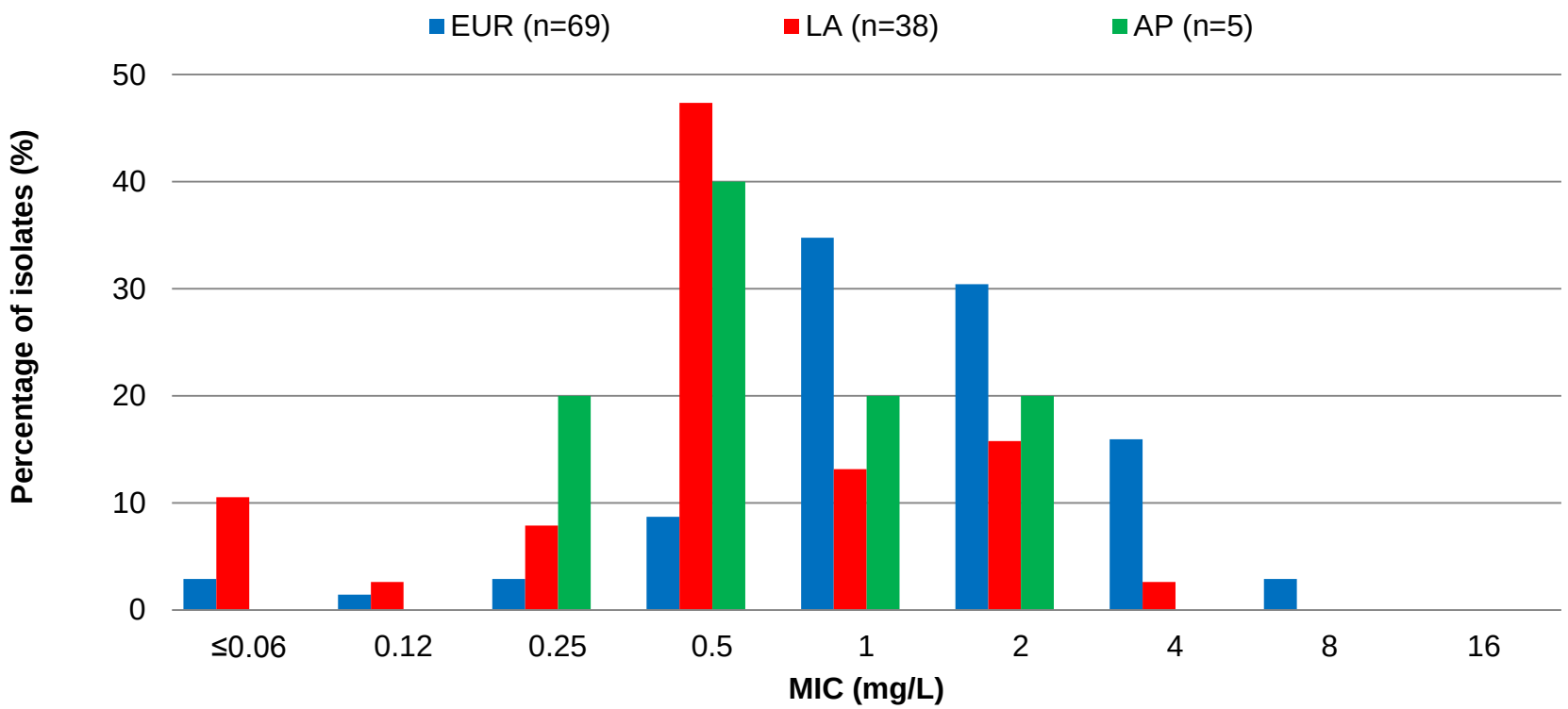
[a] Castanheira, et al. 2016. *Antimicrob Agents Chemother* 60:5623-5624.

Proportion of MBL-positive *Enterobacteriaceae* Collected in 2012-2015 According to Region



Ceftazidime-avibactam MIC distributions against KPC-positive CRE isolates collected from patients with RTI (n=112)*



