Building the Laboratory and Antimicrobial Stewardship Relationship to Improve Patient Outcomes

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Objectives

- Define antimicrobial stewardship
- List laboratory strategies that help promote appropriate antimicrobial utilization
- Identify examples of laboratory and antimicrobial stewardship collaboration that improve patient outcomes

Disclosure

- The author has no conflicts of interest relevant to this presentation

Movement Away from Fee-for-Service Healthcare Models

- **Increased focus on quality performance measures and patient outcomes**
  - Linked to hospital reimbursement
- **Tracking and public reporting of hospital data**
  - National Quality Forum (NQF)
  - Medicare and Medicaid Services (CMS)
  - Agency for Healthcare Research and Quality (AHRQ)
  - The Joint Commission (TJC)
  - The Leapfrog Group

Nagel. Clinical Infectious Diseases 59 (suppl_3), S146-S153

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Infectious Disease-Related Performance Measures

- **85 quality performance measures or clinical outcomes measures are publicly reported**
  - Examples:
    - Outcomes and readmissions for pneumonia
    - Outcomes for bacteremia in dialysis patients
    - Health-care associated UTI, bacteremia, CDI
- **Expect an increased emphasis on quality of care and patient outcomes in the future**
- **Increased focus on mitigating antimicrobial resistance**

Nagel. Clinical Infectious Diseases 59 (suppl_3), S146-S153

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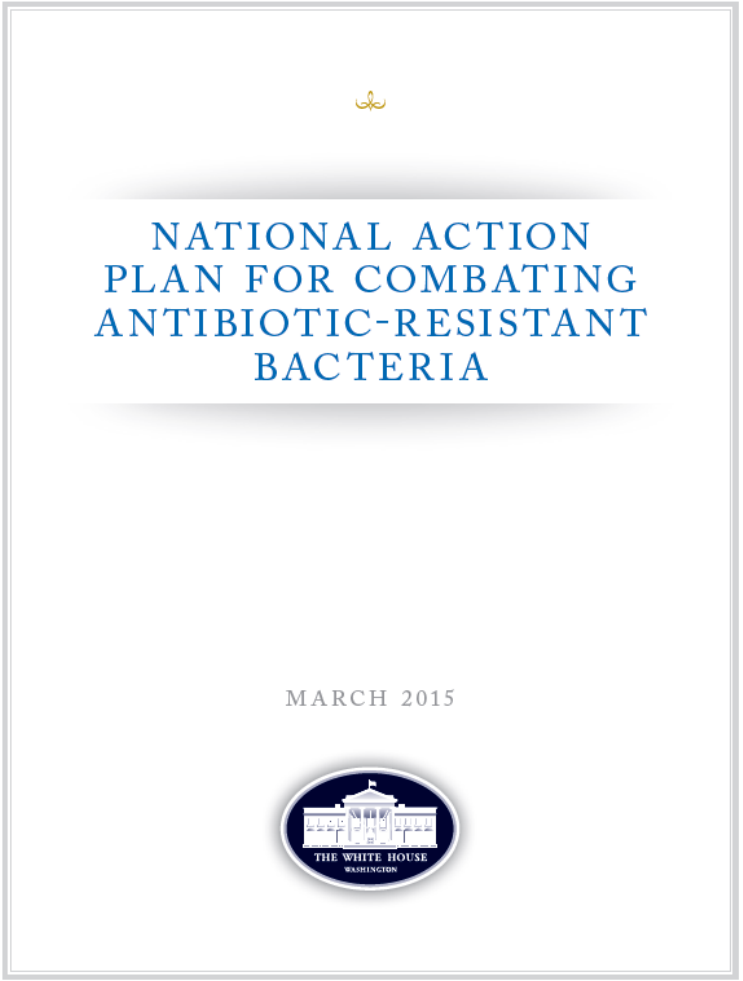
Brief History of Stewardship: Regulatory and Accreditation

- **Presidential Advisory Council on Combating Antibiotic-Resistant Bacteria (PACCARB)**
  - Included representatives from various organizations
  - Built a National Action Plan for Combating Antibiotic-Resistant Bacteria
  - Developed multifaceted approach with 3-, 5- and 10- year goals, which includes promoting of antibiotic stewardship



https://www.cdc.gov/drugresistance/pdf/national_action_plan_for_combating_antibotic-resistant_bacteria.pdf

Antimicrobial Stewardship: Regulatory and Accreditation

- **Antimicrobial Stewardship programs are now required for accreditation of acute care hospitals, long term care facilities and ambulatory care clinics**
  - Center for Disease Control and Prevention (CDC) develop “core elements”
    - Microbiology collaboration recommended in 4 of 7 core elements for acute care hospitals
- **Required by Center for Medicare and Medicare Services, as condition for payment for hospitalized patients**

https://www.cdc.gov/antibiotic-use/healthcare/implementation/core-elements.html

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Antimicrobial Stewardship Program Goals

- Promote appropriate antimicrobial use
- Optimize patient outcomes and reduce adverse events related to antimicrobials and treatment of infections
- Reduce or attenuate advancing antimicrobial resistance
- Provide cost-effective care

Barlam TF et al. Clin Infect Dis. 2016; 62:e51-77.

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Antimicrobial Stewardship Daily Patient-Care Activities

Drug-Based Stewardship

- Prior approval
- Criteria restricted

Disease-Based Stewardship

- Pneumonia
- S. aureus bacteremia
- Diabetic Foot infection
- *C. difficile* colitis

Micro-Based Stewardship

- Culture Review
- Multi-drug resistant organisms
- Real-time alerts
- De-escalation alerts

Implement Tools to Improve Appropriate Antimicrobials & Improve Quality Metrics

- Implement methods to improve management of infectious diseases and antimicrobials
- Improve publicly reported quality performance measures and outcomes measures
- Provide input for various hospital committees

Barlam TF et al. Clin Infect Dis. 2016; 62:e51-77.

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Strategies to Guide Antimicrobial Prescribing with Reporting of Antimicrobial Susceptibility Results

Types of Susceptibility Reporting

Surrogate Reporting

- The practice of testing the susceptibility of one antibiotic to infer susceptibility of another antibiotic

Selective Reporting

- The practice of reporting susceptibility results for a limited number of antibiotics instead of all tested antibiotics

Cascade Reporting

- A type of selective reporting in which susceptibility results of secondary antibiotics are only reported if an organism is resistant to the primary antibiotic within that particular class

Clin Infect Dis. 2016 May 15;62(10):e51-77.

Examples of Susceptibility Reporting

Surrogate Testing

- Ex) Tetracycline is tested for susceptibility, yet doxycycline susceptibility is reported

Selective Reporting

- Ex) Broad-spectrum agents such as daptomycin and ceftaroline may be tested for susceptibility, but not reported unless requested

Cascade Reporting

- Ex) If an organism is susceptible to cefazolin, ceftriaxone would be hidden. If the organism was cefazolin resistant, ceftriaxone would be revealed

Clin Infect Dis. 2016 May 15;62(10):e51-77.

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Selective Susceptibility Reporting: Impact on Ciprofloxacin Utilization and Susceptibility

Implementation of selective reporting policy for Enterobacteriaceae

Suppression of ciprofloxacin susceptibility results unless resistance to narrow spectrum agents

Ciprofloxacin utilization measured (defined daily doses [DDD] per 1,000 patient days)

J Clin Microbiol. 2016 Sep;54 (9):2343-7.

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Results: Ciprofloxacin and Amoxicillin-Clavulanate Utilization

	Pre-intervention (DDD per 1000 patient days)	Post-intervention (DDD per 1000 patient days)
Ciprofloxacin utilization	87 [95% CI, 83.7 – 91.2]	39 [95% CI, 35.0 – 44.0]
Amoxicillin-clavulanate utilization	3.1 [95% CI, 2.4 – 3.8]	29.8 [95% CI, 2.4 – 3.8]

DDD: defined daily dose

Reduction in ciprofloxacin usage maintained at 1, 3, 6, 12, and 24 months post-intervention ($P < 0.001$)

J Clin Microbiol. 2016 Sep;54 (9):2343-7.

