Alere™ Knowing now matters.™

Importance of Evidence Based Medicine in POCT

Agenda

1. Influenza
2. Pneumonia
3. *C. difficile*
4. HIV

Infectious Disease in the US

1970: William Stewart, the Surgeon General of the United States declared the U.S. was “ready to close the book on infectious disease as a major health threat”; modern antibiotics, vaccination, and sanitation methods had done the job.

1995: Infectious disease had again become the third leading cause of death, and its incidence is still growing!

Advantages of Rapid Testing for Infectious Diseases

Faster directed therapy to reduce:

- **antibiotic resistance**
- **hospital length-of-stay**

Less adverse consequences

Teachable moment

Reduced length-of-stay in Emergency Department

Timely application of **appropriate infection control** procedures

Inpatient Settings

One in every three patients will receive two or more antibiotics in the course of their hospital stay

Of the patients receiving antibiotics, three out of every four will receive unnecessary or redundant therapy, resulting in excessive use of antibiotics

CDC – Get Smart Campaign

Outpatient Settings

Each year, tens of millions of antibiotics are prescribed unnecessarily for upper viral respiratory infections

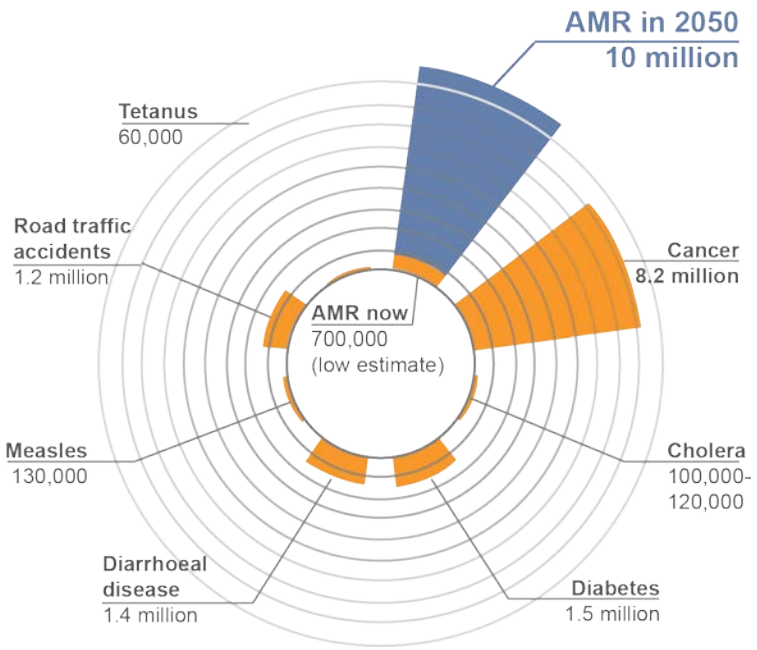
Antibiotic use in primary care is associated with antibiotic resistance at the individual patient level

The presence of antibiotic-resistant bacteria is greatest during the month following a patient's antibiotics use and may persist for up to 1 year

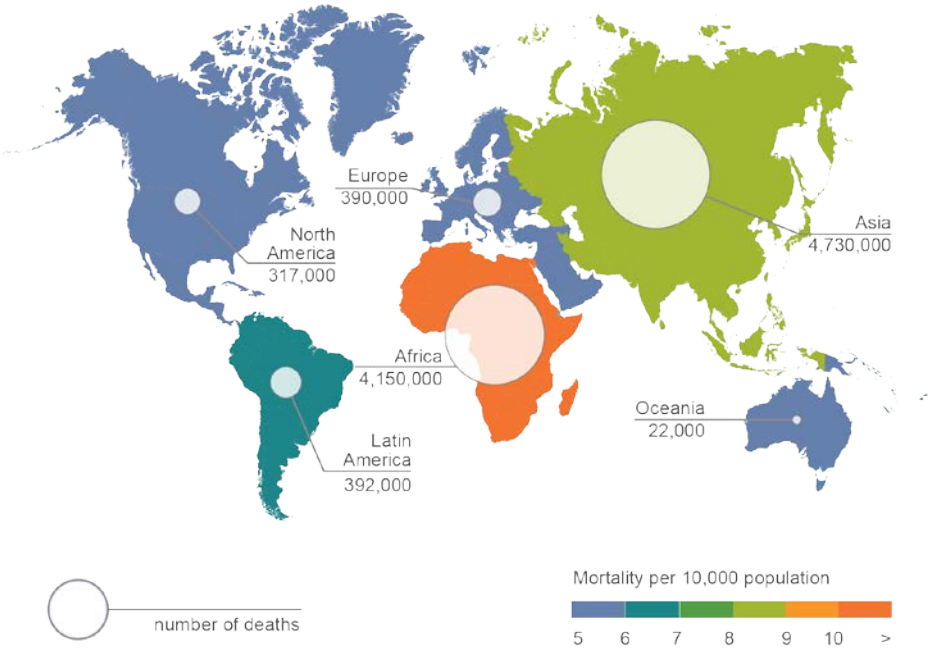
CDC – Get Smart Campaign

AMR: If We Don't Take Action Now

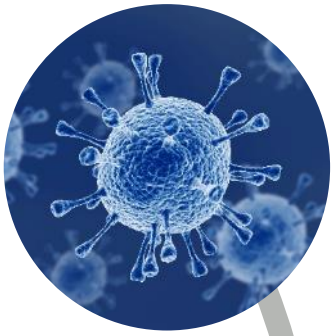
Deaths attributable to AMR every year
compared to other major causes of death



Deaths attributable to AMR every year
by 2050



The Challenge with Respiratory Patients



Influenza?

Common cold?

Pneumonia?

What are the issues of respiratory disease?

The symptoms of respiratory diseases are vague

- Pneumonia symptoms
  - Cough
  - Fever
  - Chills
  - Difficulty breathing
- Influenza
  - Cough
  - Fever
  - Chills
  - Malaise

Treatment is different

- Bacteria
  - Broad spectrum antibiotic
  - Narrow spectrum antibiotic
- Influenza
  - Antiviral
  - Treat symptoms only

Complications of mistreatment

- Mistreatment of bacterial etiology
  - May increase morbidity/ mortality
  - May have longer hospital stay
  - May get *C. difficile*
- Mistreatment of influenza
  - May have increased resistance and *C. difficile*
  - Antiviral may reduce symptoms

