

**SYNDROMIC MOLECULAR TESTING IN  
INFECTIOUS DISEASES:**

**BETTER RESULTS AND PATIENT  
OUTCOMES**

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NHICEP

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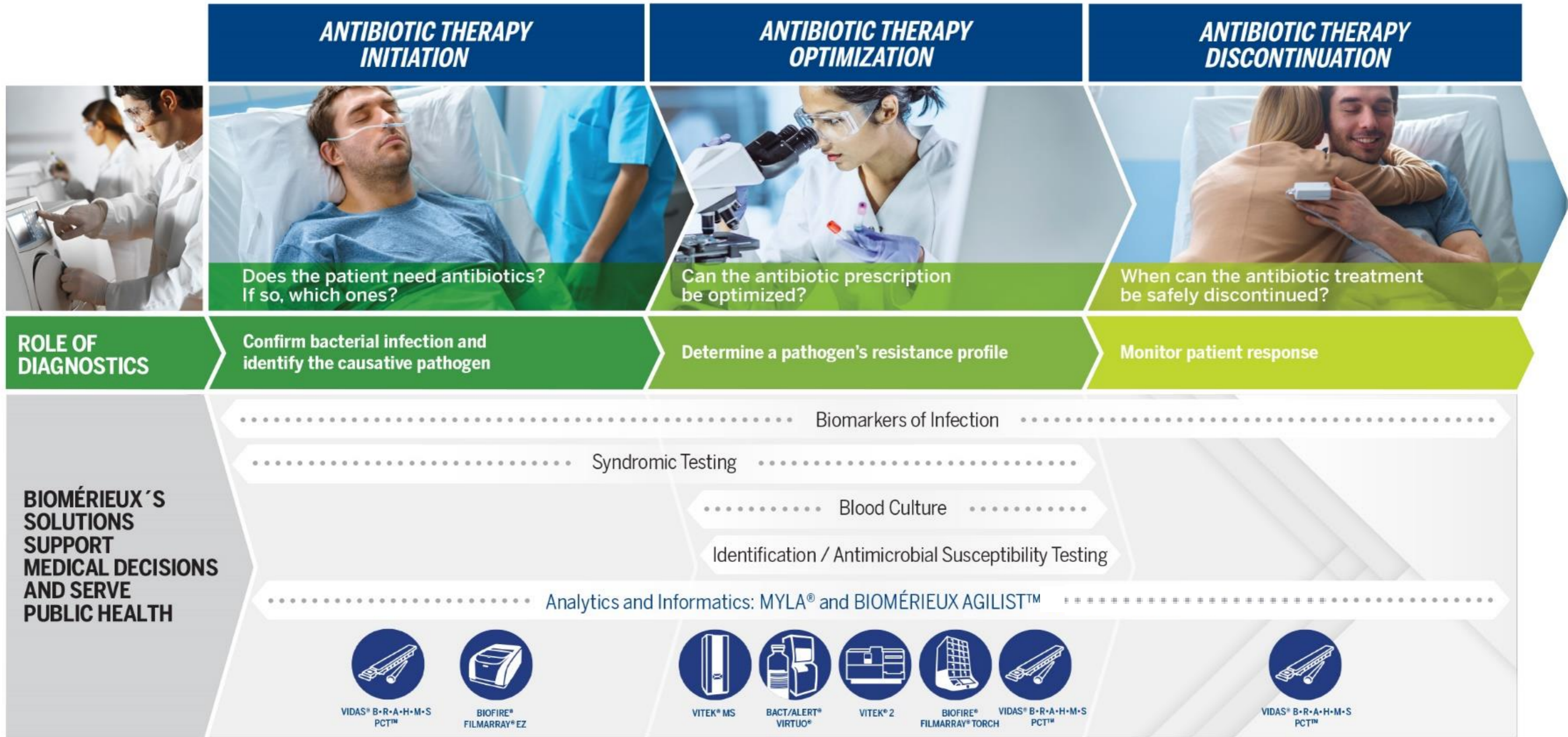
# DISCLOSURE

- I am employed by bioMérieux

# AGENDA

- **Overview of Syndromic PCR Testing**
- **The Syndromic Approach Compared to Traditional Diagnostic testing**
- **Better Understanding of:**
  - The Clinical Benefits of PCR Testing & its Relationship to Antimicrobial Stewardship
  - Patient Outcomes Post Utilization of Rapid PCR Testing
- **Overview of Current Diagnostics**

# DIAGNOSTIC STEWARDSHIP IN THE PATIENT'S JOURNEY THROUGH ANTIBIOTIC THERAPY



**BIOMÉRIEUX'S SOLUTIONS SUPPORT MEDICAL DECISIONS AND SERVE PUBLIC HEALTH**

**MOLECULAR,  
[ SYNDROMIC APPROACH ]  
TO DIAGNOSTIC  
TESTING**

# THE SYNDROMIC APPROACH

**Syndrome = Signs + Symptoms**

**Sign:** an objective indication that is detected by a physical examination

Example: Temperature of 102°F

**Symptom:** a physical or mental feature that is apparent to the patient

Example: "I am congested"

## **The Syndromic Approach**

A symptom-driven broad grouping of probable pathogens into one, rapid, molecular test that maximizes the chance of getting the right answer in a clinically relevant timeframe.

# THE SYNDROMIC APPROACH CONTINUED

## With Syndromic Testing...Informed Therapy

- Increases the probability of identifying a pathogen using the right test, the first time
- Reduces guesswork and costs of additional testing
- Informs antibiotic stewardship
- Aides in proper care management including admission, isolation, cohorting, and therapy

## Without Syndromic Testing...Educated Guess

- The infectious cause may remain unknown
- The right test may not be ordered
- The wrong tests or no test may be ordered
- Costs associated with additional testing
- Patient care may be compromised
- Risk of adverse outcomes and patient dissatisfaction

# SYNDROMIC CONSIDERATIONS VS TRADITIONAL TESTING

## Traditional Testing



## Syndromic Testing\*\*



\*\* Syndromic Testing is meant to be an Aid in Diagnostics & Does not Replace Traditional Culture \*\*

1. Martinez et al, Geisinger Health System (CVS poster, May 2016).  
2. Rogers BB et al. Arch Pathol Lab Med. 2015;139:636-641.