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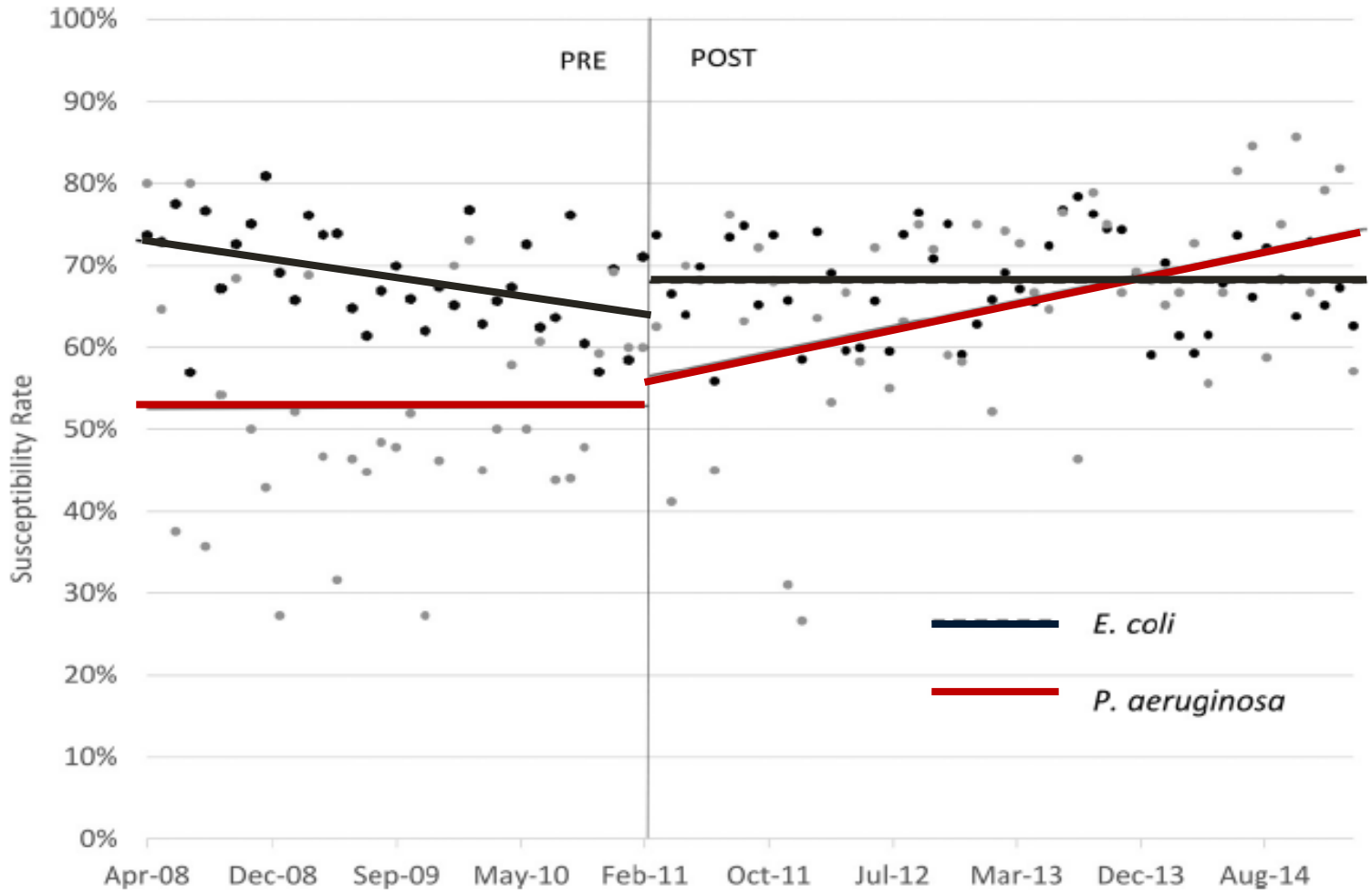
Results: Susceptibility Trends

E. coli and *P. aeruginosa* susceptibility to ciprofloxacin



J Clin Microbiol. 2016 Sep;54 (9):2343 7.

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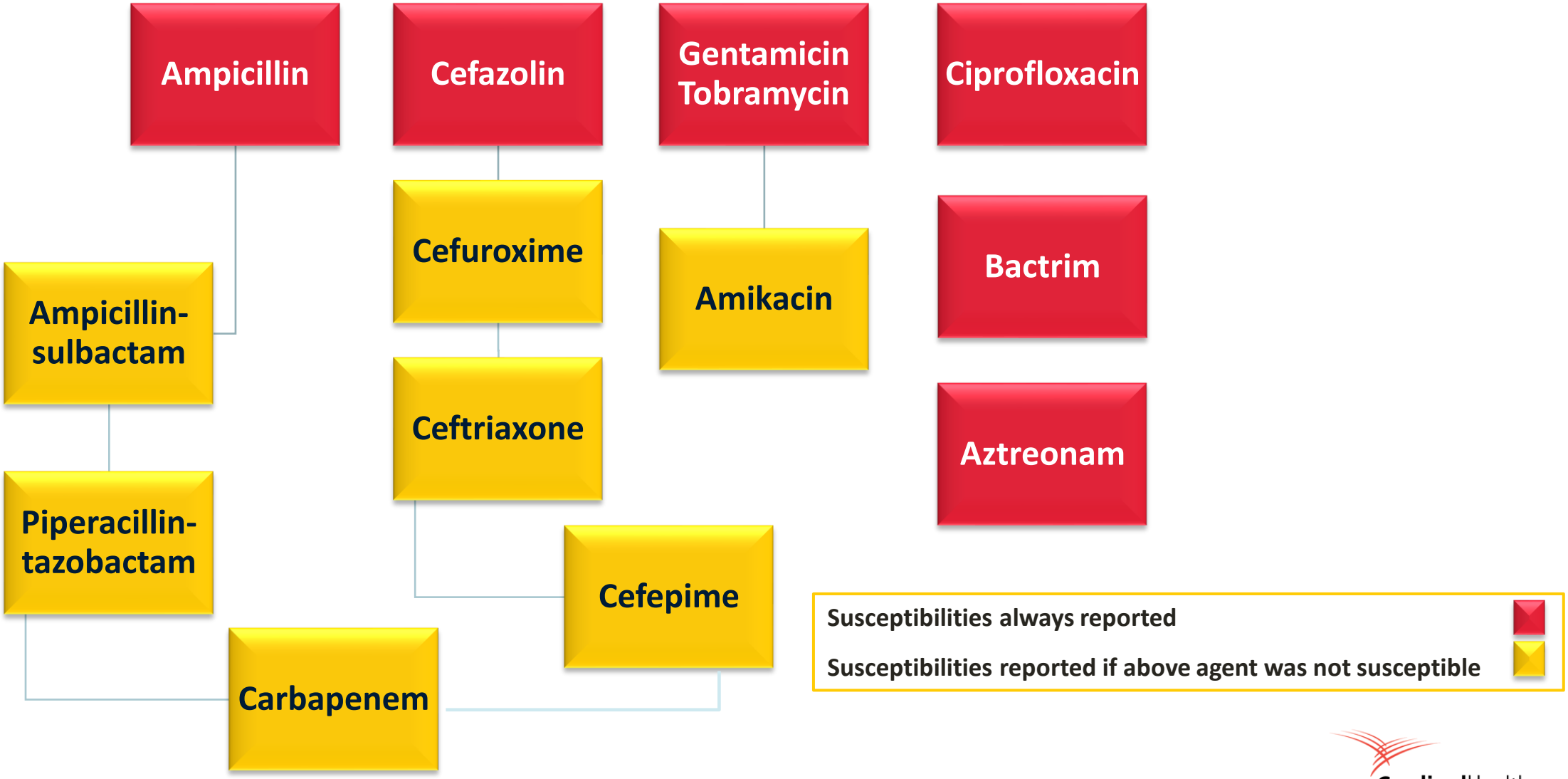
Impact of Cascade Reporting on Antibiotic de-escalation in Gram-negative bacteremia

- Retrospective pre/post study to assess the impact of cascade
- *Inclusion*: Adult patients with a blood culture positive for a Gram-negative organism susceptible to cefazolin who were empirically treated with broad-spectrum beta-lactam (BSBL) antibiotics

Eur J Clin Microbiol Infect Dis (2016) 35: 1151.

Methods: Cascade Reporting Algorithm



Eur J Clin Microbiol Infect Dis (2016) 35: 1151.

Study Endpoints

Primary Endpoint

- Percentage of patients whose BSBL agent was de-escalated to agents listed on the post-CR antibiotic susceptibility report within 48 hours

Secondary Endpoints

- Hospital length of stay
- All cause in-hospital mortality
- 30-day readmission rate
- *C. difficile* infection within 30 days
- Rate of re-initiation of an IV BSBL agent within 7 days

Eur J Clin Microbiol Infect Dis (2016) 35: 1151.

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Results: Impact on De-escalation

Outcome	Pre-CR % (n=31)	Post-CR % (n=42)	*p*-value
Therapy de-escalation	48	71	0.043
Definitive BSBL use	39	26	0.258
Definitive pip/tazo use	16	0	0.015
Definitive anti-pseudomonal β-lactam use	26	0	0.001

No differences seen in length of stay, readmission rates, or mortality

Eur J Clin Microbiol Infect Dis (2016) 35: 1151.

Caution with Selective Reporting of Susceptibilities

- Example:
  - Linezolid/daptomycin are hidden if vancomycin is susceptible for *Enterococcus* isolates

- Concerns/limitations:
  - Patient allergies
  - Location and severity of infection
  - Assumption that hidden broad-spectrum agents are susceptible
  - Potential delay in therapy

Component Results

Component

BLOOD CULTURE (Abnormal)

Enterococcus faecium

Comment:

```
No vanA or vanB resistance markers detected by DNA hybridization.
For empiric antibiotic recommendations, please copy
and paste the following link into a new browser window:
http://tinyurl.com/zesxsyc
This isolate was screened for high-level aminoglycoside
resistance. If SYN, ** SYNERGY ** will be achieved
with a cell wall active agent and this aminoglycoside.
If NOSYN, ** NO SYNERGY ** will be achieved with a
cell wall active agent and this aminoglysocide.
Treatment of this enterococcus with ampicillin alone may
not be adequate.  Please contact Infectious Disease
Service.
```

Susceptibility

	Enterococcus faecium MIC	
Ampicillin	>16 mcg/mL	R
Doxycycline	16 mcg/mL	R
Gentamicin High Level Resistance	SYN mcg/mL	S
Penicillin G	>16 mcg/mL	R
Streptomycin High Level Resistance	SYN mcg/mL	S
Vancomycin	1 mcg/mL	S