Knowing now matters™ in Influenza testing

Spread of Influenza

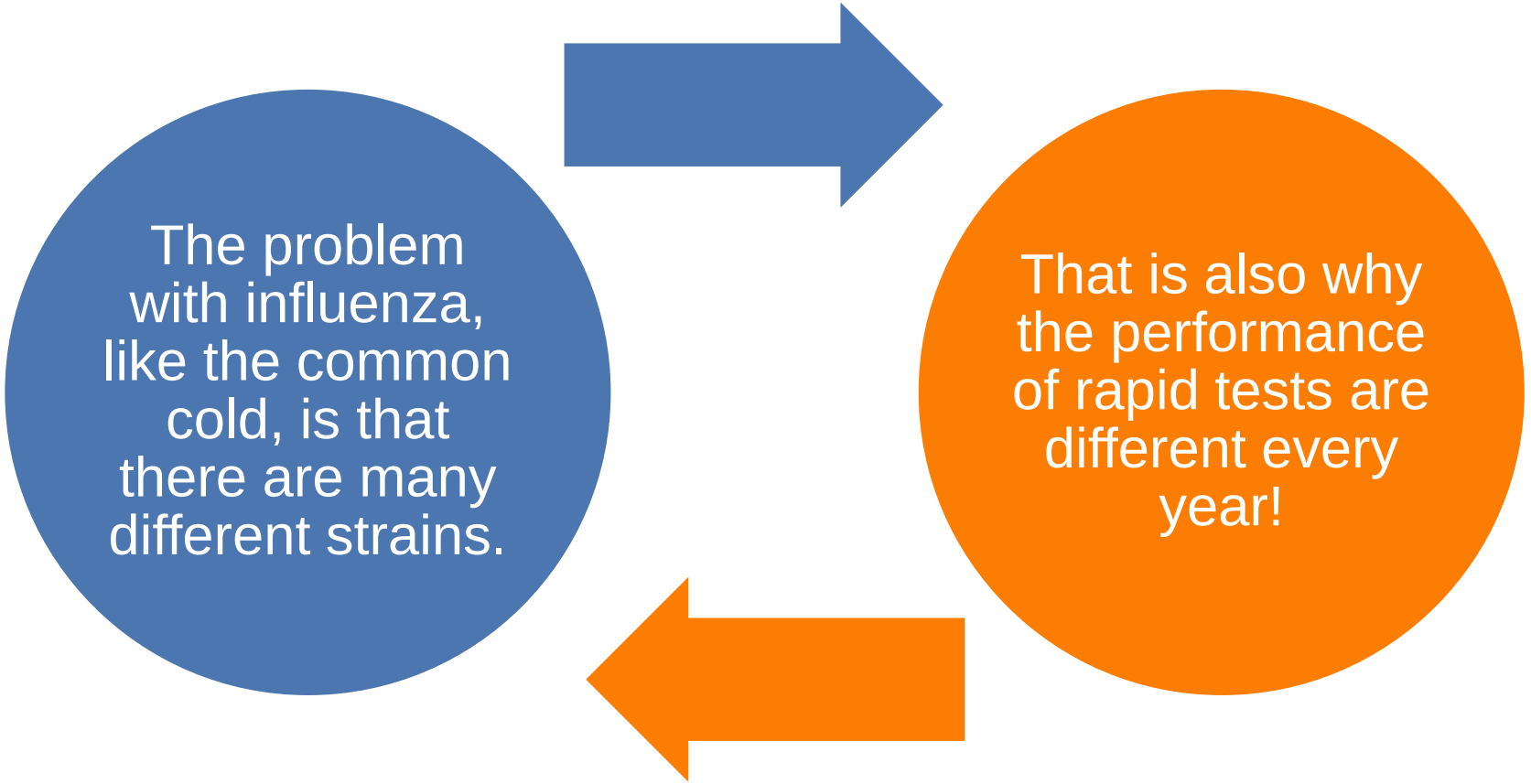
Flu is spread person-to-person through coughing or sneezing.

- Quick incubation of around 2 days

Hands can spread influenza if the person then touches their nose.

Healthy adults can infect others one day BEFORE symptoms develop and up to 5-7 days after.

Aren’t you supposed to build immunity to influenza?



Influenza Sample Collection

Appropriate specimens

- Nasal wash/aspirate, nasopharyngeal swab, or nasal swab
- Throat swabs have dramatically reduced sensitivity

Samples should be collected within first 24 to 48 hours of symptoms since that is when viral titers are highest and antiviral therapy is effective

Testing can be done immediately with rapids or sample placed in transport media

- Infectivity is maintained up to 5 days when stored @ 4-8°C
- If the sample cannot be evaluated in this time period, the sample should be frozen @ -70°C.

Influenza Testing with Rapid Direct Antigen Tests

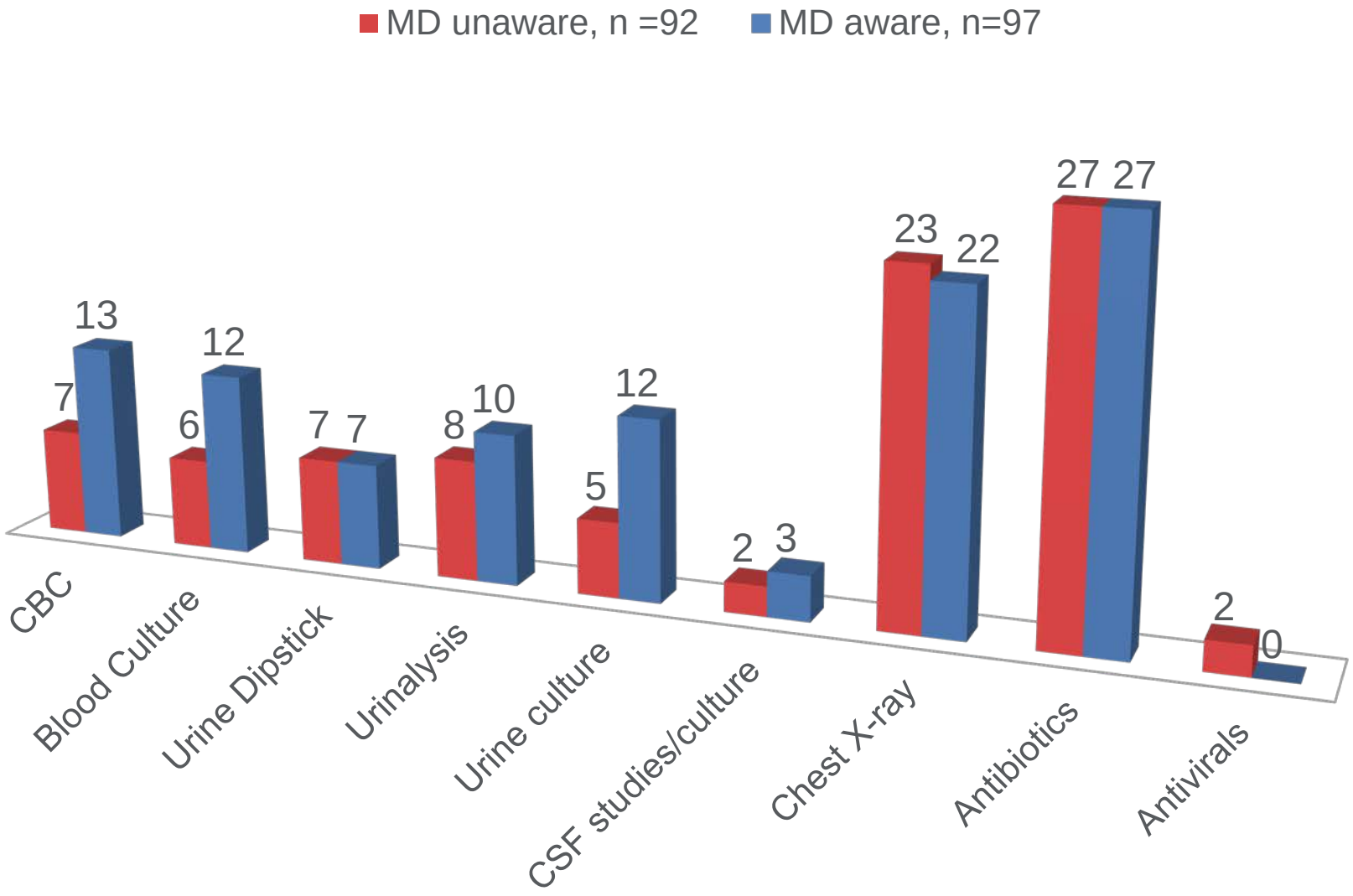
PROS

- Economical
- CLIA-waived
- High specificity so no confirmatory testing for positive results
- Easy to batch