# THE MOLECULAR ADVANTAGES OVER TRADITIONAL TESTING



## Molecular – Advantages













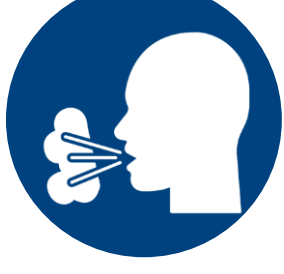
- ↑ Sensitivity & Specificity
- Detection of Difficult to Culture Viruses (e.g., CoVs)
- Detection of Virus that Risk Rapidly Becoming Non-viable (e.g. RSV)
- Multi-Organism Detection within a Single Test
- Not affected by prior antibiotic use



## Traditional – Disadvantages

- Complicated; Technically Demanding (Dedicated technologists)
- Need Dedicated Lab Space
- Long Turnaround Time (6–24 hrs.)<sup>1</sup>
- Labor Intensive; Generally, Performed During Daytime Hours in Larger Medical Centers
- Sensitive to Fastidious/Difficult to Grow Organisms & Prone to False Negatives
- Not Replaced by Molecular Testing\*

# THE EVOLVING SUITE OF PCR TESTING

PANEL TYPE		TARGETS TESTED	
	Respiratory		Bacteria (gram +/-)
	Pneumonia		Atypical Bacteria
	Gastrointestinal		Viruses
	Blood stream		Yeast
	Meningitis/Encephalitis		Parasites
	STD Panels		Resistance Genes
	Flu A + B		

# MULTIPLE STUDIES PROVE THE CLINICAL AND ECONOMIC BENEFITS

## Large Multiplex PCR Panels Should be First Line Tests for Detection of Respiratory and Intestinal Pathogens.<sup>1</sup>

- Empiric therapy is actually guess therapy. Only **13%** of 1,761 viral respiratory tests were positive for Flu A/B. **87%** of adult patients tested negative when only Flu A/B was ordered
- Syndromic panels should be used to ensure rapid and accurate diagnosis
- Syndromic testing can reduce healthcare costs, and the rapidity of results is extremely satisfying to both patients and medical providers
- “Our physicians could test for the 20 most common agents causing acute respiratory infection with results in about an hour at a total cost that was less than one send-out PCR test. Syndromic, multiplex PCR panels offer the chance to have a definitive diagnosis in less than two hours, allowing timely decisions about hospital admission, treatment, infection control, and return to work and family. They can be performed near the patient with minimal training and labor cost.”

Alexander McAdam, MD, PhD CAP Today 2016 When to fire up large Multiplex PCR.

# DIAGNOSTIC TESTS PLAY A CRITICAL ROLE ALONG *THE ENTIRE PATIENT PATHWAY*



Screening

Early diagnosis

Prognosis

Treatment decisions

Patient monitoring

**From the initial contact with an outpatient clinician to the completion of treatment**

# ANTIMICROBIAL STEWARDSHIP

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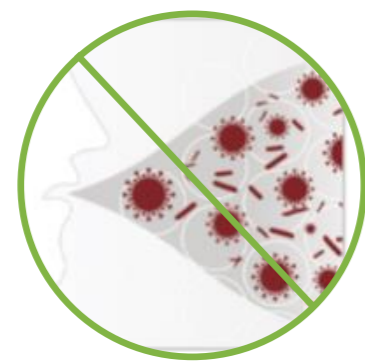
- **Antimicrobial stewardship information**
- Antimicrobial stewardship can help prevent the development of multidrug resistant organisms and reduce unnecessary drug use and costs associated with expensive, broad-spectrum therapies used to treat HAIs. Resources include a free toolkit that provides guidance to healthcare organizations building or looking to improve antimicrobial stewardship programs.
- **California July 1, 2015**
- Section 1288.85 is added to the Health and Safety Code, immediately following Section 1288.8, to read:
- Each general acute care hospital, as defined in subdivision (a) of Section 1250, shall do all of the following by July 1, 2015:
  - (a) Adopt and implement an antimicrobial stewardship policy in accordance with guidelines established by the federal government and professional organizations. This policy shall include a process to evaluate the judicious use of antibiotics in accordance with paragraph (3) of subdivision (a) of Section 1288.8.
  - (b) Develop a physician supervised multidisciplinary antimicrobial stewardship committee, subcommittee, or workgroup.
  - (c) Appoint to the physician supervised multidisciplinary antimicrobial stewardship committee, subcommittee, or workgroup, at least one physician or pharmacist who is knowledgeable about the subject of antimicrobial stewardship through prior training or attendance at continuing education programs, including programs offered by the federal Centers for Disease Control and Prevention, the Society for Healthcare Epidemiology of America, or similar recognized professional organizations.
  - (d) Report antimicrobial stewardship program activities to each appropriate hospital committee undertaking clinical quality improvement activities.
- **January 1, 2017 – All hospitals must adopt and implement an antimicrobial stewardship program to include above references**

# ASPS TAKE A MULTIDISCIPLINARY APPROACH TO IMPROVE ANTIMICROBIAL PRESCRIBING AND REDUCE RESISTANCE

Promoted by the CDC in response to the increasing threat of antimicrobial resistance

Collaborative approach among clinical pharmacists with ID training, ID physicians, clinical microbiologists, infection control professionals, information system specialists, and hospital epidemiologists<sup>2</sup>