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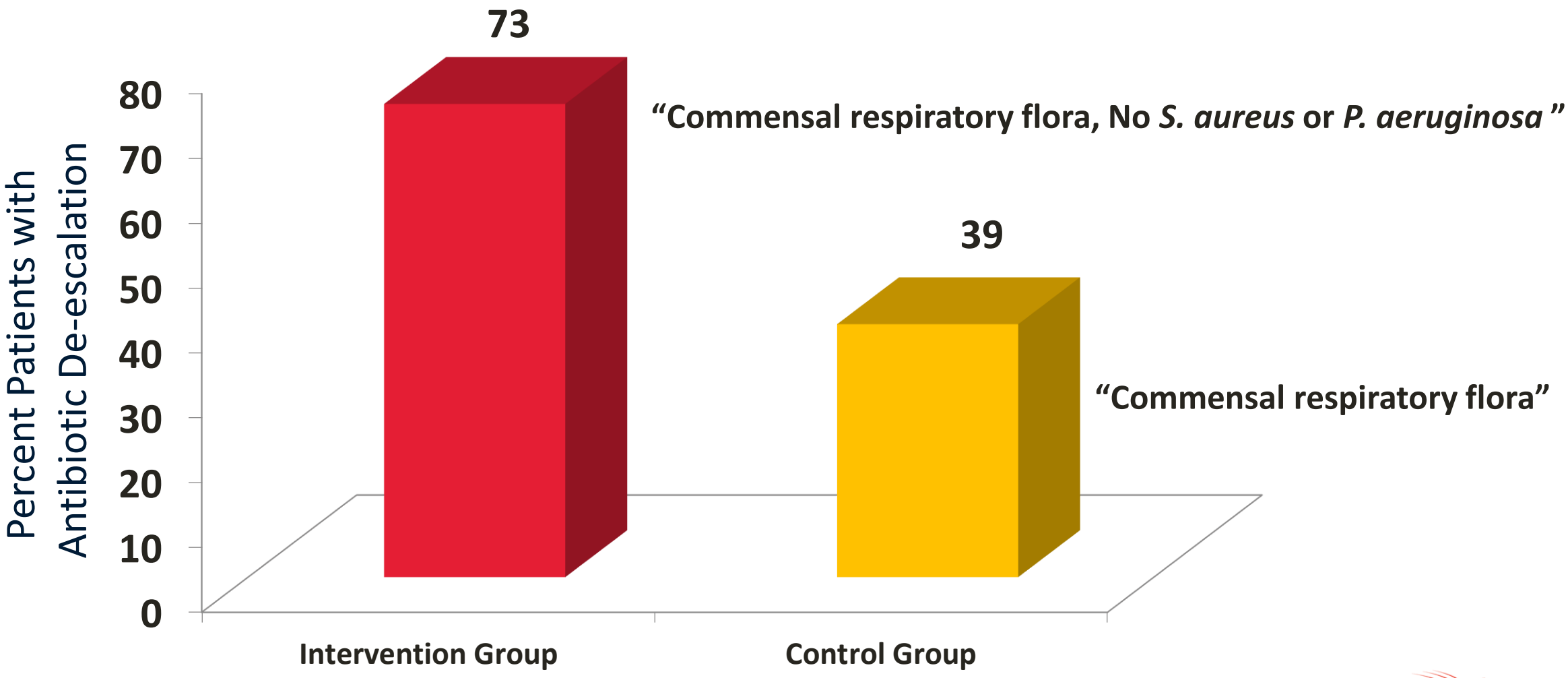
Simple Modification to Sputum Gram Stain Reporting



Musgrove. OFID. 2018

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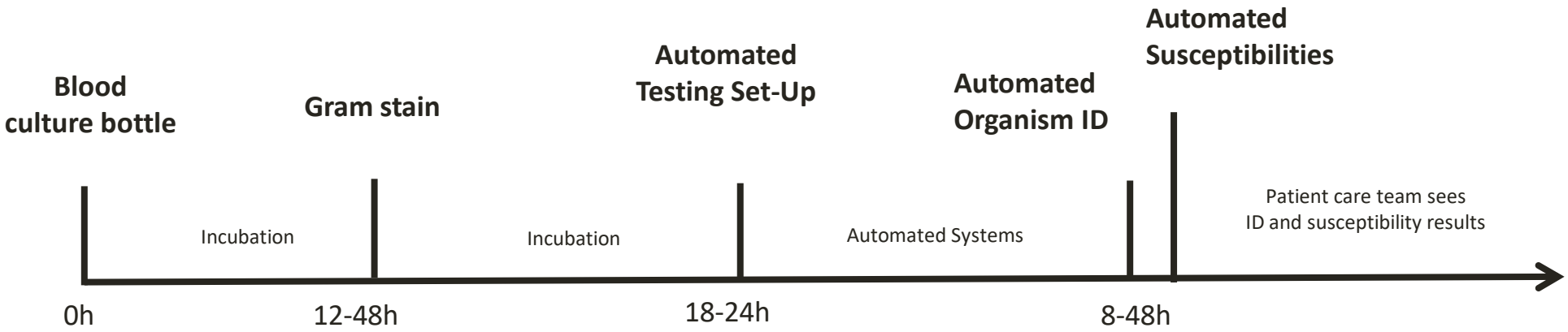
Collaborative Approaches to Optimizing Patient Outcomes

Timeline for Organism Identification and Susceptibility Results



Time from blood draw till microbiology results	
Gram stain	30.1 hours
Organism identification	84.0 hours
Organism susceptibilities	87.3 hours

Huang, Clin Infect Dis. 2014

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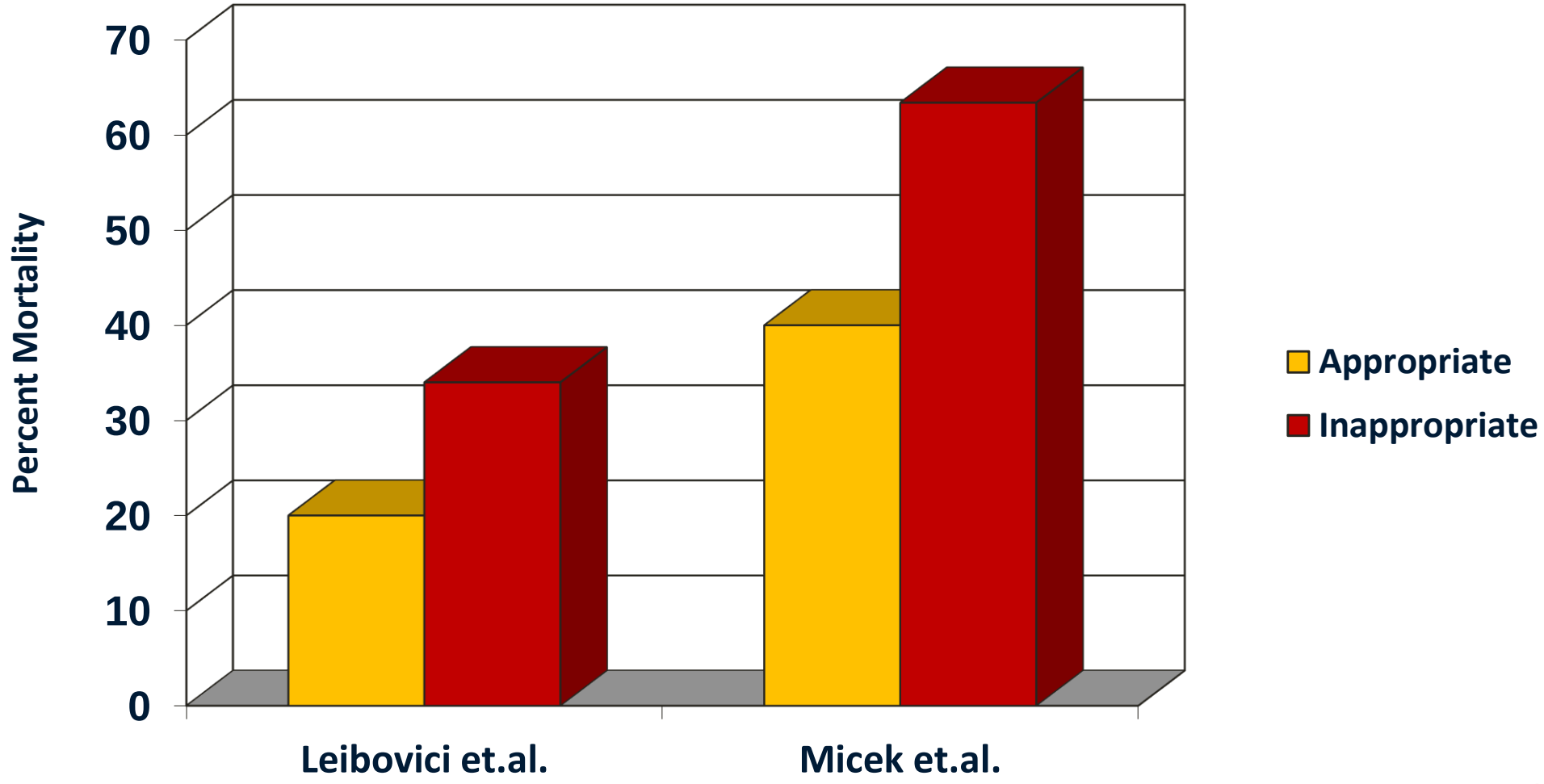
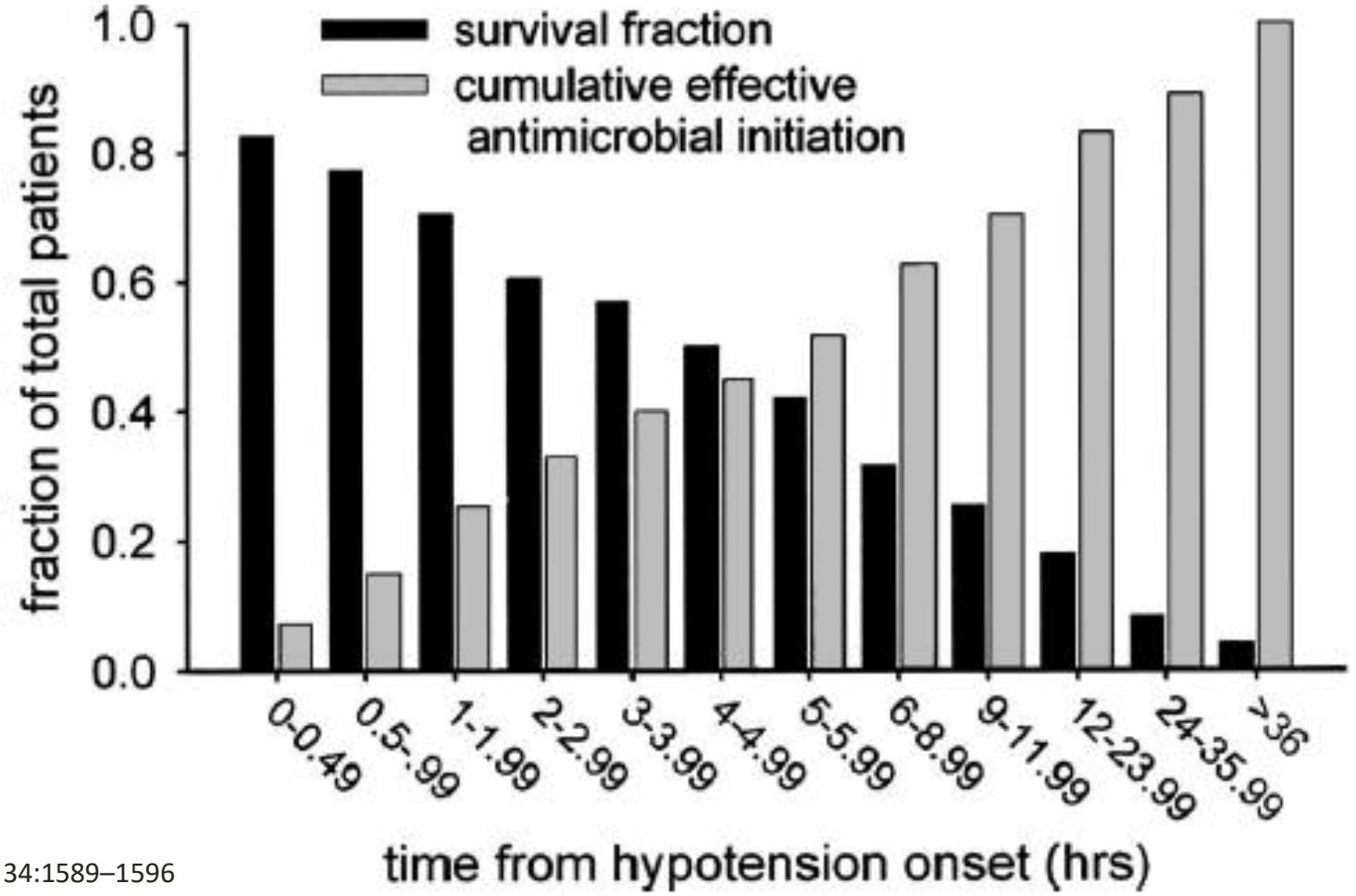
Importance of Appropriate Initial Therapy in Patients with Bacteremia