CON

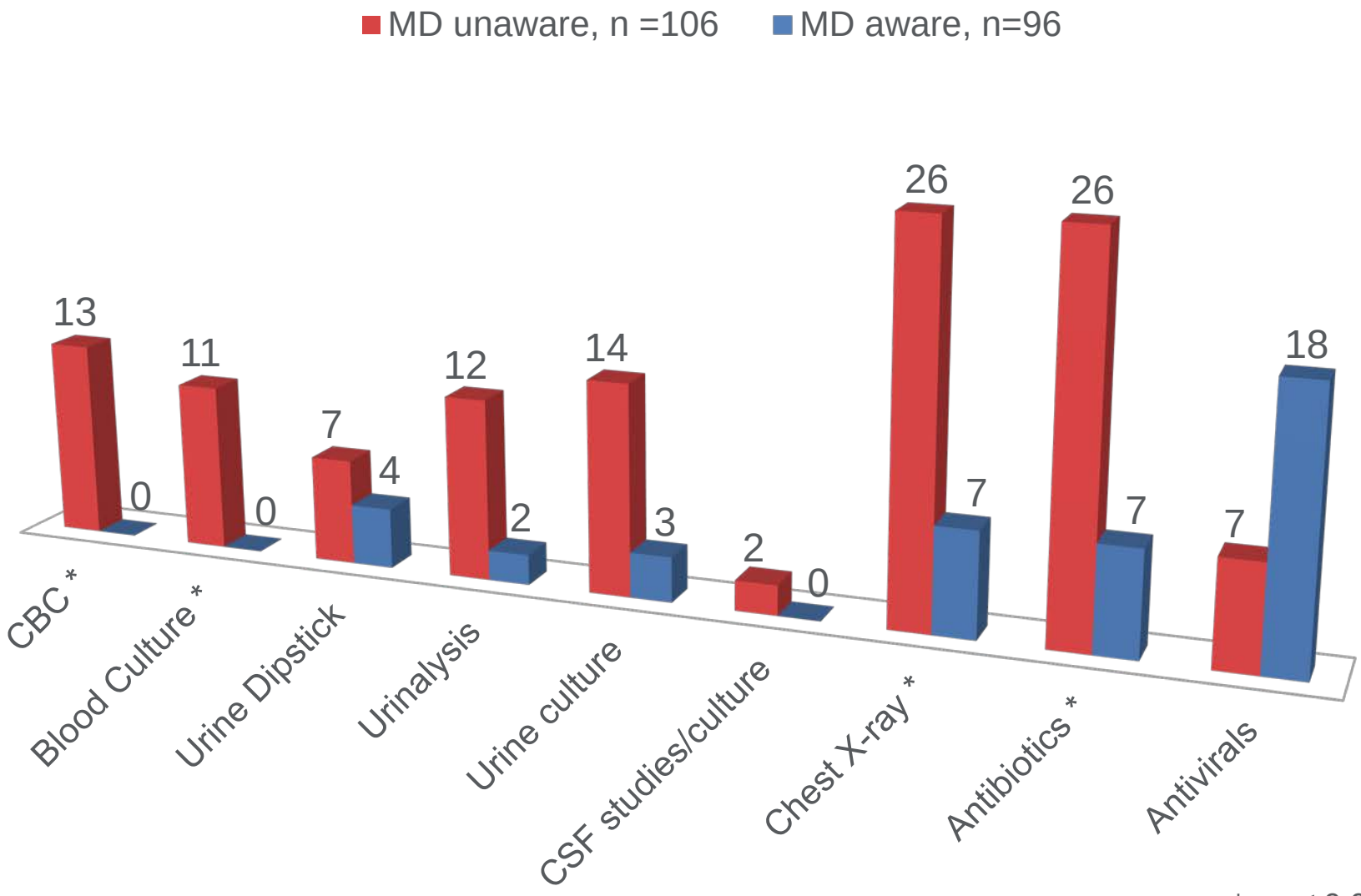
Variable sensitivity so negatives should be backed up by molecular or culture testing