*Kazmierczak et al., ECCMID 2017

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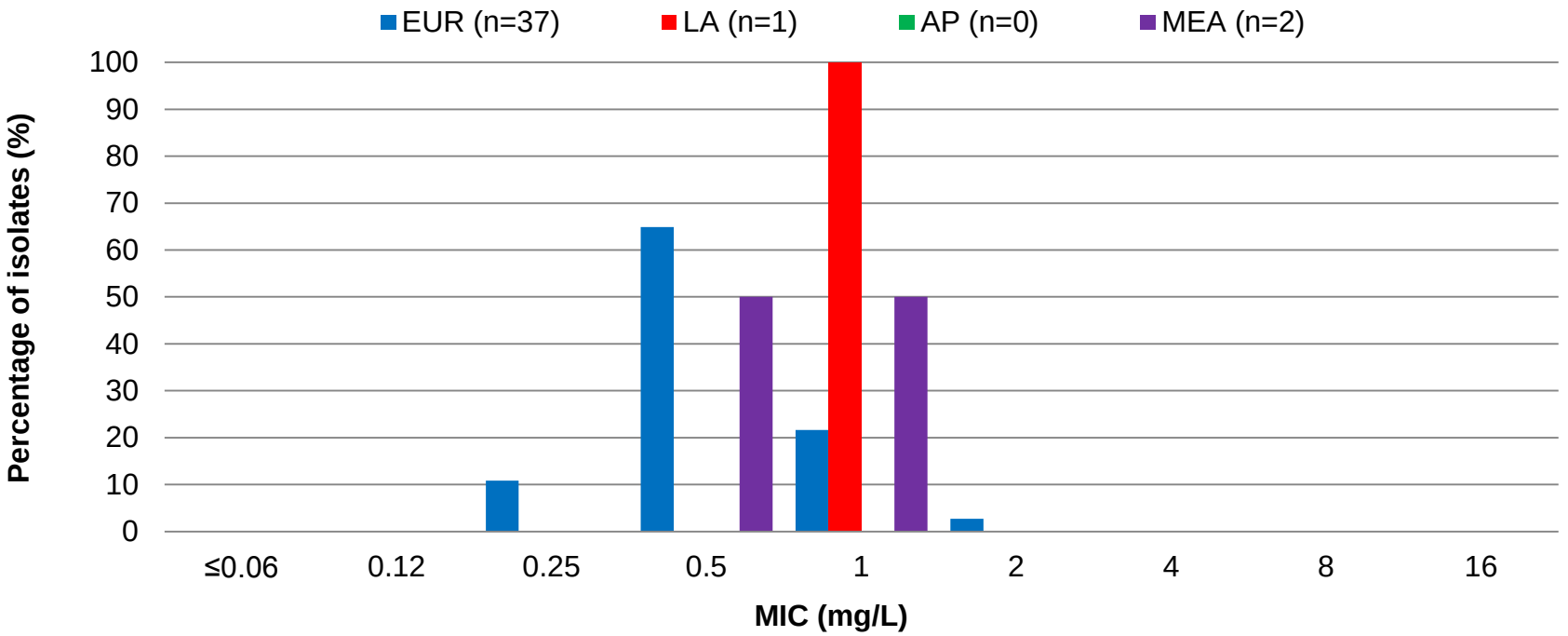
Ceftazidime-avibactam MIC distributions against OXA-48-like-positive CRE isolates collected from patients with RTI (n=40)*



*Kazmierczak et al., ECCMID 2017

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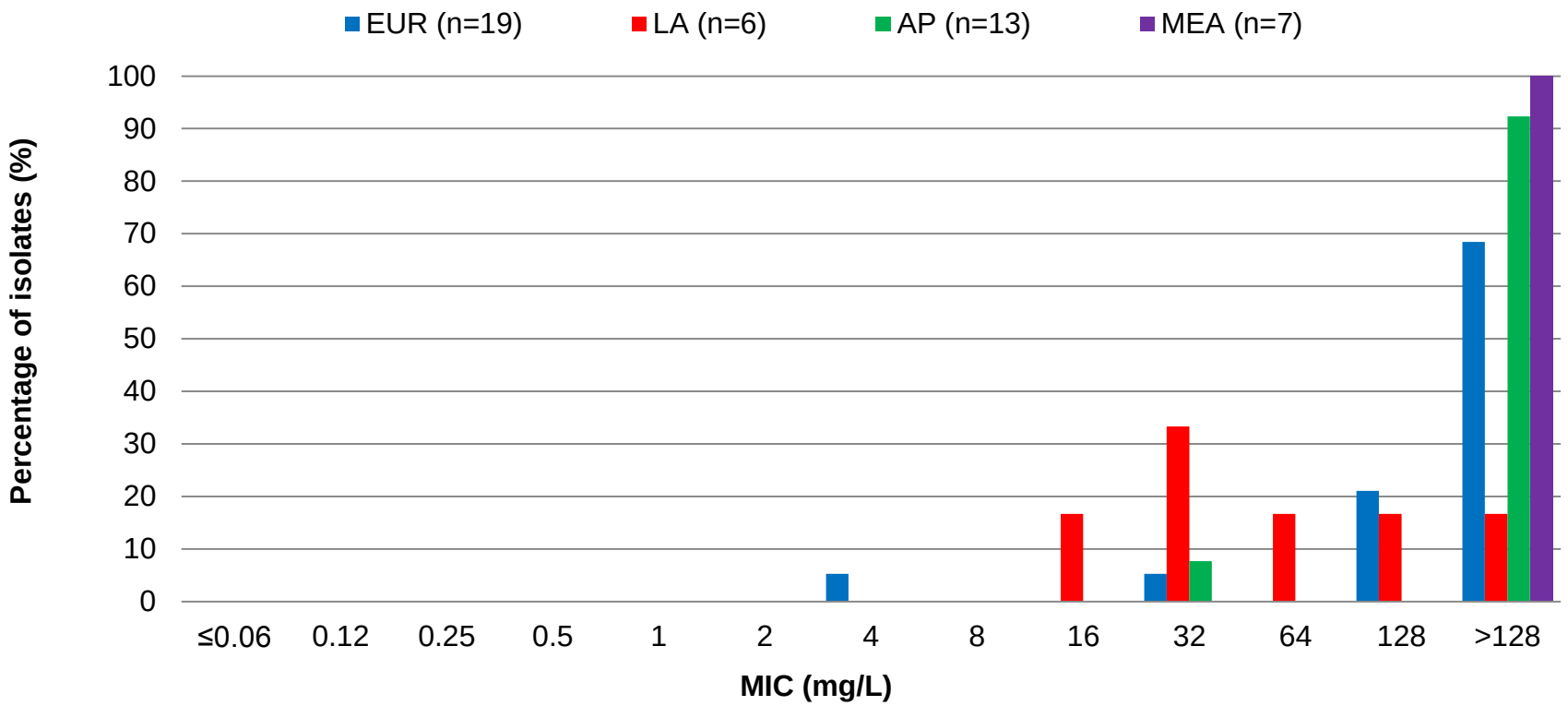
Ceftazidime-avibactam MIC distributions against MBL-positive CRE isolates collected from patients with RTI (n=45)*