Leibovici L et.al. J Int Med 1998; Micek ST et.al. J Hosp Med

Impact of Delayed Effective Antibiotic Therapy in Septic Shock



Kumar A, et al. Crit Care Med 2006; 34:1589–1596

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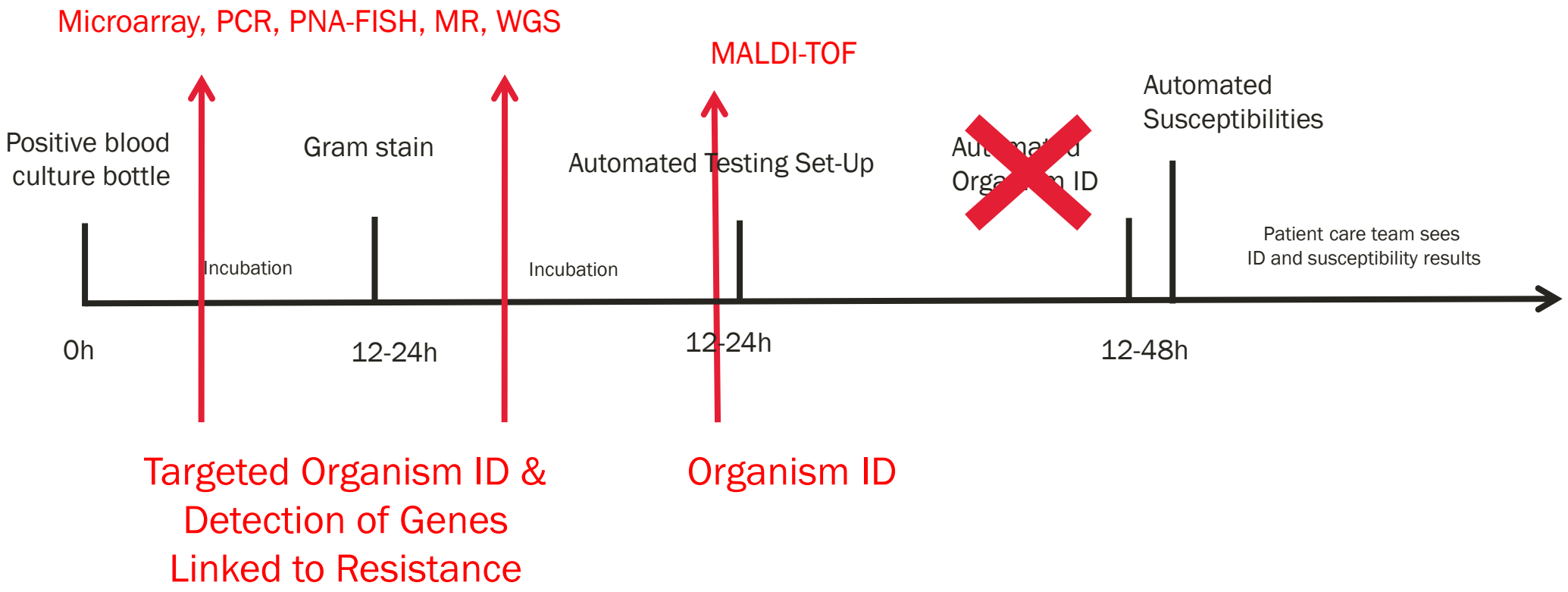
Advances in Clinical Microbiology

- **Mass spectrometry**
  - MALDI-TOF
- **Nucleic acid hybridization**
  - PNA-FISH™
- **Nucleic acid amplification**
  - Real-time PCR, Multiplex arrays
- **Magnetic resonance imaging**
  - T2 Biosystems ™
- **Next generation whole genome sequencing**

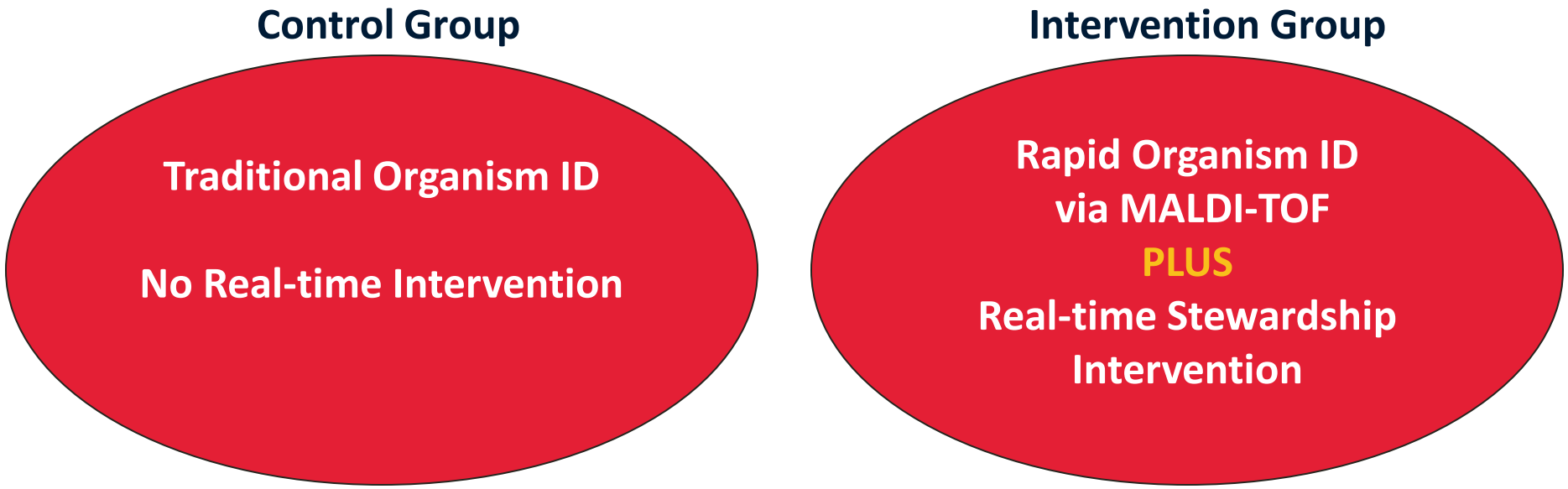
Rapid Molecular Diagnostics for Infectious Diseases