## Goals of ASPs



Prevent infections<sup>2</sup>



Diagnose and treat infections<sup>2</sup>



Prevent transmission<sup>2</sup>



Optimize use of antimicrobial agents including antibiotics<sup>2</sup>



Reduce microbial resistance

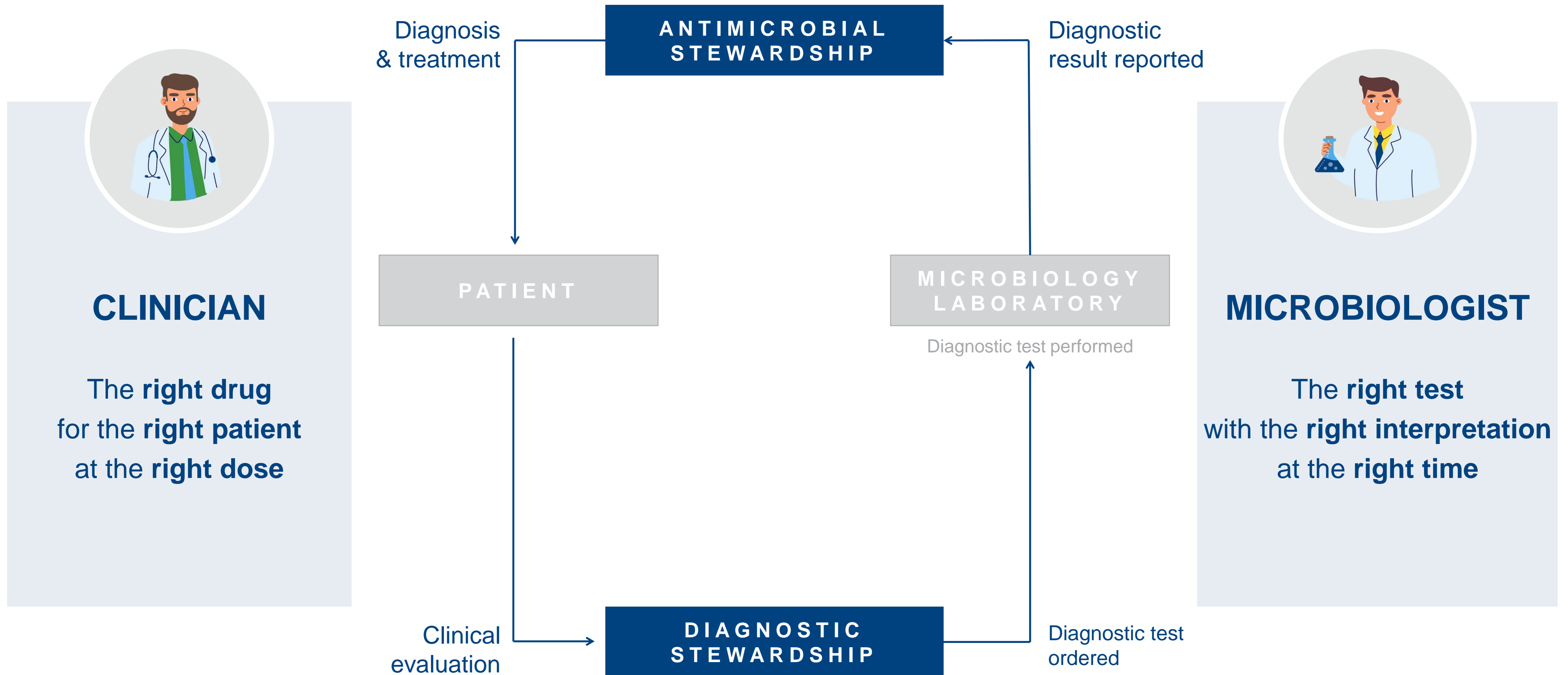


Improve patient outcomes

ASP=antimicrobial stewardship program.

1. CDC. Core Elements of Hospital Antibiotic Stewardship Programs. Atlanta, GA: US Department of Health and Human Services, CDC; 2014.
2. ASHP. A Hospital Pharmacist's Guide to Antimicrobial Stewardship Programs. Stewardship White Paper. 2015.
3. APIC. Antimicrobial stewardship. [www.apic.org/Professional-Practice/Practice-Resources/Antimicrobial-Stewardship](http://www.apic.org/Professional-Practice/Practice-Resources/Antimicrobial-Stewardship). Accessed March 31, 2016.

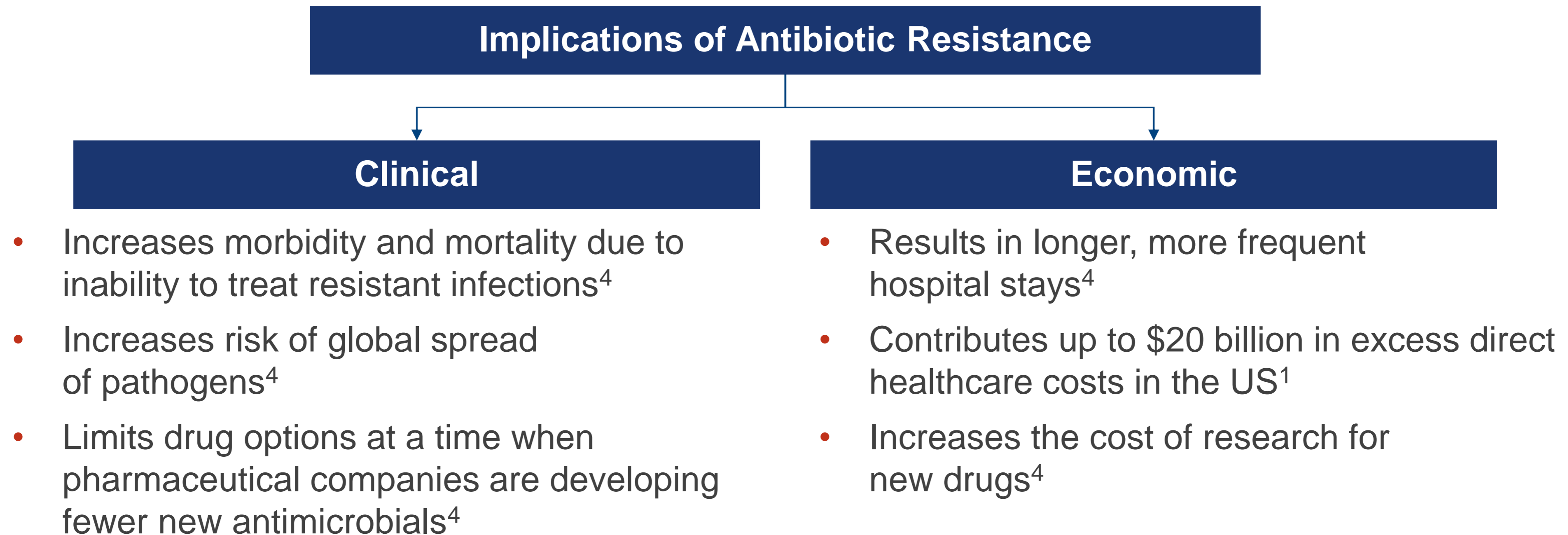
# DIAGNOSTIC TESTS AND EDUCATION FOR HEALTHCARE PROFESSIONALS SUPPORT ANTIMICROBIAL STEWARDSHIP TO PROVIDE PRECISION MEDICINE



# ANTIBIOTIC RESISTANCE IS ONE OF THE KEY MICROBIAL THREATS TO HEALTH IN THE UNITED STATES

Up to 50% of all antibiotics prescribed in acute care hospitals in the United States are unnecessary or inappropriate<sup>1</sup>

Antibiotic misuse contributes to antibiotic resistance, which is one of the most serious and growing threats to public health worldwide<sup>2,3</sup>



1. CDC. Antibiotic Resistance Threats in the United States, 2013. [www.cdc.gov/drugresistance/pdf/ar-threats-2013-508.pdf](http://www.cdc.gov/drugresistance/pdf/ar-threats-2013-508.pdf). Accessed March 29, 2016.  
2. CDC. Core Elements of Hospital Antibiotic Stewardship Programs. Atlanta, GA: US Department of Health and Human Services, CDC; 2014.  
3. World Health Organization. Antimicrobial resistance. <http://www.who.int/mediacentre/factsheets/fs194/en/>. Updated April 2015. Accessed May 6, 2016.  
4. Smolinski M et al. Microbial Threats to Health: Emergence, Detection, and Response. Washington, DC: The National Academies Press; 2003.



# **CLINICAL IMPACT OF RAPID MULTIPLEX PCR TESTING**

# RESPIRATORY TRACT INFECTIONS

- Acute respiratory infections (ARIs) (including pneumonia, flu-like illnesses, and bronchiolitis) are multifactorial, **responsible for 4.25 million deaths each year, and are the third-largest cause of mortality across the globe.**<sup>1</sup>
- Every year, 3–5 million people globally get severe flu infections and as many as 500,000 people die.<sup>1</sup>
- **The estimated economic impact of non-influenza related upper respiratory tract infections (URTI) is \$40 billion annually in the US alone.**<sup>1</sup>

1. Acute Respiratory Infections Atlas, World Lung Foundation, 2010

2. Ruuskanen, O; Lahti, E; Jennings, LC; Murdoch, DR (2011-04-09). "Viral pneumonia.". *Lancet* 377 (9773): 1264–75. [3] Kabra SK; Lodha R; Pandey RM (2010). "Antibiotics for community-acquired pneumonia in children". *Cochrane Database Syst Rev* 3 (3).