Results – Flu Negative



Bonner, *et al,* Pediatrics (2003) **112:**363-367

Results – Flu Positive

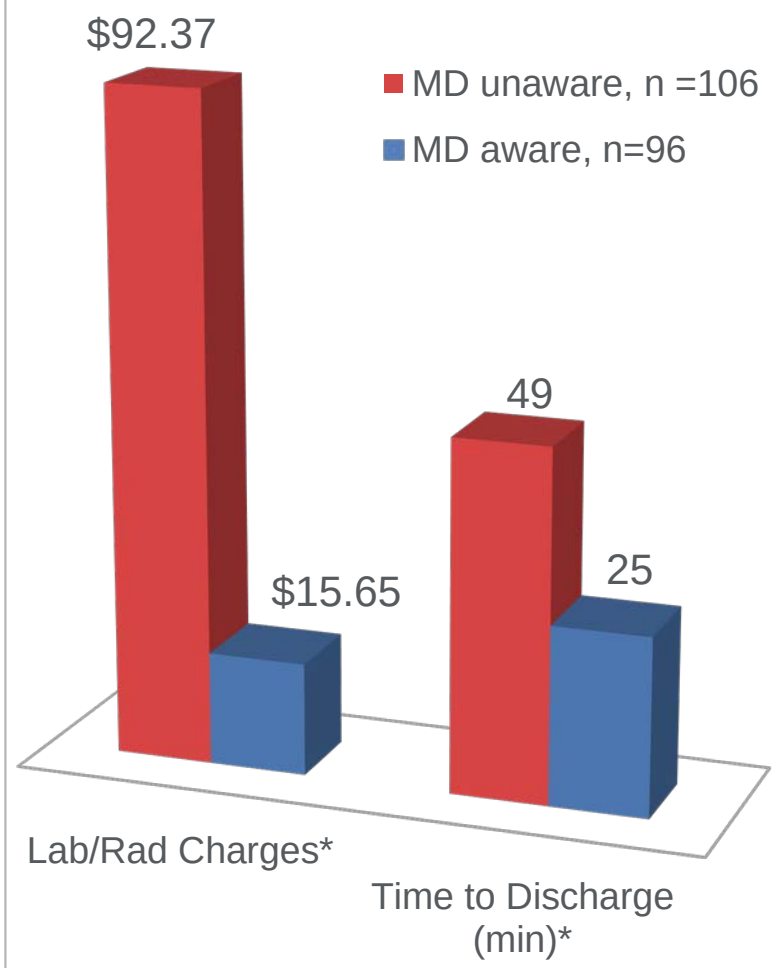


* - p ≤ 0.001

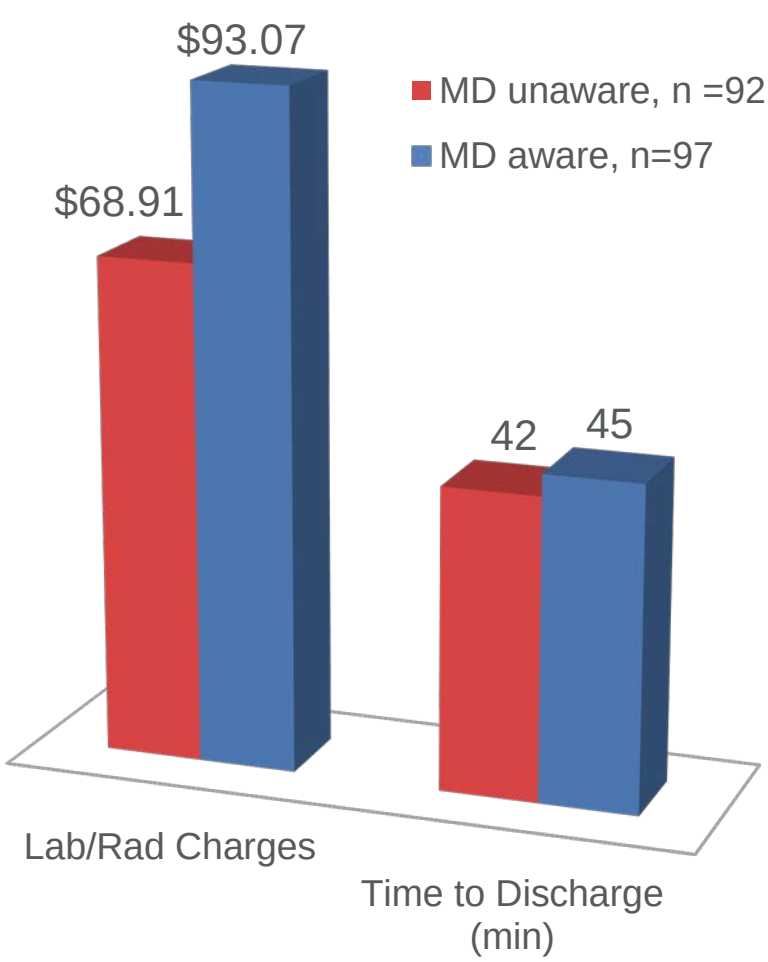
Bonner, *et al,* Pediatrics (2003) **112:**363-367

Key Operational Metrics

FLU POSITIVE



FLU NEGATIVE



* p ≤ 0.001

Bonner, et al, Pediatrics (2003) 112:363-367

Why molecular?

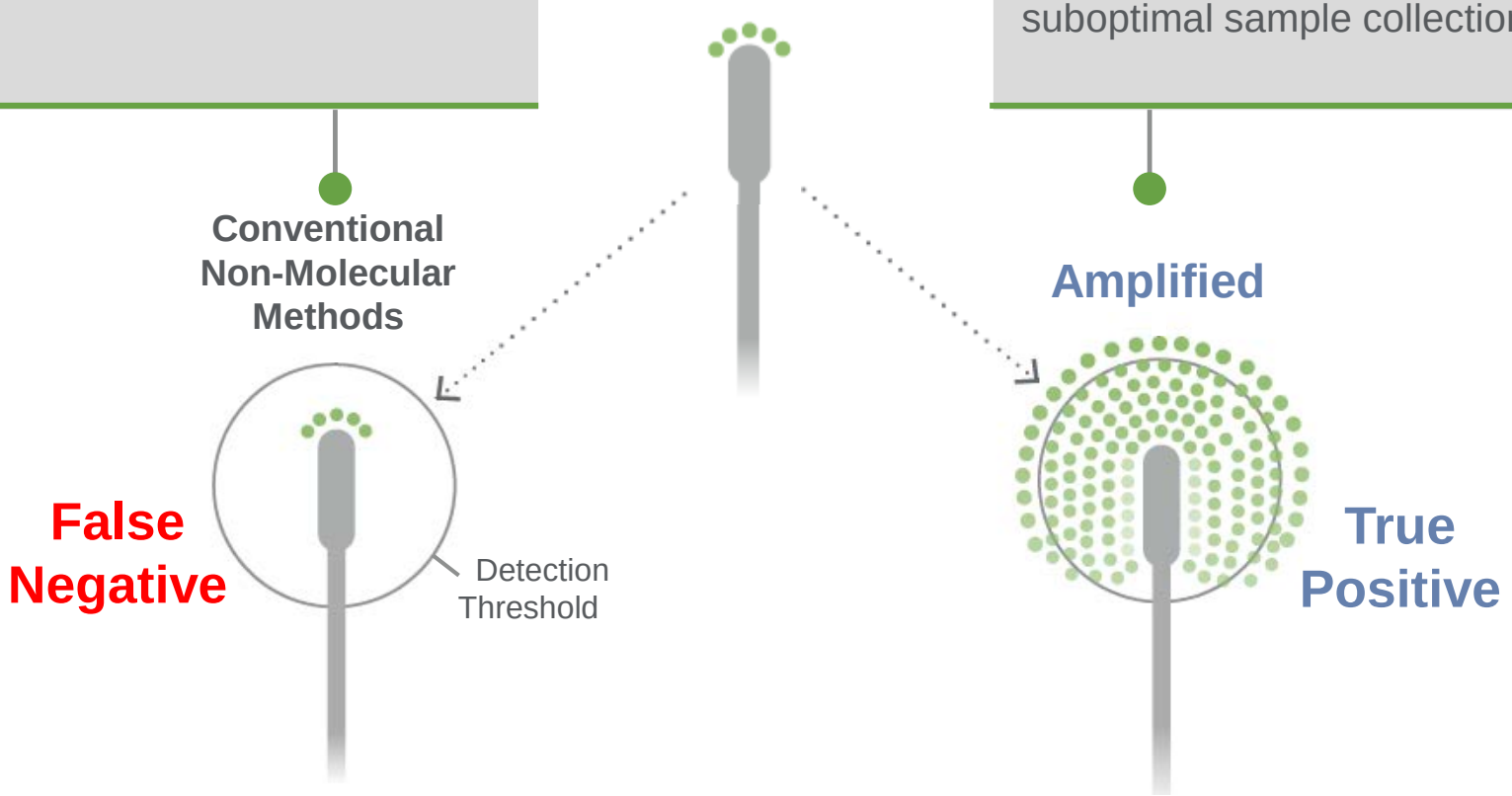
The power of sample amplification

Conventional **non-molecular** methods can have suboptimal limits of detection.

Samples with low viral or bacterial load could result in a false negative.

With **molecular**, even a few hundred infectious particles can be amplified billions of times!