*Kazmierczak et al., ECCMID 2017

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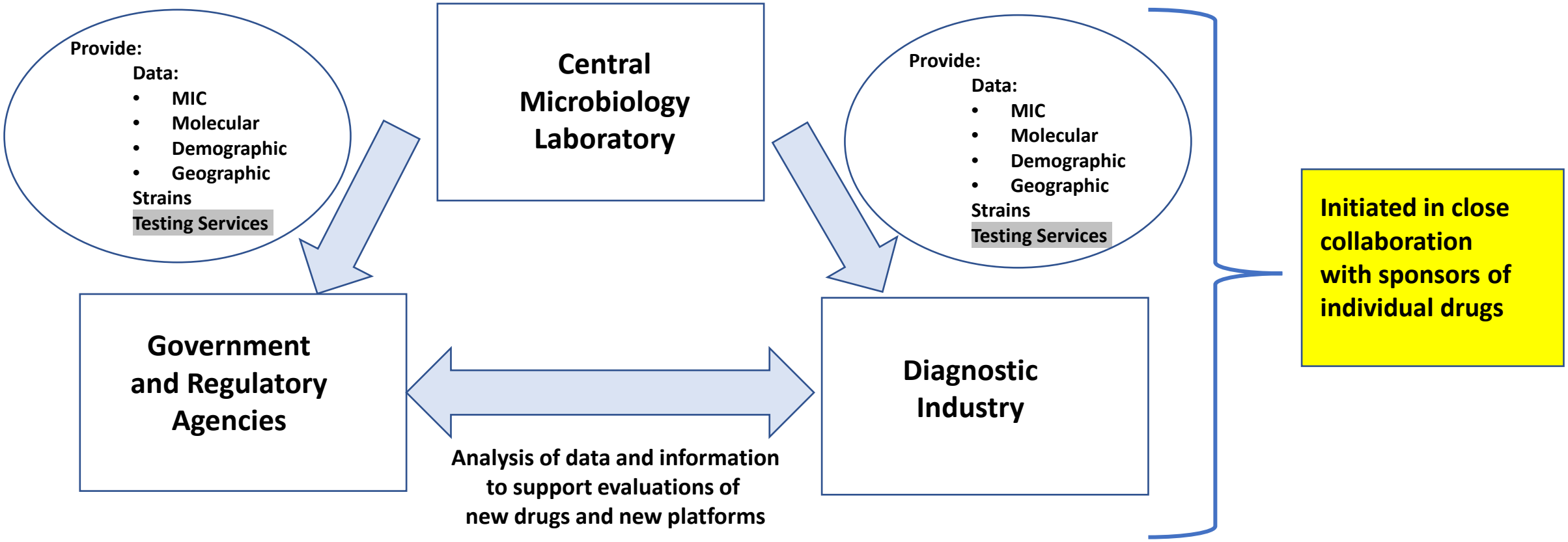
Potential Collaborative Structure to Expedite Development and Deployment of AST Capabilities for New Drugs and Platforms