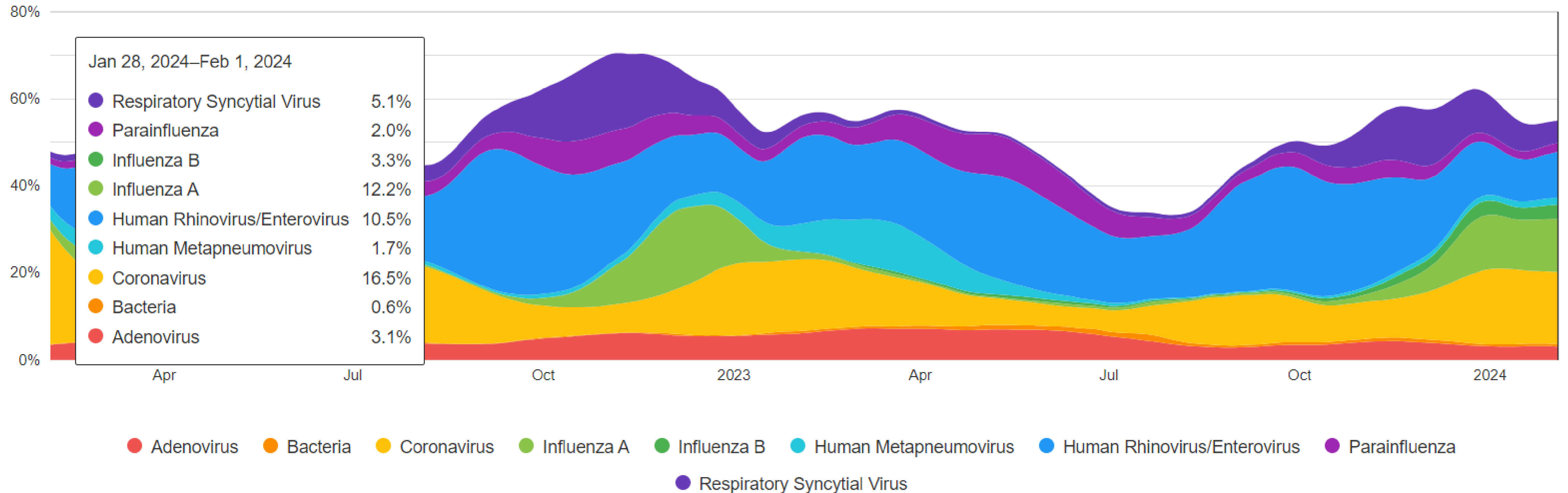
3. WHO Fact sheet N°331, November 2015.

4. American Thoracic Society, Top 20 Pneumonia Facts 2015; <https://www.thoracic.org/patients/patient-resources/resources/top-pneumonia-facts.pdf> accessed April 21, 2016.

# THE NEED FOR SYNDROMIC TESTING<sup>1</sup>

Respiratory Pathogen Trends (RP2.1)