Amplification increases likelihood of detection, and may compensate for suboptimal sample collection.



Why Test?

Knowledge of a Positive Test Has Been Shown to:

- Limit unnecessary antibiotic use
- Limit unnecessary diagnostic procedures
- Increase the appropriate use of antivirals

How many people have had RSV in their lives?

THE POWER OF now

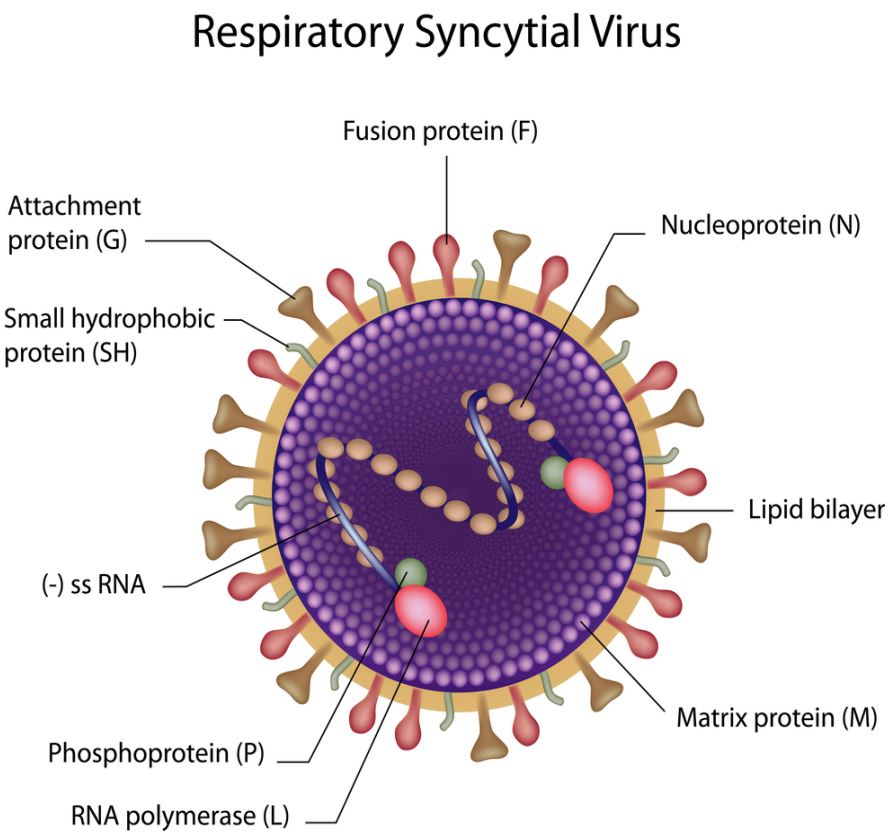
Almost ALL people in this room

had RSV by the age of 2!

Alere™

What is RSV?[1]

RSV is a single-stranded RNA virus of the family paramyxoviridae, which includes common respiratory viruses such as those causing measles and mumps



RSV is divided into 2 subtypes: A and B. More severe clinical illnesses involve subtype A strains, which tend to predominate in most outbreaks.

RSV—A significant global pathogen[2]

The **single most important cause of severe respiratory illness** in infants/young children

RSV disease burden is estimated at **64M cases and 160,000 deaths** every year.

RSV is **the most frequent cause of hospitalization** of infants and young children in industrialized countries.

RSV believed to represent a **similar burden to Flu** in >64yrs

RSV-related illness represents a **significant healthcare burden** in the US

US Burden of RSV

In the US, the **hospitalization rate is three times** higher than that from influenza in children <5 years old [3]

Over **2 million children 5 years old and younger** receive care for RSV infection in US each year (Extrapolated data[4])[3]:

57,500 require hospitalization [3]

518,000 receive care in the ED [3]

Over 1.5 million children are treated each year in practices.[3]

RSV-associated costs based on US Medicaid databases for full-term infants:[3]

$11,000 for each RSV hospitalization[3]

>$3,000 for RSV-related outpatient visit [3]

Total US Healthcare believed to be **~$2.6bN per year** for RSV associated infections[5]

Prevalence / Incidence

RSV accounts for
1 in every 13 visits to pediatrician[3]

177,000 hospitalizations & 14,000 deaths
per year in over 65[6]

126,000 infants hospitalized every year with RSV[7]

20% are premature infants

Most common cause of pneumonia in < 1 year old

By age 3, virtually every child has had RSV!

Infects 50% infants in first year of life

400 children each year[7]
under the age of 1 die due to RSV

RSV around the Country[6]

Source: http: illance.html

How is RSV spread

People infected with RSV are usually contagious for 3 to 8 days. However, in the young and elderly with weakened immune systems, RSV can be contagious for up to 4 weeks. RSV can be spread by[8]:

- Infected person coughs or sneezes into the air, creating virus-containing droplets that can linger briefly in the air.
- Direct and indirect contact with nasal or oral secretions from infected people and then rub their eyes or nose.
- RSV can survive on hard surfaces such as tables and crib rails for many hours. However, RSV typically lives on soft surfaces such as tissues and hands for shorter amounts of time.

RSV is Contagious![9]

- RSV is one of the most contagious human pathogens
- Comparable to measles virus.
- In prospective studies, the natural introduction of RSV into a day-care setting resulted in infection of more than 90% of infants and children
- Children pass RSV onto adults and vice versa
- RSV is readily introduced and spreads with ease in hospitals, nursing homes, families, and other close-contact settings

RSV Symptoms

RSV disease includes a wide array of symptoms, including[2]:

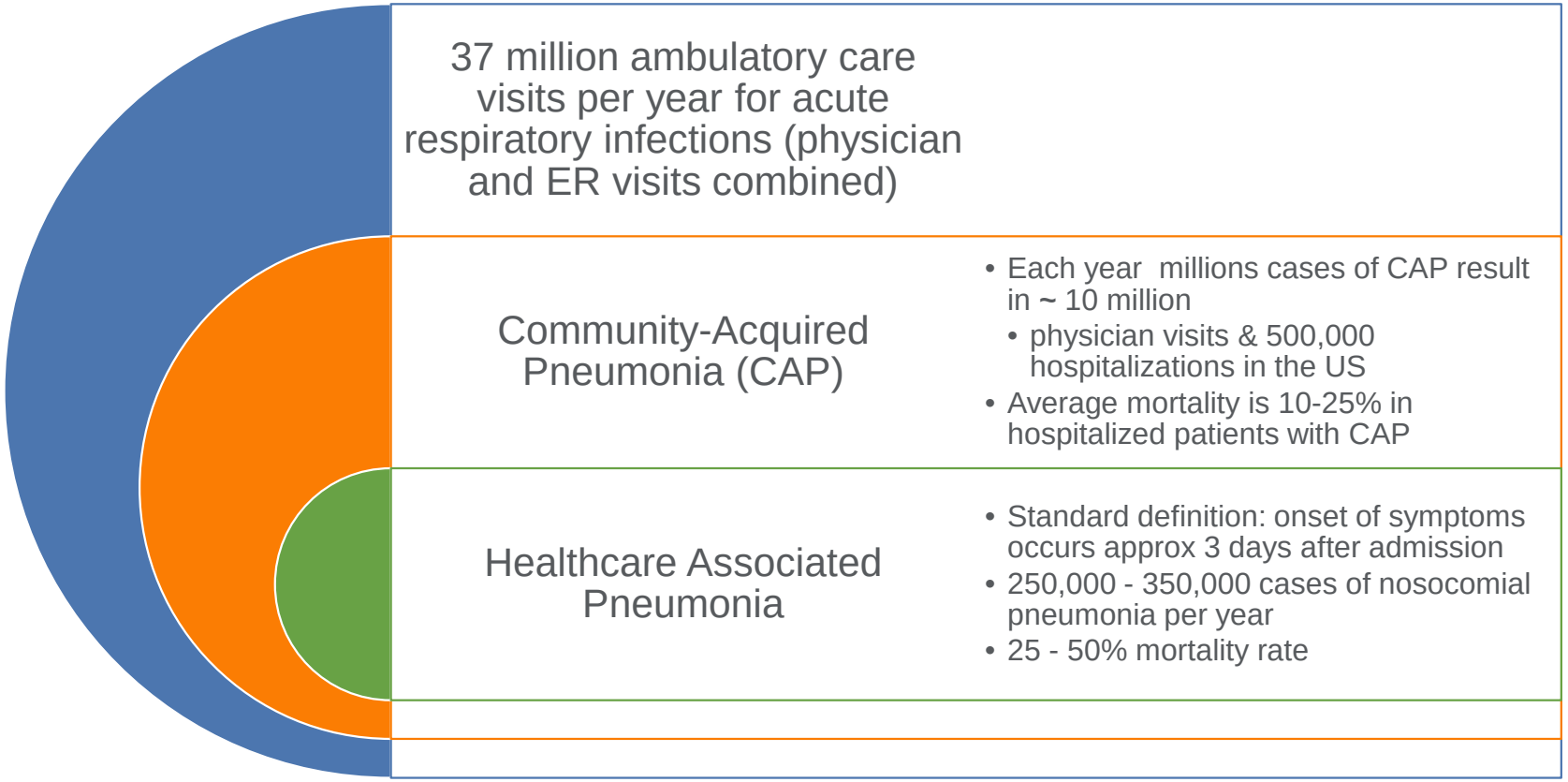
Rhinitis	Croup	Pneumonia	Bronchiolitis
Inflammation of mucous membranes inside the nose	Inflammation of larynx & trachea causing breathing problems	Inflammation of the lungs	Inflammation of the bronchioles

However, these symptoms are not specific and can be linked to other respiratory illnesses therefore making rapid and accurate diagnosis of RSV essential for the treatment and management of patients.

It may also cause other diseases like otitis media (ear aches) that RSV tests aren't currently meant to test for.

Knowing now matters™ in Pneumonia

Current Number of Pneumonia Cases (US)



Joint Infectious Disease Society of America and American Thoracic Society Guidelines

Directed, rather than broad spectrum therapy has significant advantages and can:

Lead to more effective antibiotics for the pathogen

Reduce morbidity/ mortality and hospital length of stay

Reduce antibiotic resistant micro-organisms

Mandell. Clinical Infectious Diseases (2007) **44**:S27–72

Etiological Agents

Newborns (0 to 30 days)

- Group B *Streptococcus*, *Lysteria monocytogenes*, or Gram negative rods are common
- RSV in premature babies

Infants and toddlers

- 90% of lower respiratory tract infections are viral with the most common being RSV, Influenza A&B, and parainfluenza. Bacterial infections are rare, but could be *S. pneumoniae*, Hib, or *S. aureus*.

Etiological Agents

Outpatient

- *S. pneumoniae*, *H. influenzae*, *M. pneumoniae*, *C. pneumoniae*, and respiratory viruses

Inpatient (non-ICU)

- With the above agents, add *L. pneumophila*

Inpatient (ICU)

- *S. pneumoniae*, *S. aureus*, *L. pneumophila*, Gram-negative bacteria, and *H. influenzae*

The Future of Pneumococcal Pneumonia

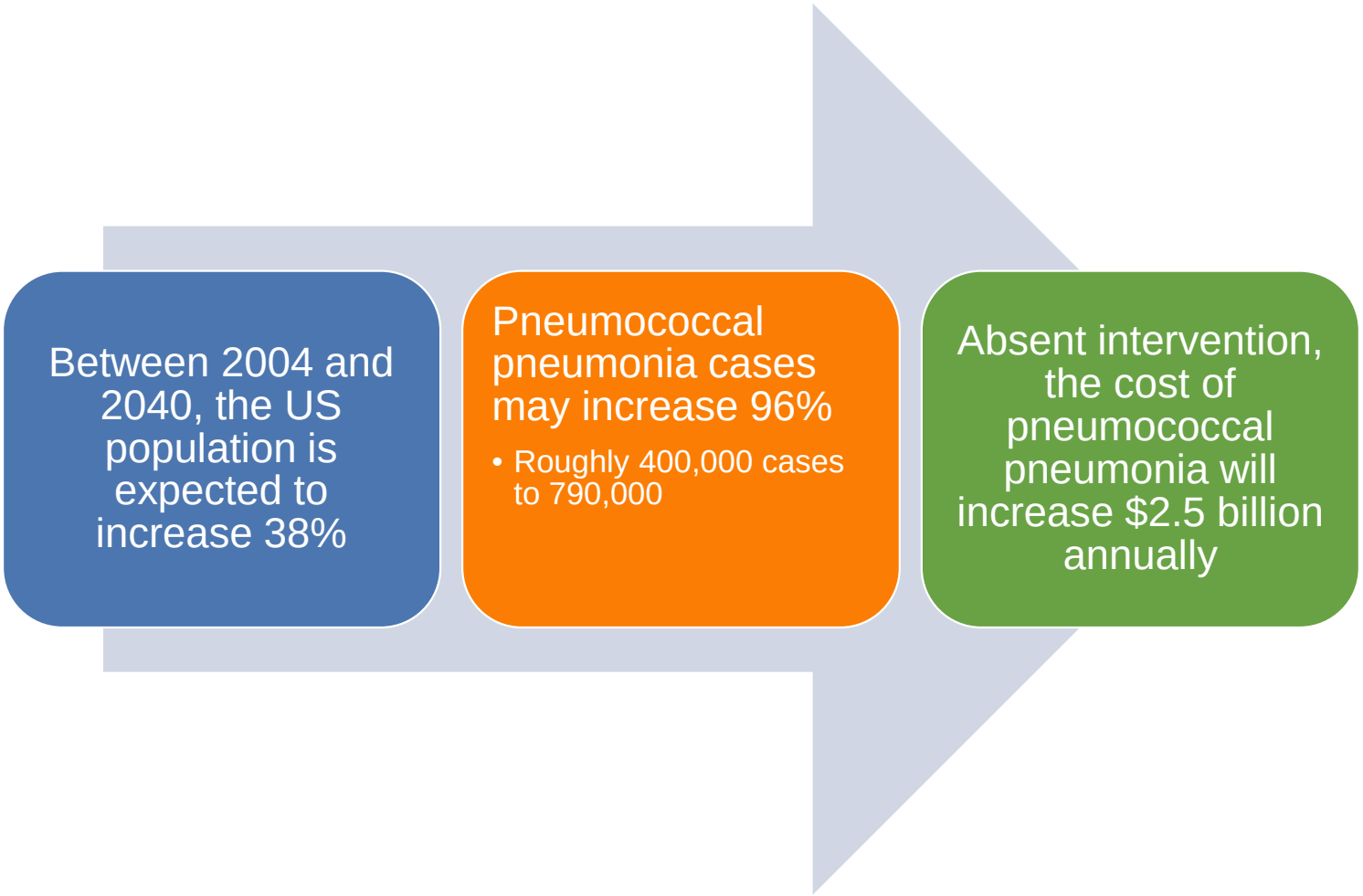


Table 5. Clinical indications for more extensive diagnostic testing.