It's NOT Enough to Simply Report Results for Rapid Diagnostic Testing

Study	RDT/pathogen(s)	Study Design	Outcomes
Forrest, 2006	PNA-FISH *Candida spp.*	Pre/post-intervention: RDT + AST	ID of *C. albicans* 3 days earlier (9.5h vs 44h), ↓ antifungal costs by $1,978/patient
Forrest, 2008	PNA-FISH Enterococcus spp.	Pre/post-intervention: RDT + AST	↓ mortality (45% vs 35%), ↓ time to appropriate abx (1.3 vs 3.1 days)
Ly, 2008	PNA-FISH *S. aureus* vs GPCs	RDT and pre/post AST	↓ mortality (17% vs 8%), ↓ inappropriate abx use by 2.5 days*, trend towards ↓ LOS and cost
Carver, 2008	RT-PCR *mecA* (MRSA)	mecA gene reporting and pre/post AST	↓ time to optimal abx (64.7h vs 39.9h), ↓ duration of *S. aureus* BSI
Wong, 2010	rPCR *S. aureus*	Pre/post intervention: RDT + AST	↓ LOS (21.5d vs 15.3d)
Perez, 2013	*MALDI-TOF GNRs*	Pre/post intervention: RDT + AST	↓ LOS (11.9d vs 9.3d), Trend towards ↓mortality (10.7 vs 5.6%)
Huang, 2013	*MALDI-TOF All Pathogens*	Pre/post intervention: RDT + AST	↓ 30d mortality (20.3 vs 12.7%), ↓ LOS (21 vs 16.7d)

Rapid Organism Identification plus Real-Time Stewardship Team Review & Intervention

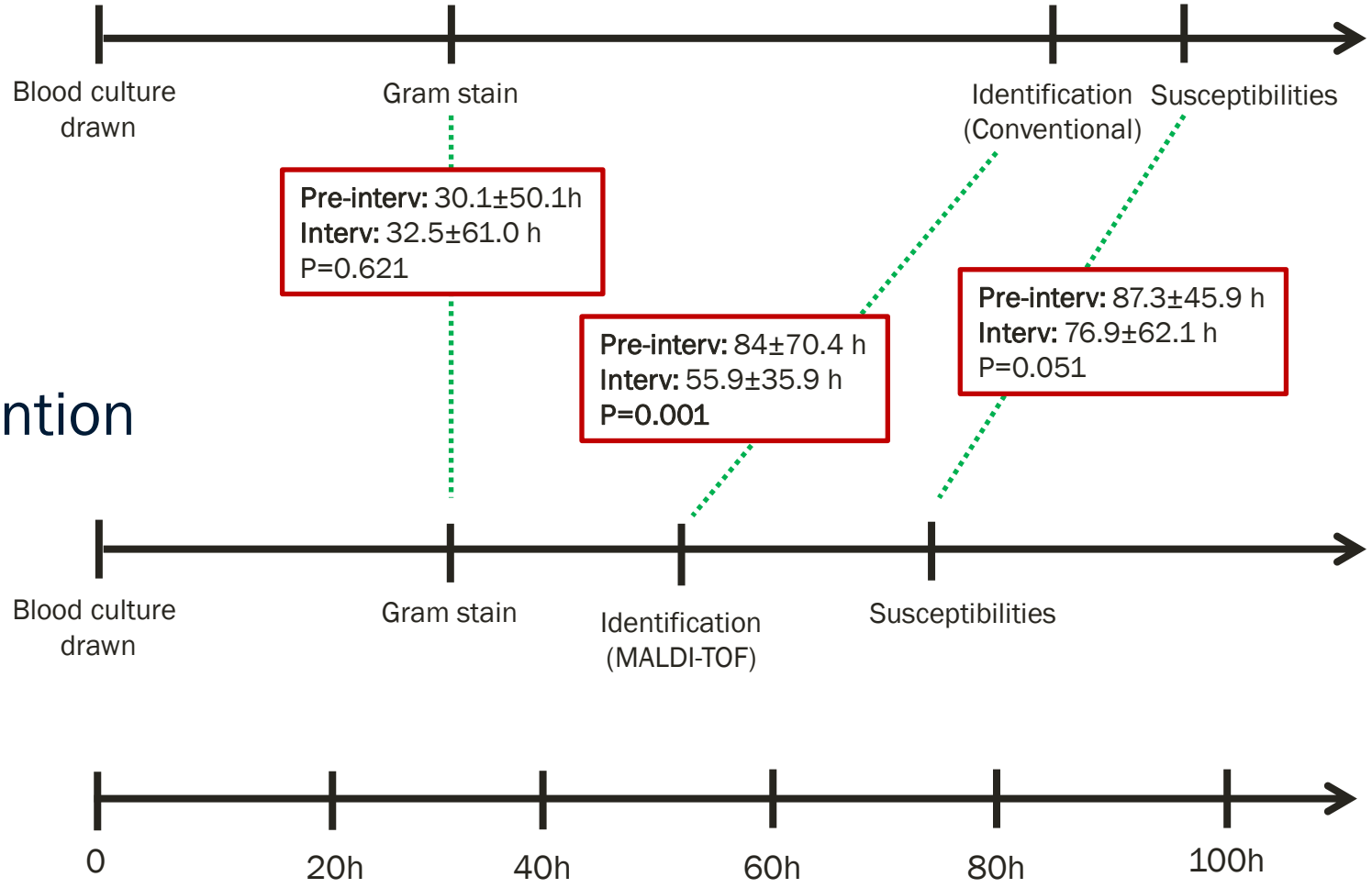


Implemented an automatic relay system to send 3 real-time alerts to an antimicrobial stewardship pager from 0700-2300:

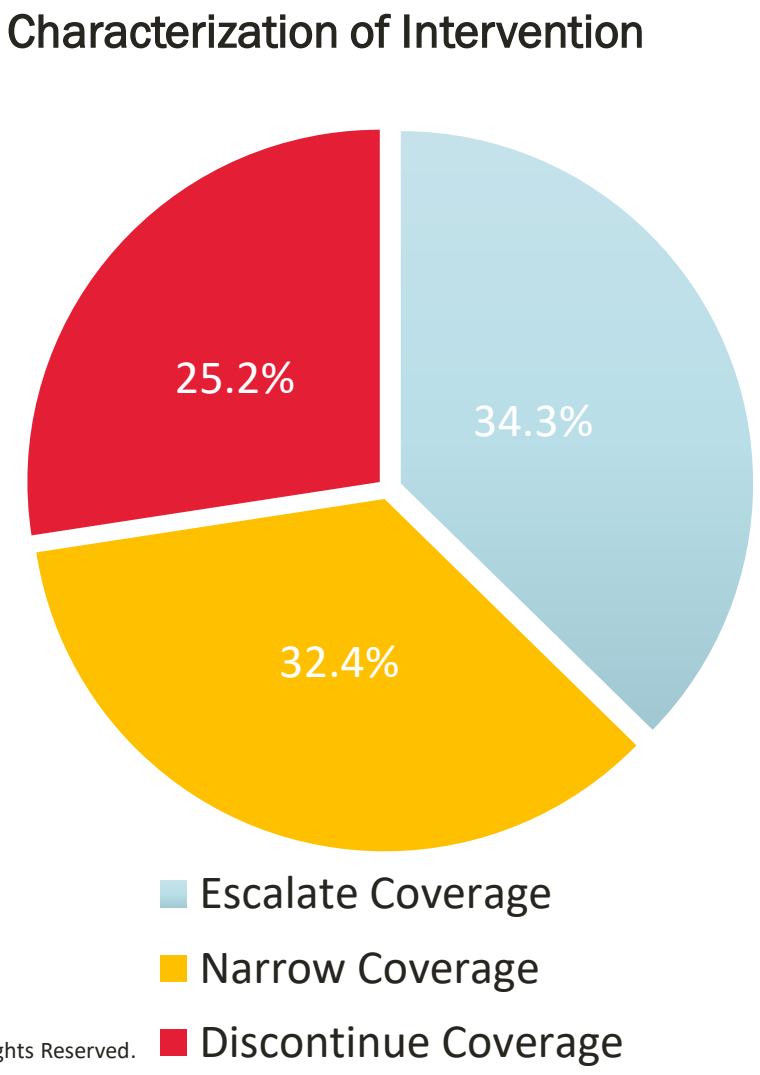
- Positive Gram stain
- Organism identification
- Susceptibility results