Area  Line

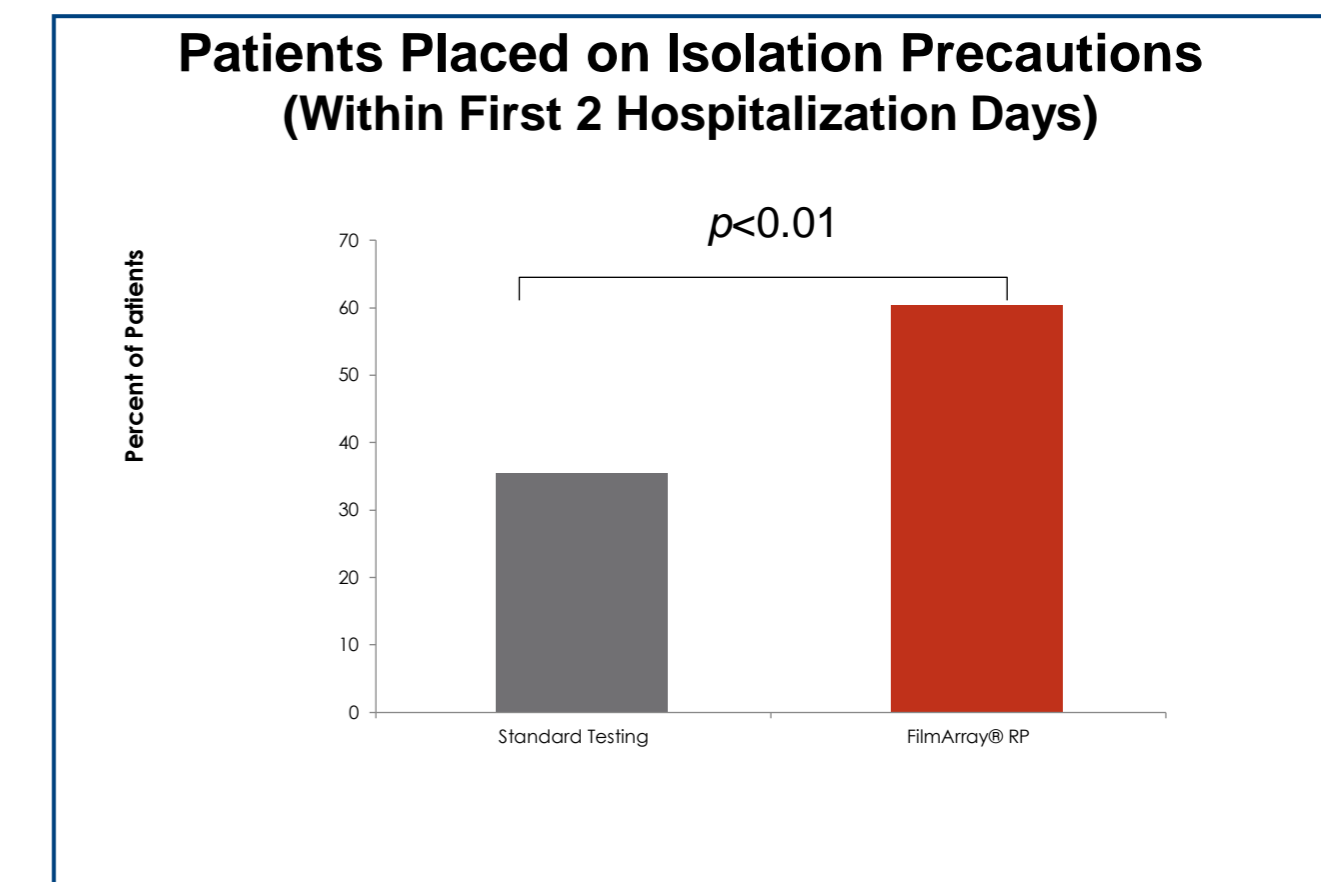
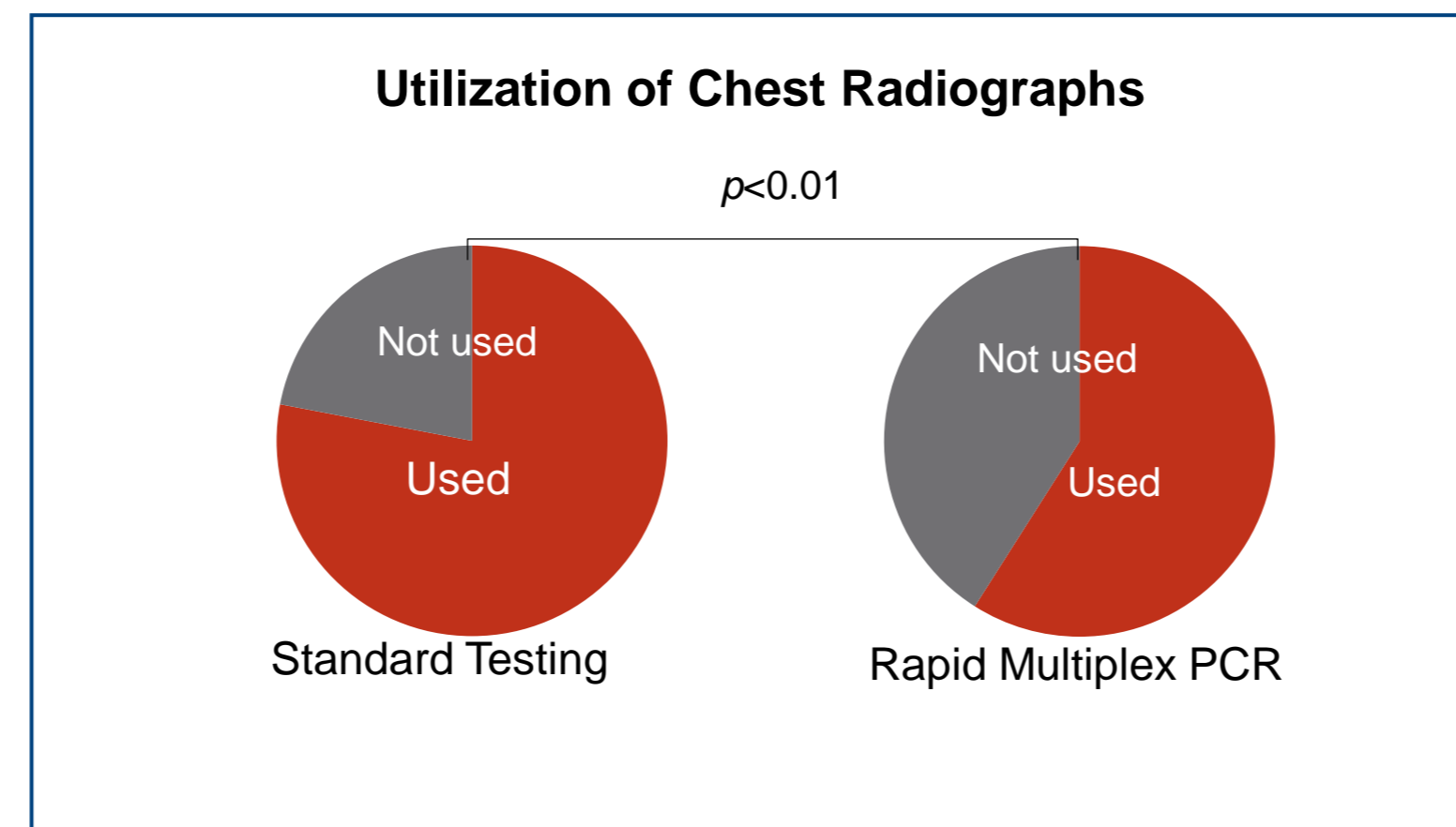
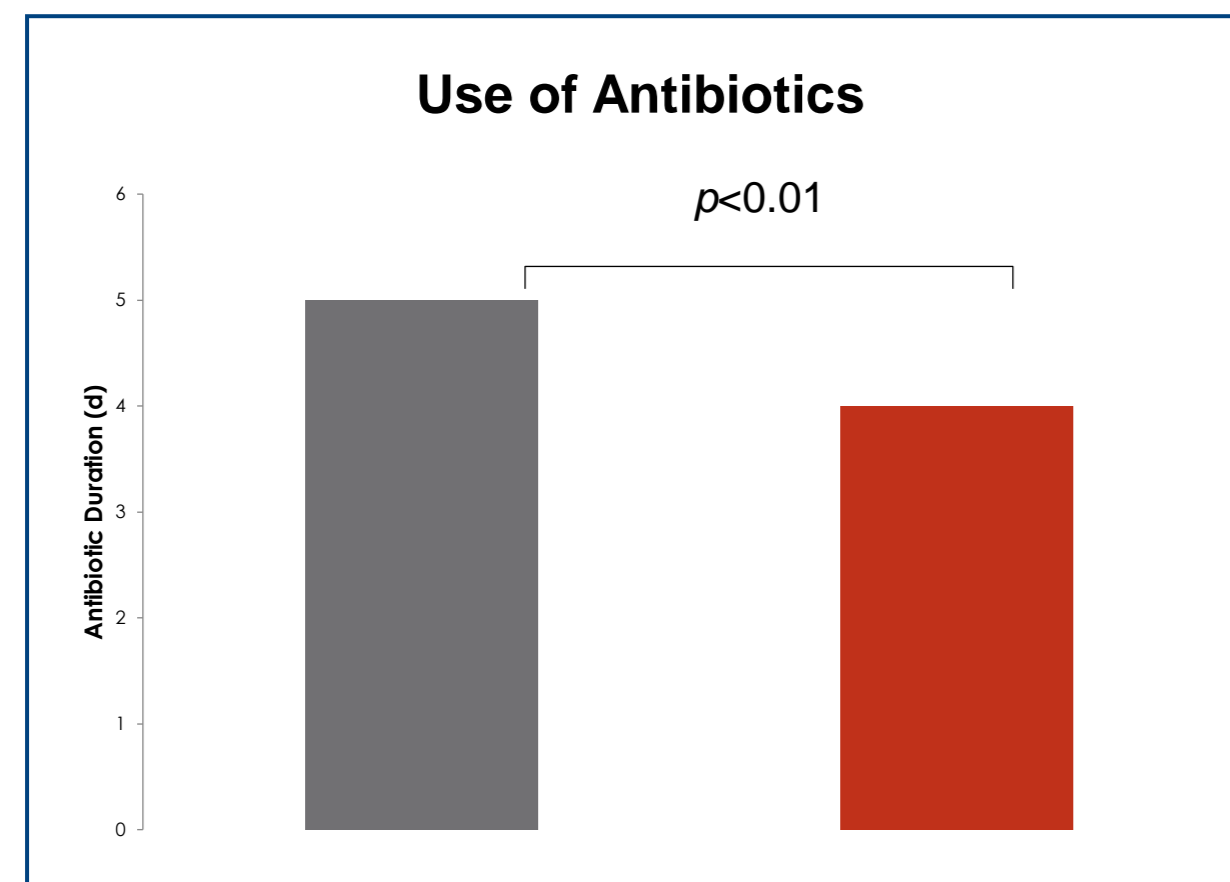


**Infectious disease syndromes have many potential symptoms and causes. Testing for only 2–3 may lead to many missed infections**

1. "Respiratory Pathogen Trends". Syndromic Trends, (2024) [www.syndromictrends.com](http://www.syndromictrends.com).