Indication	Blood culture	Sputum culture	*Legionella* UAT	Pneumococcal UAT	Other
Intensive care unit admission	X	X	X	X	X[a]
Failure of outpatient antibiotic therapy		X	X	X	
Cavitary infiltrates	X	X			X[b]
Leukopenia	X			X	
Active alcohol abuse	X	X	X	X	
Chronic severe liver disease	X			X	
Severe obstructive/structural lung disease		X			
Asplenia (anatomic or functional)	X			X	
Recent travel (within past 2 weeks)			X		X[c]
Positive *Legionella* UAT result		X[d]	NA		
Positive pneumococcal UAT result	X	X		NA	
Pleural effusion	X	X	X	X	X[e]

NOTE. NA, not applicable; UAT, urinary antigen test.

[a] Endotracheal aspirate if intubated, possibly bronchoscopy or nonbronchoscopic bronchoalveolar lavage.
[b] Fungal and tuberculosis cultures.
[c] See table 6 for details.
[d] Special media for *Legionella*.
[e] Thoracentesis and pleural fluid cultures.

Economic Impact of Reduced Length of Stay: *Legionella* and *S. pneumoniae* Urinary Antigen

In 2009 dollars, **eliminating a day during the course of a CAP admission** is potentially worth $2,273 to $2,373 per patient

Decreasing total cost of a community-acquired pneumonia (CAP) admission may best be achieved with **improving processes and treatments**.

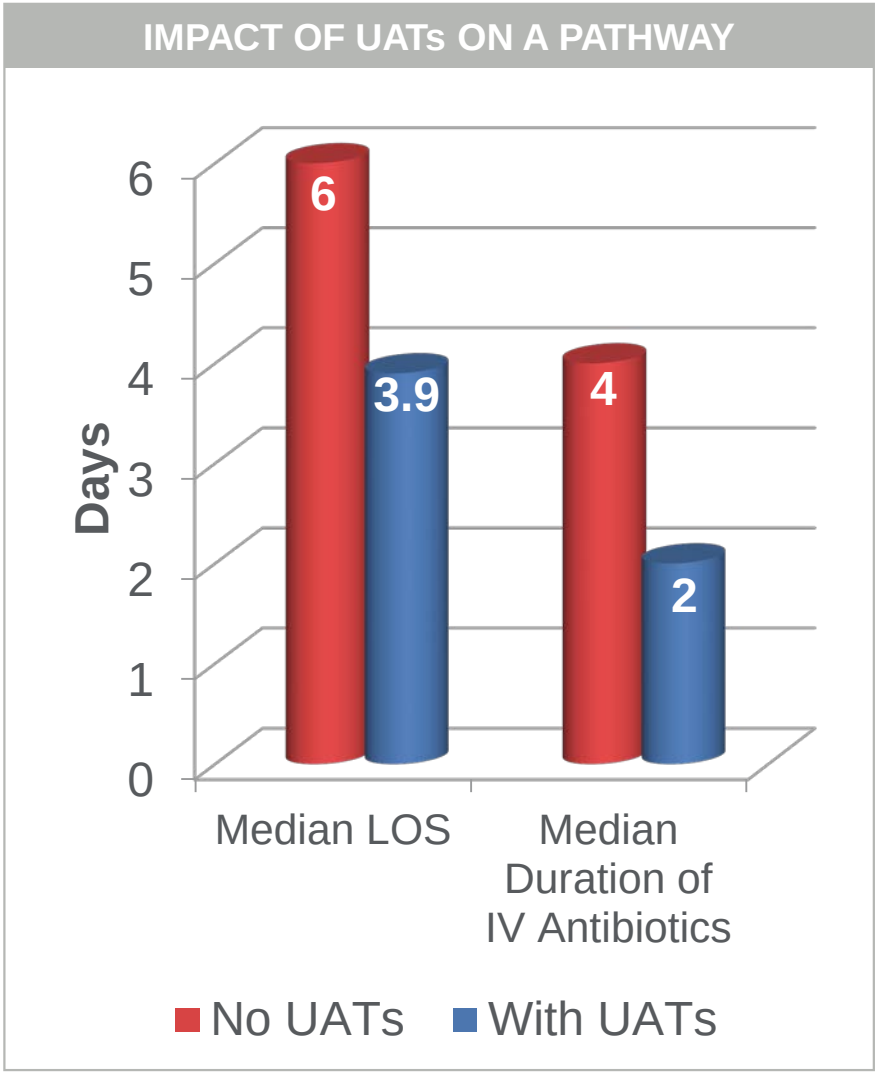
In this study, “1-day reduced” is the result of **efficiencies or improved outcomes** throughout the hospitalization

Kozma. J. Medical Economics. (2010) **13**:719-727.

Operational Impact

Using *Legionella* and *S. pneumoniae* as part of the pathway for community-acquired pneumonia led to. . .

- Fewer adverse drug reactions
- No reduction in hospital readmission, case fatality, or patient satisfaction