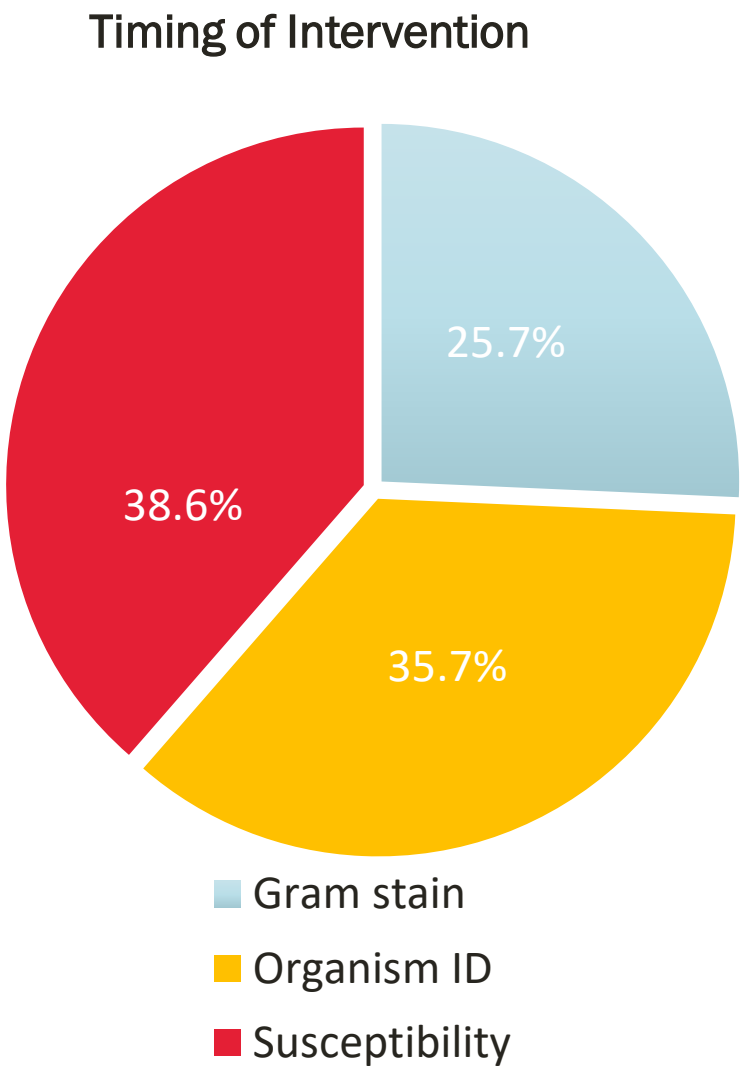
Clinical Microbiology Timeline

Pre-Intervention

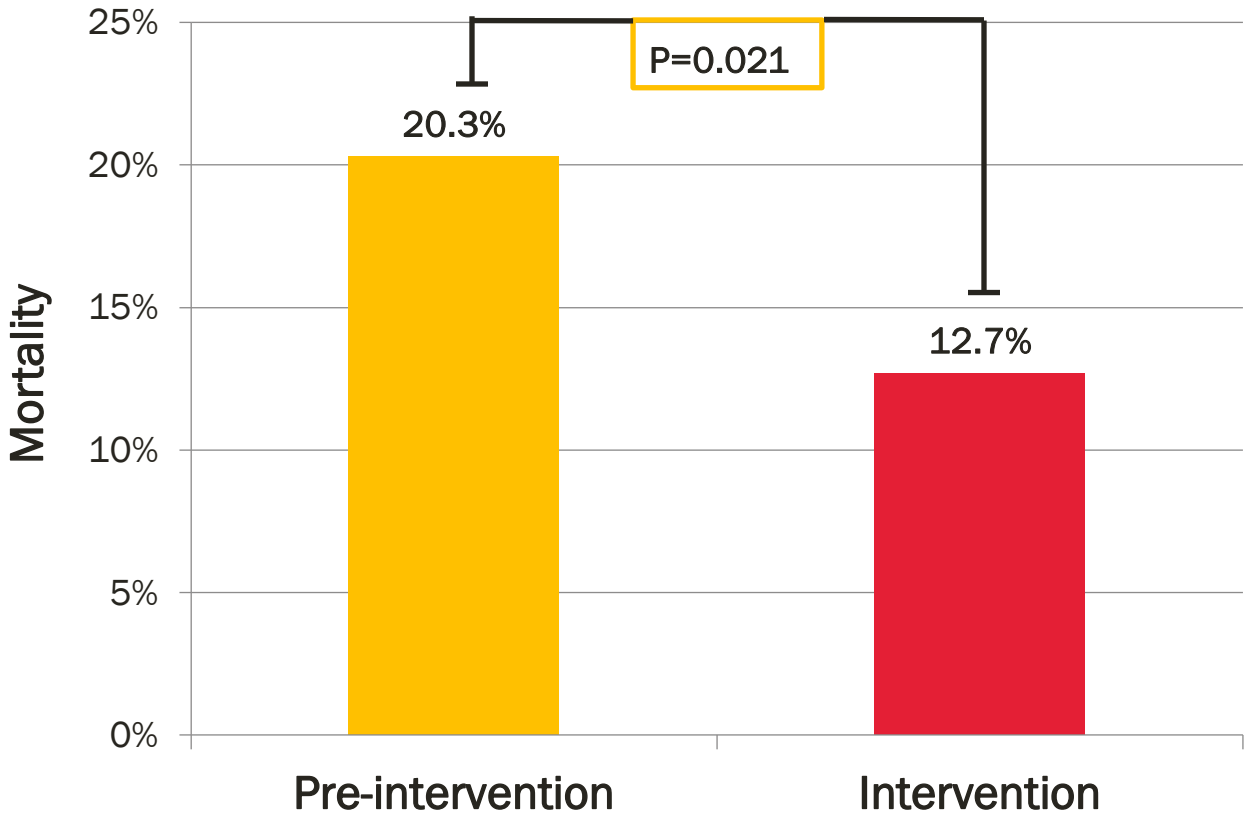


Timing a Characterization of Interventions





Outcomes: 30-day All-cause Mortality



Secondary Outcomes

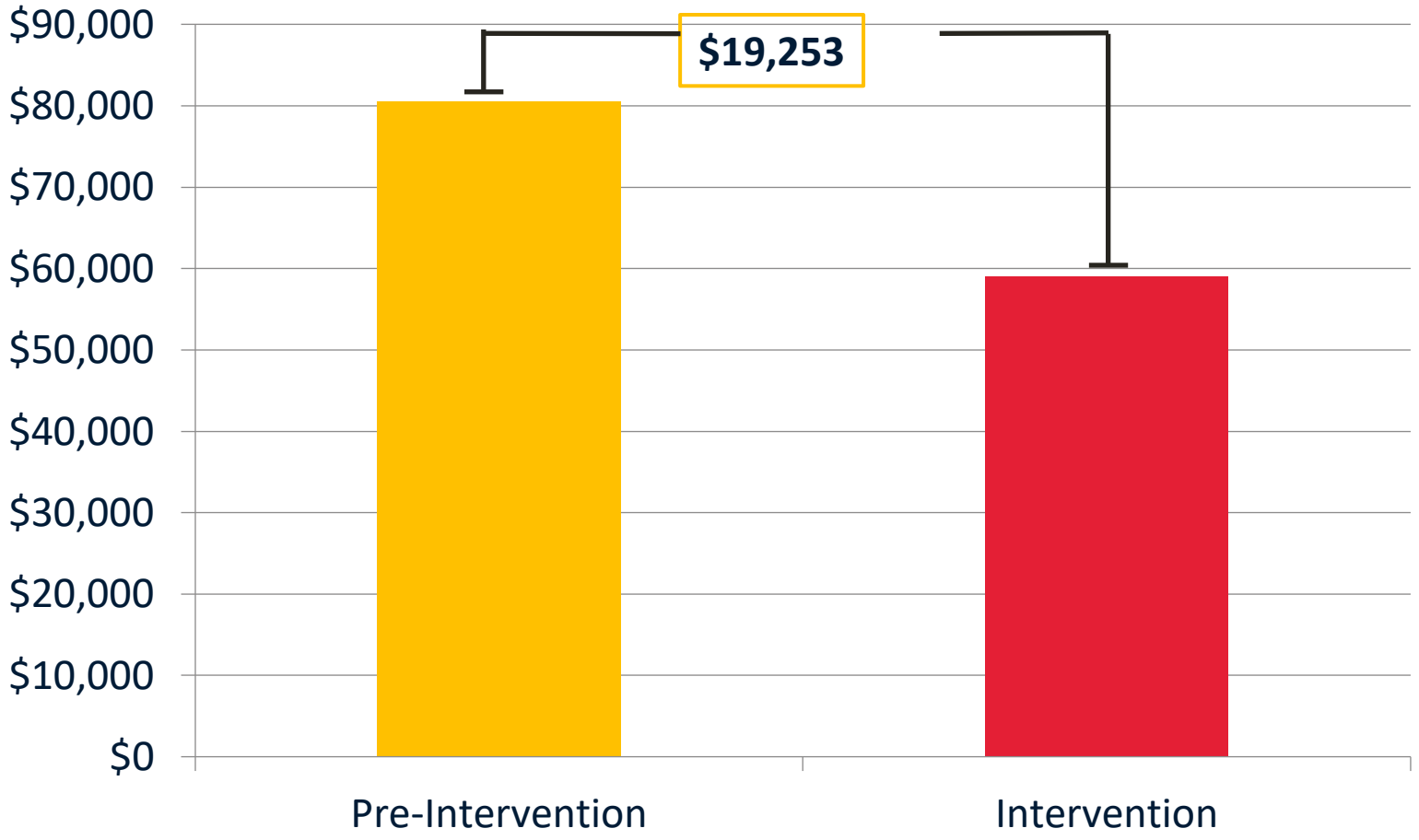
Therapy-Related Outcome	Pre-Interv (n=256)	Interv (n=245)	P-value
Time to Effective Therapy (hrs)	30.06	20.35	0.021
Time to Optimal Therapy (hrs)	90.34	47.25	<0.001

Clinical Outcome	Pre-Interv (n=256)	Interv (n=245)	P-value
Time to clinical response (days)	3.97	2.5	<0.001
Time to microbiological cure (days)	3.32	3.27	0.928
Length of hospitalization (days)	21.03	16.73	0.054
Length of ICU stay (days)	16.58	9.15	0.012
Recurrence of same BSI (%)	15 (5.9)	5 (2.0)	0.038
30-day Readmission with same BSI (%)	9 (3.5)	4 (1.6)	0.262