# Impact of a Respiratory Multiplex PCR Assay on Healthcare Resource Utilization for Pediatric Inpatients

A single-center, retrospective cohort study conducted at New York-Presbyterian Morgan Stanley Children's Hospital in 4,779 pediatric patients.



- Use of the RP multiplex PCR was associated with:
  - **Decreased use of antibiotics** (4 vs. 5 days) and chest radiographs (59% vs. 78%)
  - **Increased use of isolation measures** within first 2 hospitalization days (60.3% vs. 35.3%)
  - **Decreased turnaround time** (order entry to results being viewed by providers) from 2–5 days to approximately 3 hours
  - **Displacement of five older methods** for detecting respiratory pathogens (rapid antigen, Prodesse ProFlu PCR, Luminex PCR, DFA, and viral cultures)

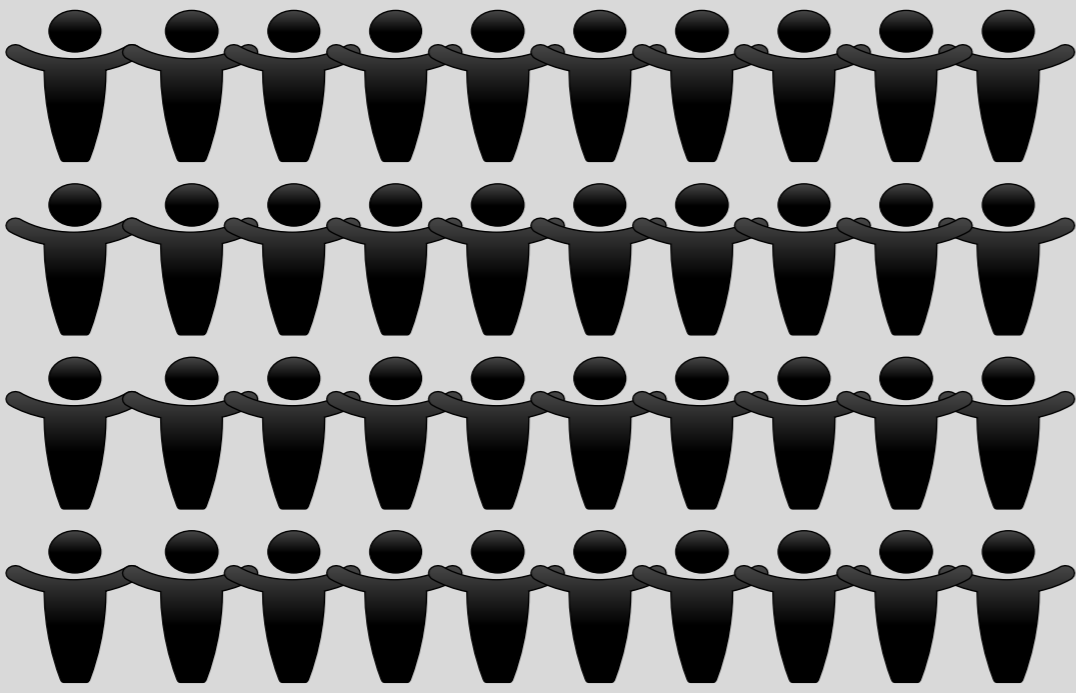
# SEPSIS MORTALITY AND COSTS

- Septicemia remains a **leading cause of death** in both adults and infants in the United States and is the leading cause of death in non-cardiac ICUs<sup>1,2</sup>
- Sepsis-related mortality is **>40%**<sup>2</sup>
- In the United States, there are **>1.1 million** cases of sepsis per year, at an annual cost of **\$24.3 billion**<sup>2</sup>
- **Populations at risk**<sup>2,3</sup>
  - Surgical patients
  - Patients in ICU
  - Immunocompromised patients
  - Elderly
  - Very young


1. Heron M. *Nat Vit Stat Rep.* 2012;60:1-95. 2. Moore LJ, Moore FA. *Surg Clin North Am.* 2012;92(6):1425-1443.  
2. Sepsis. Mayo Clinic. <http://www.mayoclinic.com/health/sepsis/DS01004>. Accessed July 17, 2013.  
3. Al Mohajer M, Darouiche RO. *Med Clin North Am.* 2012;96(6):1203-1223.

# UNMET NEEDS IN TREATING SEPSIS

A retrospective cohort analysis of 760 patients with sepsis<sup>1</sup>




31% received inappropriate antibiotic treatment



In 58%, therapy was delayed



42% had resistance to the antibiotic administered



**Patients who progress to septic shock have a 7.6% increase in mortality every hour while not on appropriate therapy<sup>2</sup>**

1. Shorr AF et al. *Crit Care Med.* 2011;39(1):46-51.  
2. Kumar A et al. *Crit Care Med.* 2006;34(6):1589-1596.

# TIME TO EFFECTIVE EMPIRIC THERAPY BY PATHOGEN

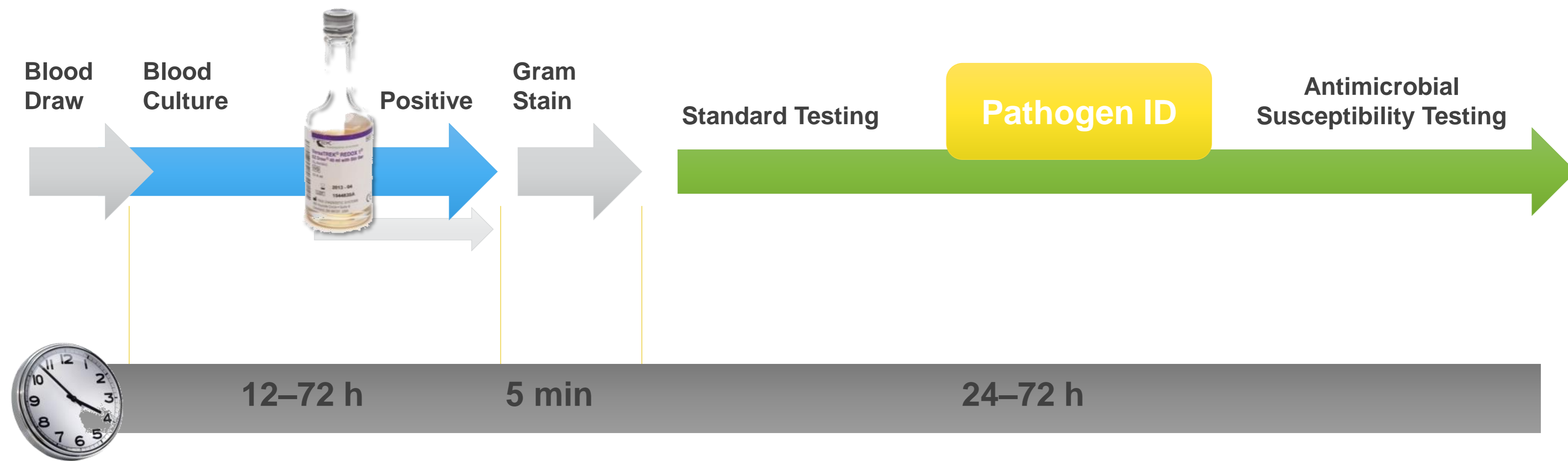
Washington University ICU, Jan 2008-Dec 2012