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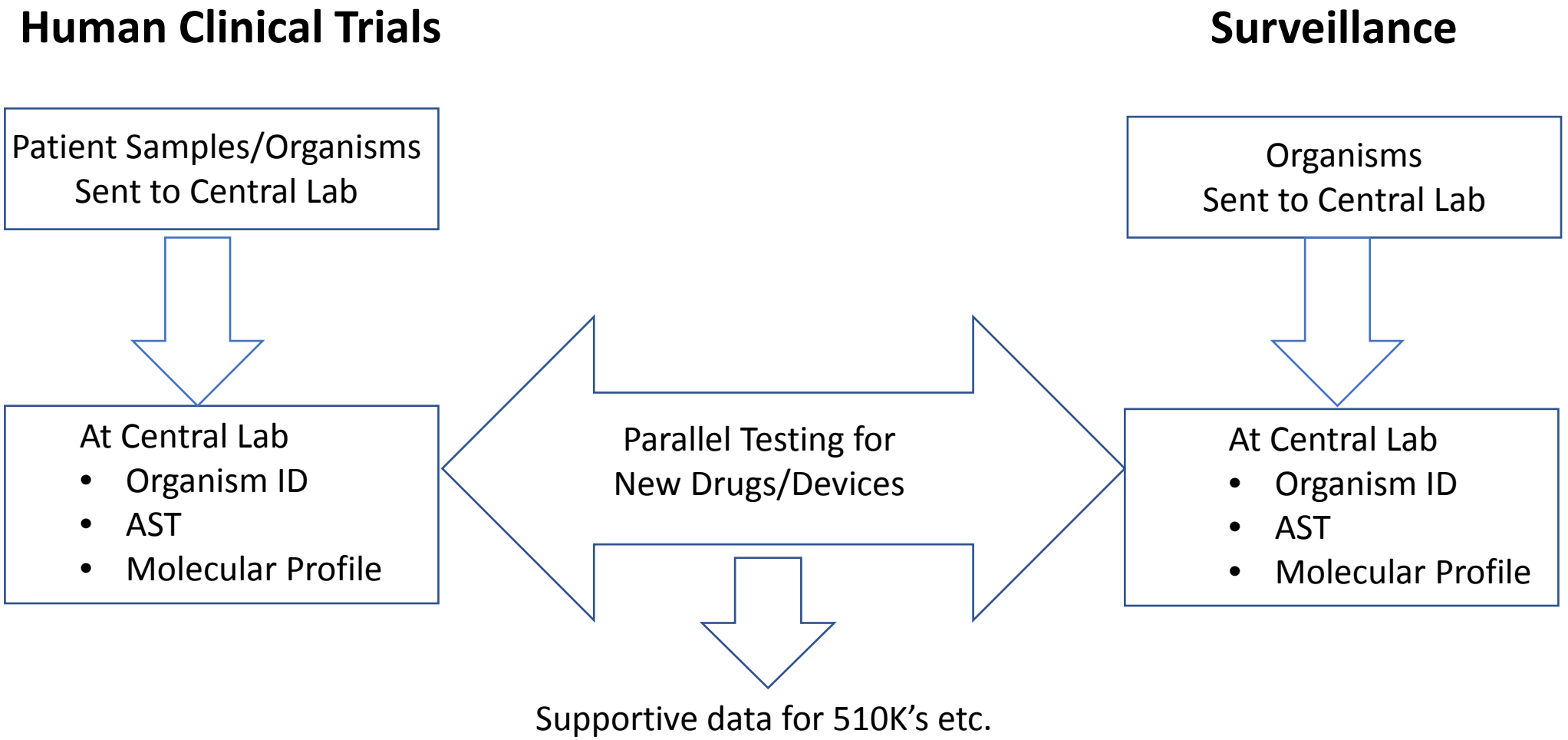
Potential Central Microbiology Testing Services to Support New Drugs and Platforms



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Summary

- Application of Central Microbiology Laboratory resources could be leveraged to expedite deployment of critical susceptibility capabilities to clinical laboratories
- Clinical laboratories are the front line for detecting and monitoring resistance; with more timely capabilities of testing either new drugs on current platforms or all drugs on new platforms the ability to track emerging and changing resistance landscapes would be greatly enhanced.
- A working relationships already exist between the Central Microbiology Laboratory and the FDA, Drug Sponsors, Diagnostic Manufacturer's and Clinical Laboratories
- We are well positioned to take next steps so that these relationships can be optimally leveraged to most effectively ensure that critical testing capabilities reach our clinical laboratories in a timely and reliable fashion