Contaminated Blood Cultures with Coagulase-Negative *Staphylococci*

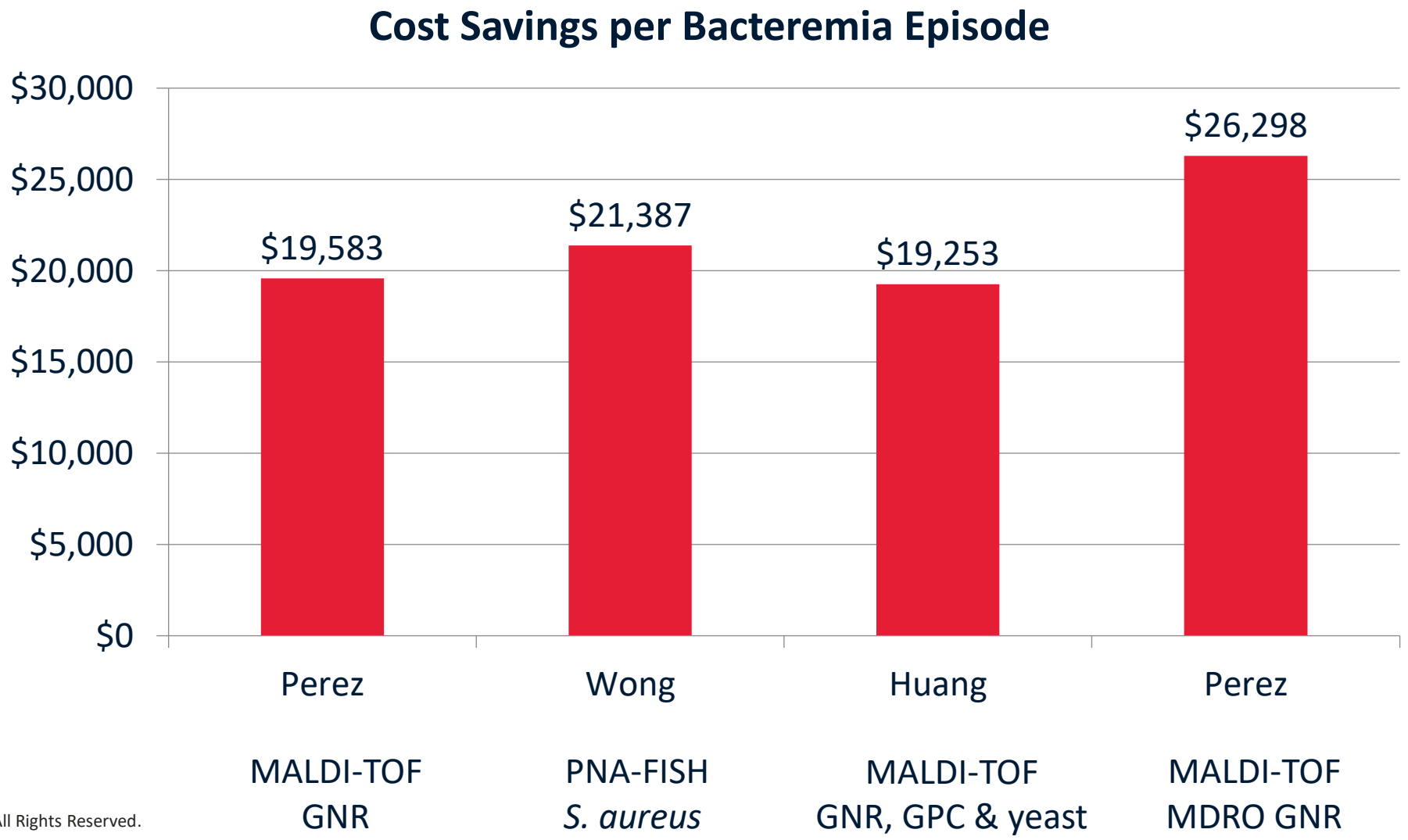
Outcome	Pre-Intervention Group (n=83)	Intervention Group (n=85)	P-value
Days of antibiotic therapy	4.4	3.0	0.015
Number of vancomycin assays	2.0	0.9	<0.001
Mortality	10.8%	11.8%	>0.99
Length of hospitalization, days	14.6	15.8	0.7
Recurrent bacteremia with CoNS	3.6%	2.4%	0.68
Rehospitalization with CoNS	2.4%	1.2%	0.62
Positive *C. difficilie* assay	8.4%	4.7%	0.37

Total Cost per Bacteremic Episode

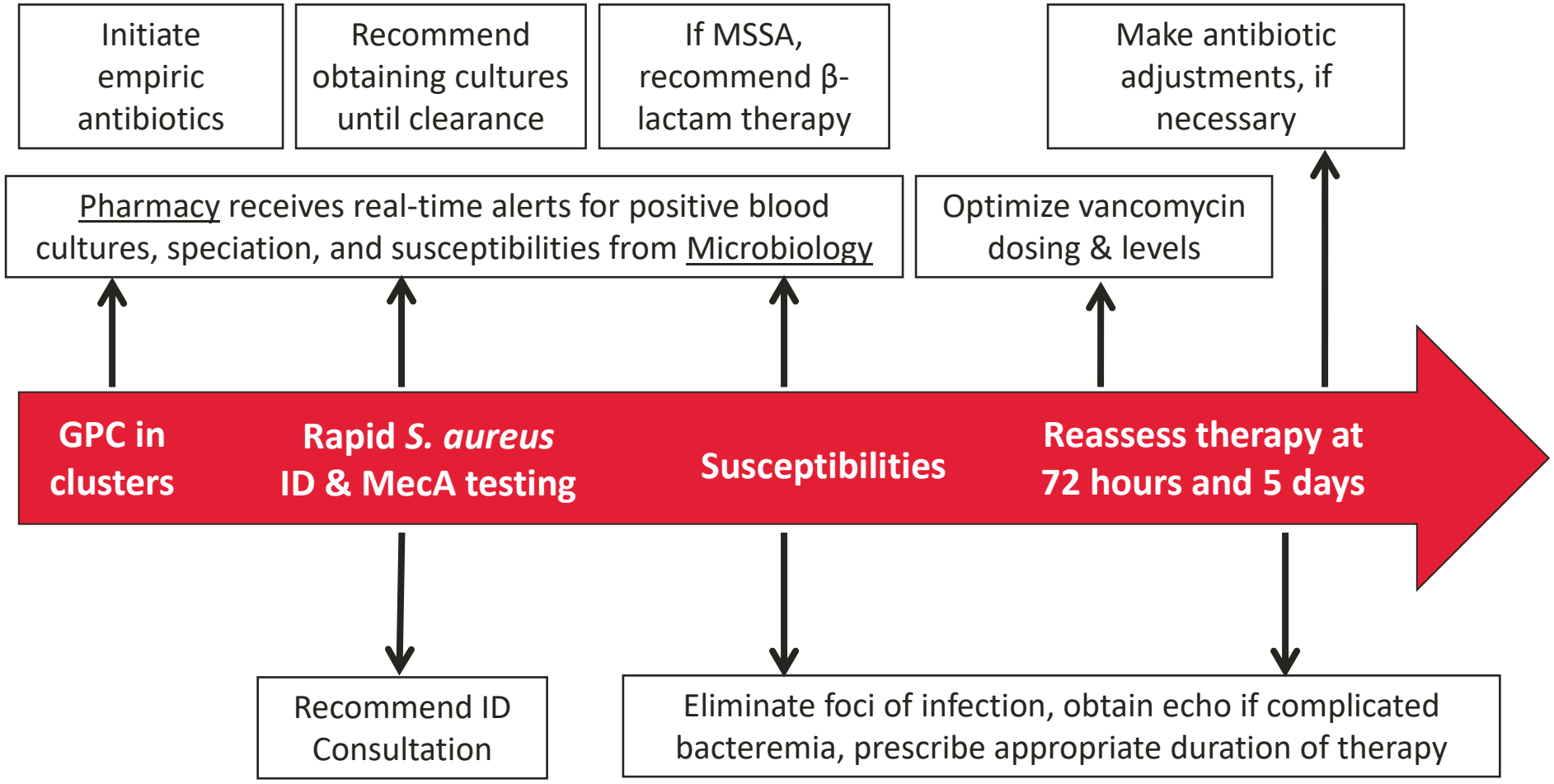


Total Cost Saving for 3-month Intervention Period: $4.8 million

Reduction in Total Hospital Costs with Rapid Diagnostic Testing plus Real-time Culture Review



Stewardship-Lead Comprehensive Collaborative Approach to Improving Outcomes with *S. aureus* Bacteremia



Nguyen CT et al. *Antimicrob Chemother.* 2015; 70:3390-6

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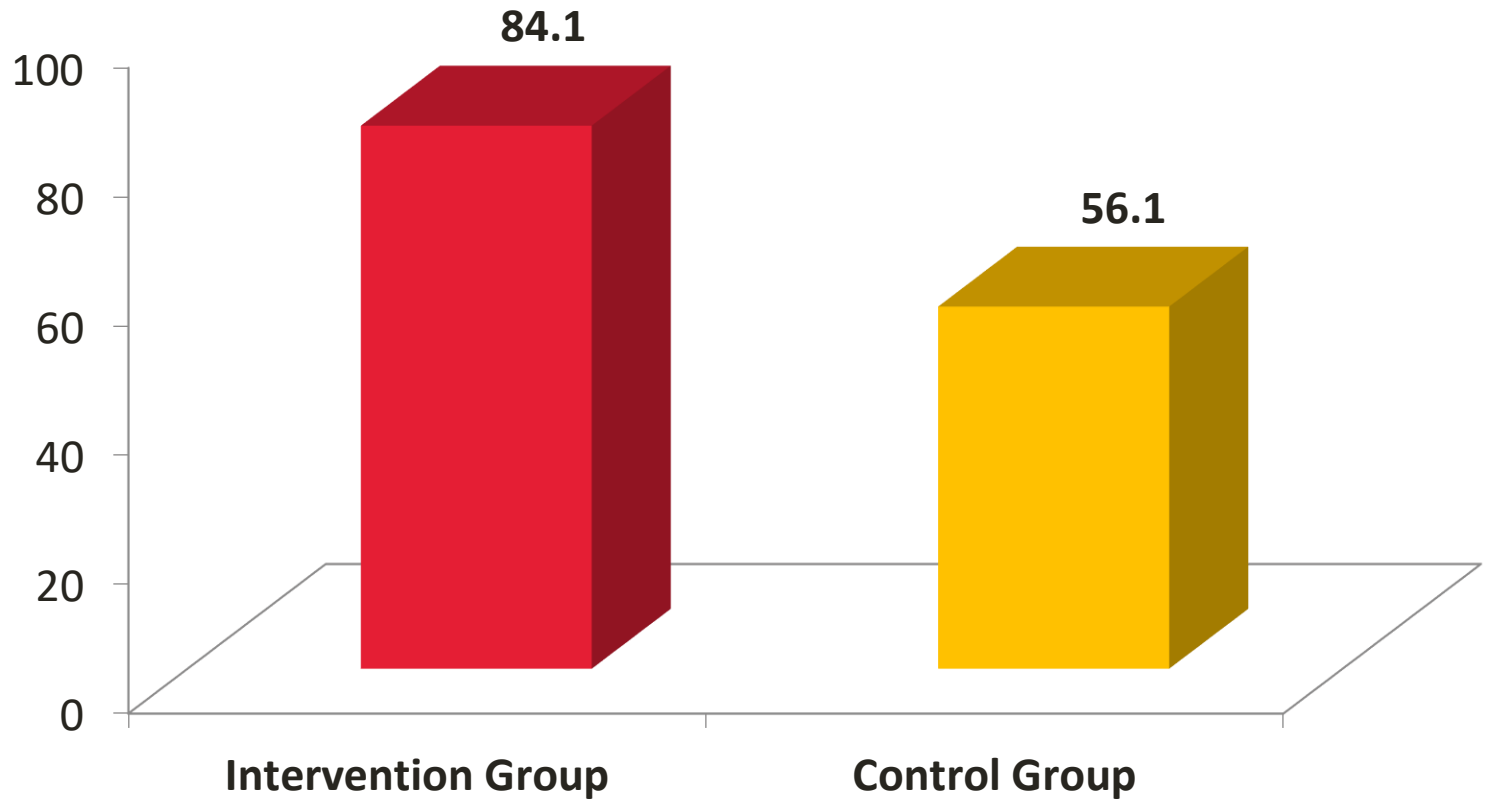
Overall Bundle Compliance with Quality Performance Measures for *S. aureus* Bacteremia