MRKT-PR1-0393-01

Pathogens	N = 1,058 (%)	Time to Appropriate Antibiotic Therapy (Hr)
<i>Acinetobacter</i> species	33 (3.1)	15.5 (4.0–58.0)
<i>Bacteroides</i> species	41 (3.9)	12.0 (3.0–42.0)
<i>Burkholderia cepacia</i>	7 (0.7)	3.0 (0.0–10.0)
<i>Candida albicans</i>	65 (6.1)	32.0 (10.0–40.0)
Other <i>Candida</i> species	79 (7.5)	30.0 (4.5–41.5)
<i>Enterobacter</i> species	44 (4.2)	4.5 (0.0–16.0)
<i>Enterococcus faecalis</i>	70 (6.6)	13.0 (0.0–26.0)
<i>Enterococcus faecium</i>	59 (5.6)	30.0 (20.0–46.0)
<i>Escherichia coli</i>	105 (9.9)	3.0 (0.0–9.0)
<i>Klebsiella</i> species	74 (7.0)	3.0 (0.0–13.0)
<i>Proteus</i> species	15 (1.4)	6.0 (0.0–17.0)
<i>Pseudomonas aeruginosa</i>	60 (5.7)	5.4 (0.0–19.3)
<i>Serratia marcescens</i>	20 (1.9)	12.0 (0.0–29.0)
<i>Staphylococcus aureus</i>	248 (23.4)	4.0 (0.0–12.5)
<i>Stenotrophomonas maltophilia</i>	10 (0.9)	28.0 (4.0–65.0)
<i>Streptococcus pneumoniae</i>	22 (2.1)	6.5 (0.8–9.3)
Other streptococcal species	41 (3.9)	4.0 (0.0–15.0)

**“30.2% of patients received an initial empiric antibiotic regimen that did not cover the causative pathogen.”**

# THE CURRENT STATE OF BLOOD CULTURE TESTING



**This delay can lead to inadequate or overly broad antimicrobial therapy and result in therapy-related complications, antimicrobial resistance, and increases in patient morbidity, mortality, and costs.**

**Rapid Multiplex PCR can provide pathogen identification in just over one hour from positive blood culture with higher sensitivity, specificity while detecting for multiple pathogens!**



# JUSTIFICATION FOR USE OF THE RAPID DIAGNOSTIC TESTS (RDTs) IN PATIENTS WITH BLOODSTREAM INFECTIONS (BSI's)

In a recent meta-analysis (31 studies, 5920 patients), RDTs:



**(↓) Decrease Time to Effective Therapy**

5.03 hours (95% CI, 8.60 to 1.45 hours)



**(↓) Reduce Risk of Mortality**

(OR 0.66, 95% CI 0.54 – 0.80)

Number needed to treat (NNT) = 20



**(↓) Lower Length of Stay**

2.48 days (3.90 to 1.06 days)

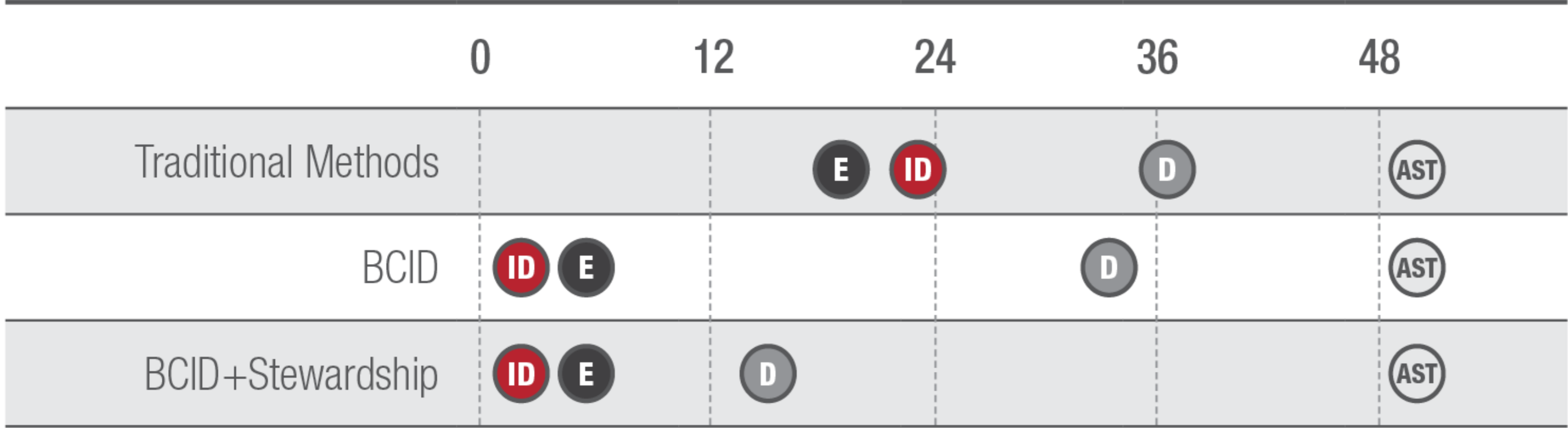
**RDT+ASP in BSI should be the Standard of Care to ensure improved management of antimicrobial therapy**

# IMPACT OF THE SYNDROMIC PCR PANEL WITH AN ANTIMICROBIAL STEWARDSHIP PROGRAM<sup>1</sup>

## Outcome Comparisons

Prospective randomized study arms

Timeline in hours post Gram stain results



- ID** Organism Identification
- E** Antimicrobial Escalation
- D** Antimicrobial De-Escalation
- AST** Antimicrobial Susceptibility Report

1. Banerjee, R, et al. Clinical Infectious Diseases. 2015;61(7):1071–80. Graphic used with permission of Oxford University Press.

# GASTROINTESTINAL INFECTIONS DATA

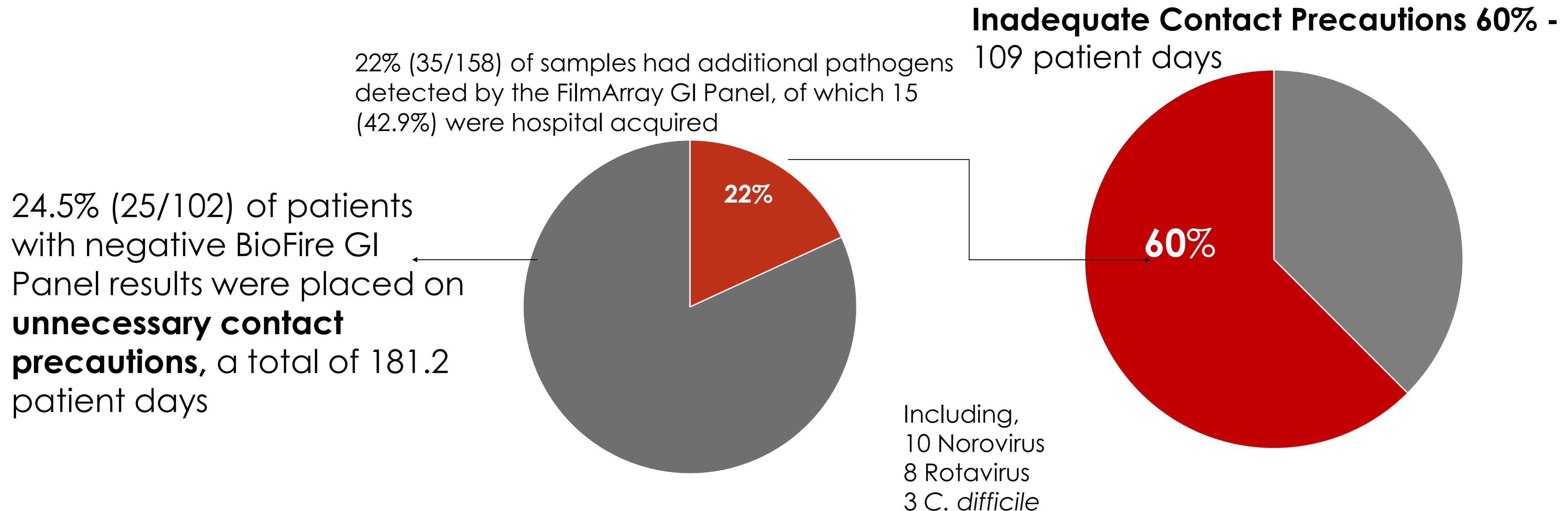
- **180–375 million episodes of acute gastroenteritis occur in the United States annually, resulting in:<sup>1,2,3,4</sup>**
  - 73 million physician consultations
  - 600,000–1.8 million hospitalizations
  - 3,100–6,000 deaths
  - \$6 billion spent on medical care and lost productivity
- **1.7 billion cases of diarrheal disease occur every year globally:<sup>2,5</sup>**
  - Each year diarrhea kills 760,000–2 million children under five years of age
  - Diarrhea is a leading cause of malnutrition in children under five years of age

1. Scallan E et al. *Emerg Infect Dis*. 2011;17:16-22.
2. World Gastroenterology Organisation Practice Guidelines: Acute Diarrhea. 2008.
3. [https://wwwnc.cdc.gov/eid/article/17/8/10-1533\\_article](https://wwwnc.cdc.gov/eid/article/17/8/10-1533_article)
4. Guerrant RL et al. *Clin Infect Dis*. 2001;32:331-351.
5. WHO: Diarrhoeal disease. Fact Sheet N°330. 2013.

# Use of the BioFire® FilmArray® Gastrointestinal (GI) Panel has the Potential to Improve Infection Control Practices

## Multiplex Gastrointestinal Pathogen Panels: Implications for Infection Control:<sup>1</sup>

- Samples previously characterized as *C. difficile* and/or rotavirus negative were tested with the BioFire GI Panel and infection control practices were evaluated:



# MENINGITIS/ENCEPHALITIS

- **Meningitis** is defined as inflammation of the meninges and is characterized by an increased number of white blood cells in the CSF<sup>1,2</sup>

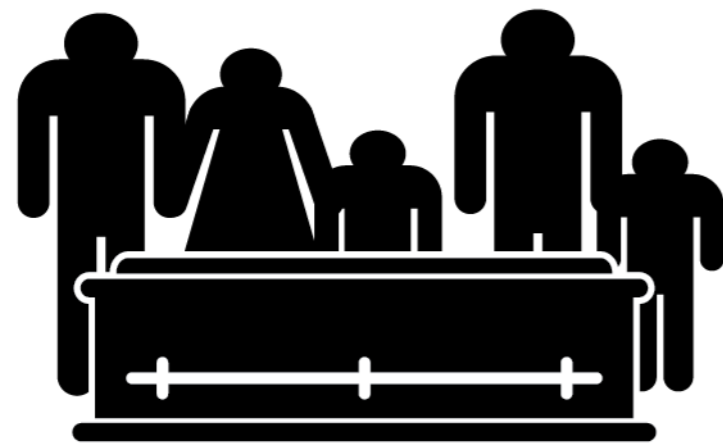


- **Encephalitis** is inflammation of the brain parenchyma that causes neurologic dysfunction<sup>3,4</sup>

Meningitis and encephalitis can be caused by a number of infectious agents, including bacteria, viruses, and fungi, as well as non-infectious causes, and often present with very similar symptoms<sup>5</sup>

# A FAST AND ACCURATE DIAGNOSIS CAN IMPROVE TREATMENT OUTCOMES

Benefits of a fast and accurate diagnosis of bacterial meningitis include:<sup>1,2</sup>



**Reduced mortality**  
and adverse  
outcomes<sup>1</sup>



**Specific therapy**  
administered in a  
timely manner<sup>2</sup>



**Infection control**  
precaution  
implementation and  
chemoprophylaxis to  
prevent spread of  
infection<sup>2</sup>



**Decreased costs**  
associated with  
inappropriate  
therapies and adverse  
outcomes<sup>2</sup>

**For every hour delay in antibiotic therapy, the odds for adverse outcomes of bacterial meningitis may increase by up to 30%<sup>3</sup>**

1. Bahr NC et al. *Biomark Med.* 2014;9:1085-1103.  
2. Putz K et al. *Prim Care Clin Office Pract.* 2013;40:707-726.  
3. Køster-Rasmussen R et al. *J Infect.* 2008;57:449-454.

# TO SUMMARIZE...

- Rapid multiplex PCR tests are available for a variety of infections
- New panels are being developed to cover an even broader range of infections
- Innovative rapid multiplex PCR tests are:
  - Saving lives, decreasing morbidity, and improving patient satisfaction
  - Helping to decrease antimicrobial resistance
  - Improving infection control
  - Decreasing hospital length of stay