Nguyen CT et al. *J Antimicrob Chemother.* 2015; 70:3390-6.

Compliance with Individual Performance Measures for *S. aureus* Bacteremia

Performance measure	Historic Group	Intervention Group	p-value
Antibiotic initiation within 24 h	97.5%	98.9%	0.612
Document clearance of cultures	85.0%	96.5%	0.013
Appropriate duration of therapy	86.4%	94.9%	0.088
IV Beta-lactam therapy for MSSA	86.8%	94.0%	0.321
Appropriate vancomycin trough	93%	97.6%	0.616
Echo for complicated bacteremia	96.2%	96.7%	0.999
Source control	78.6%	97.2%	0.037

Nguyen CT et al. *J Antimicrob Chemother.* 2015; 70:3390-6.

Clinical Outcomes Following Stewardship Syndrome-Specific Intervention for *S. aureus* Bacteremia

Outcome	Historic Group	Intervention Group	p-value
Mortality	19.5%	11.4%	0.200
Length of stay, from bacteremia (IQR)	9 (5-17)	9 (5-20)	0.474
30-Day readmission with *S. aureus* bacteremia	11.0%	1.1%	0.008
Persistent bacteremia	13.4%	9.1%	0.467

Nguyen CT et al. *J Antimicrob Chemother.* 2015; 70:3390-6.

Comprehensive Management of *S. aureus* Bacteremia

Author, year	Intervention	Clinical Outcomes
Lopez-Cortes, 2013 (n=508)	Multicenter pre-post study Develop guideline: ID consult and compliance with 6 process measures	• 14-day mortality: 17.8% pre vs. 11.3% post • Adjusted 14-day mortality: OR 0.49 (0.28-0.87), p=0.016
Saunderson, 2014 (n=66)	Pediatric guideline, and intervention to promote compliance with 4 process measures	• Length of stay: 14 days vs. 16.5 days, NS • 30-day mortality: 0% vs. 8.6%, NS
Borde, 2014 (n=59)	Develop guideline and promote compliance with bundle process measures	• In-hospital mortality: 43.6% vs. 10.0%, p=0.009
Nagao, 2017 (n=477)	Single center retrospective analysis of compliance with 5 bundle endpoints	• Adherence to ≥ four measures: increased from 47.5 % in 2006 to 79.3 % in 2014 (P = 0.001); • 30-day mortality decreased from 10.0% to 3.4%
Wenzler, 2017 (n=89)	Automated pharmacist-driven intervention to improve compliance with performance measures	• All-cause mortality: 15.6% vs. 2.6%, P=0.063

Complex Problems Often Require Multifaceted "Bundle" Solutions

Prevent Hospital-Acquired C. difficile

- Hand hygiene
- Appropriate cleaning
- Contract precautions
- Minimize use of high-risk antibiotics
- Minimize use of proton pump inhibitors
- Send test in the correct scenario
- Avoid testing formed stool
- Targeted therapeutics to prevent disease or recurrent disease

Improve Sepsis Outcomes

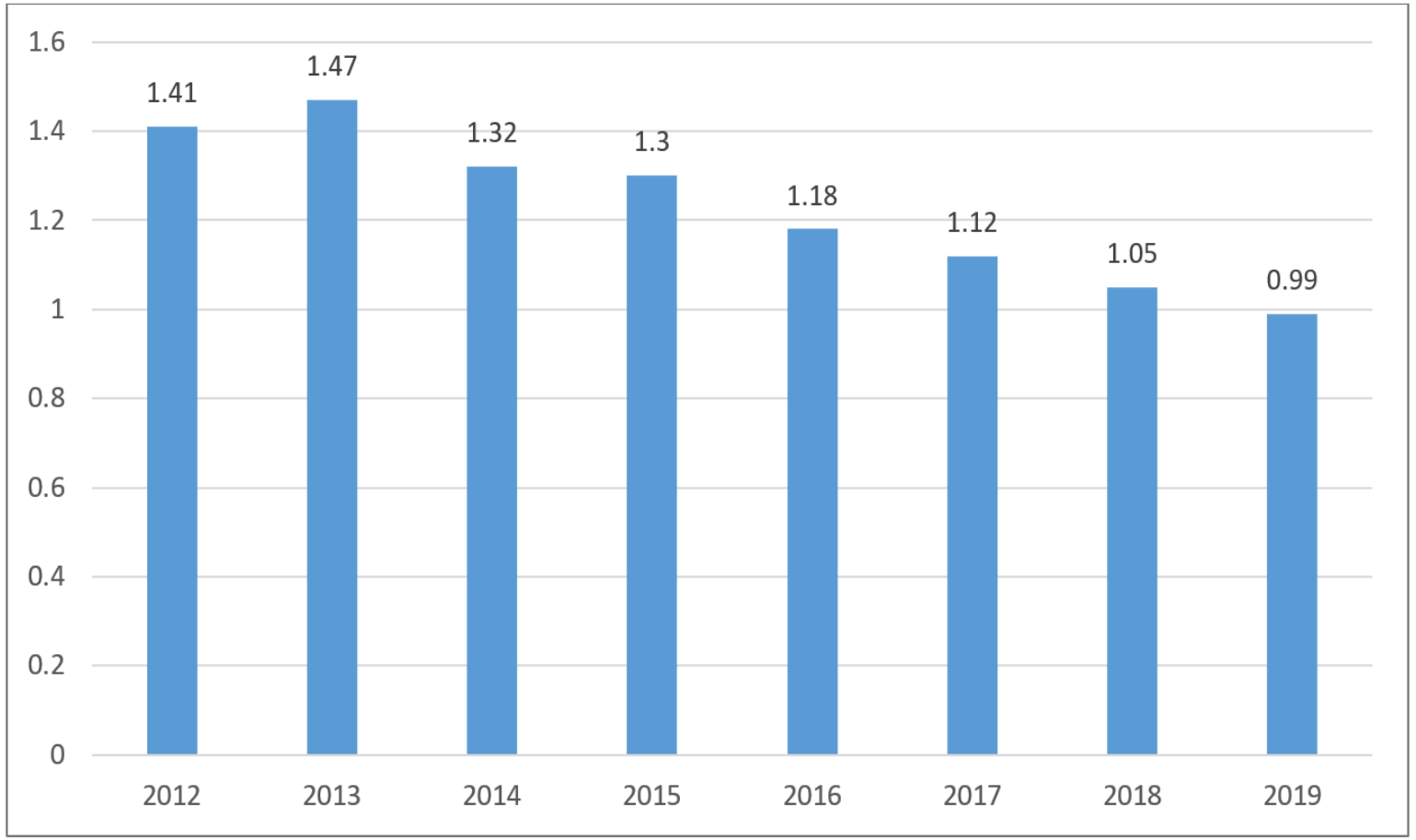
- Improve triage upon presentation
- Frequent evaluation of vitals
- Appropriate laboratory testing
- Prompt antibiotics
- Appropriate antibiotics
- Supportive therapy
- Diagnostic testing that helps quickly identify infection with resistant organism

Summary

- Collaboration with microbiology is essential for the success of a stewardship program
- Selective reporting, reporting cascades and education can significantly impact antimicrobial prescribing
- Antimicrobial stewardship programs can help improve patient outcomes through timely initiation of antimicrobial therapy when utilizing rapid diagnostic tests
- Solving complex problems often requires collaboration across departments, and antimicrobial stewardship-microbiology departments can help lead successful initiatives!

Step-Wise Bundle Approach: Impact on *C. difficile* SAAR Score

- 2013- Education on importance of hand hygiene, cleaning and contact precautions
- 2014- Restrict ceftriaxone, quinolones, clindamycin
- 2015- Excessive durations of antibiotics for common infections
- 2017- Avoid testing formed stool
- 2018- Proton pump inhibitor reduction program
- 2019- Prior authorization for *C. difficile* test for targeted patients



Michigan Medicine Internal Data

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