Carratalà. Arch Intern Med. (2012) **172**:922-928

Clinical Usefulness of *S. pneumoniae* Urinary Antigen Test

The study evaluated 474 episodes of community-acquired pneumonia

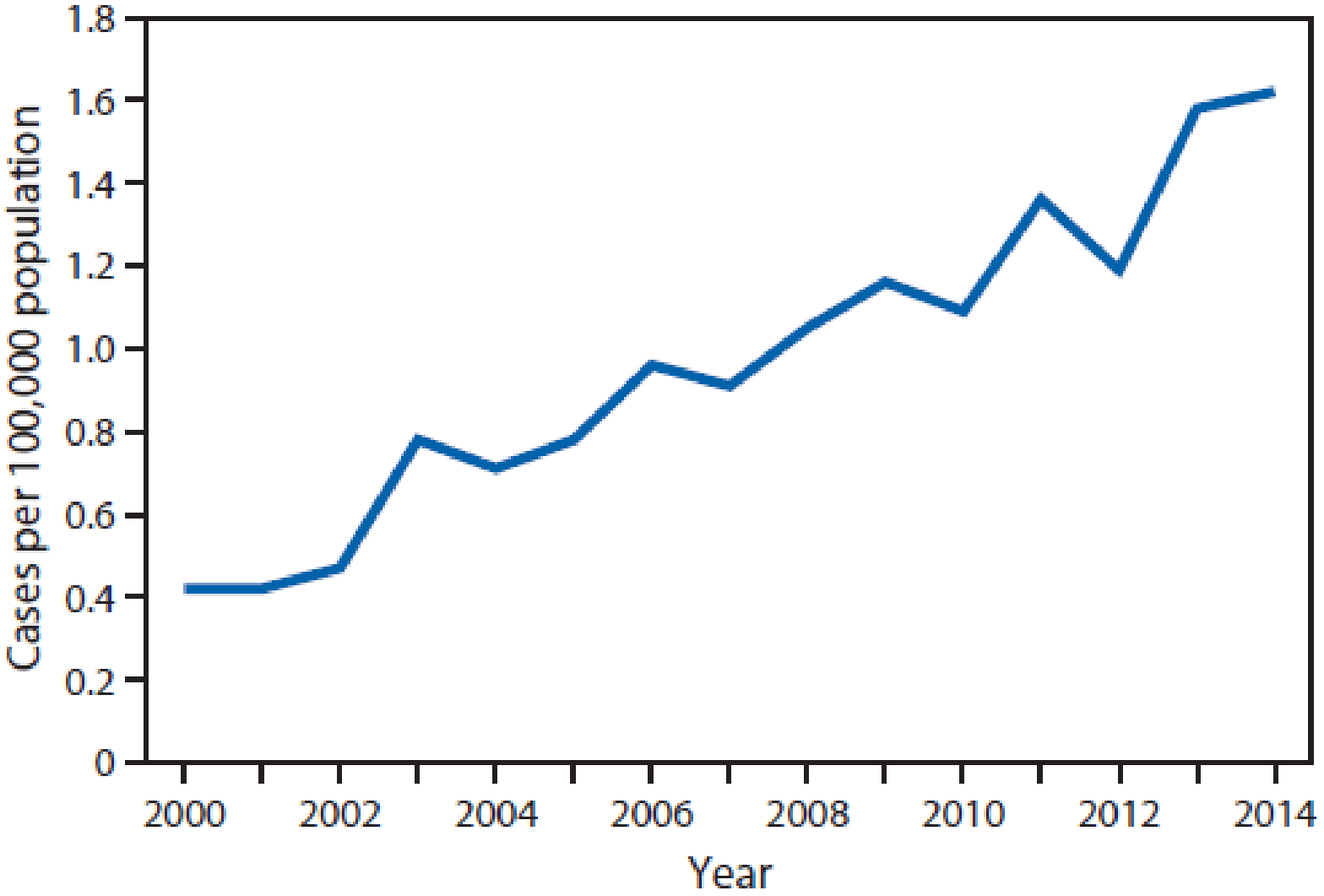
- *Streptococcus pneumoniae* was the causative pathogen in 171 cases (36.1%).
- It was detected exclusively by urinary antigen test in 75 cases (43.8%).

Resulting in…

- Narrowing the broad spectrum to IV penicillin or ampicillin or switch to oral amoxicillin.
- removing macrolide in patients empirically treated with ß-lactam and macrolide combination or partial reduction of broad spectrum.

Sorde. Arch Intern Med (2011) **171**:166-72.

CDC Reported cases of legionellosis per 100,000 population, by year — United States, 2000–2014



http://www.cdc.gov/mmwr/volumes/65/wr/mm6522e1.htm?s_cid=mm6522e1_e#

CDC Reported cases of legionellosis per 100,000 population, by year — United States, 2000–2014

Legionellosis cases are increasing in the US and the mortality is “substantial.”

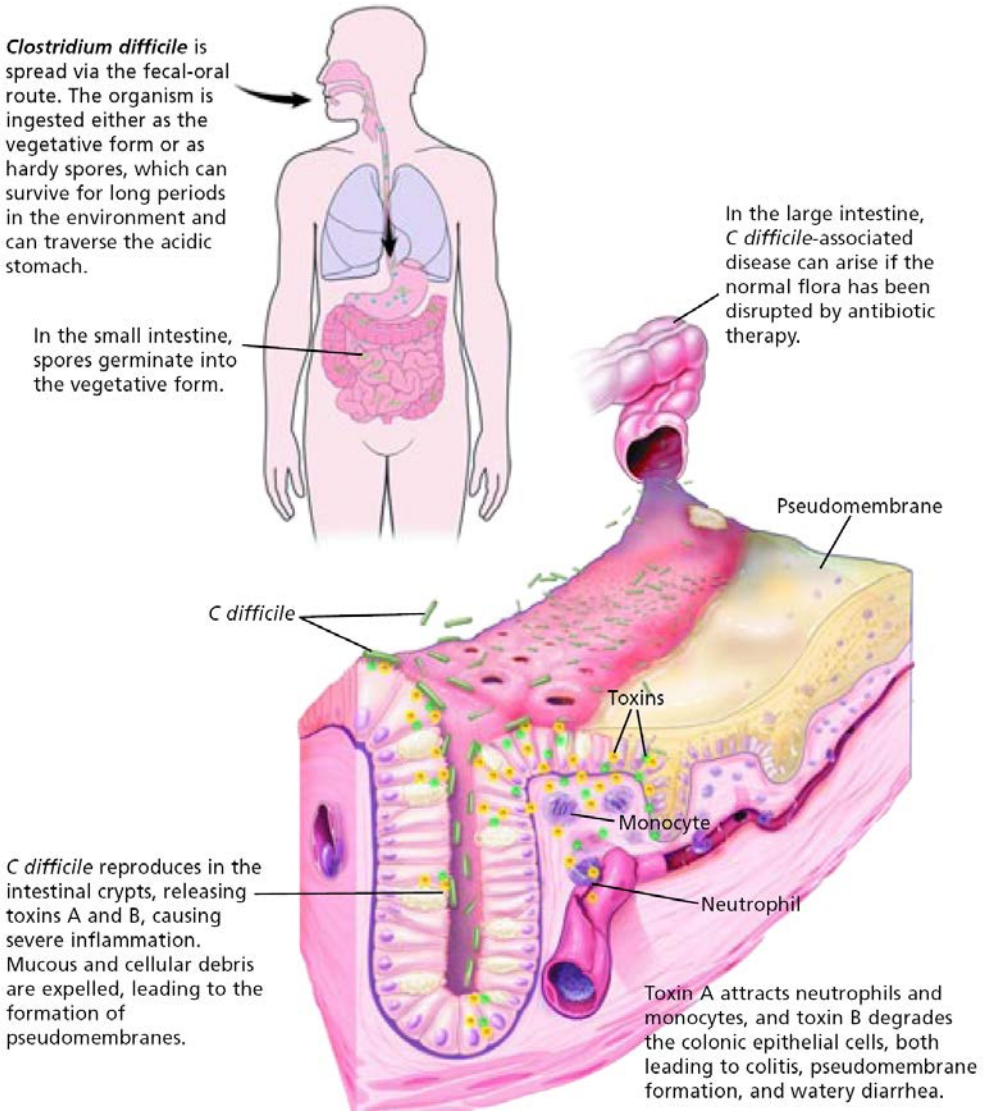
- Cases have risen dramatically over a 14 year period
- Seeing about a 10% mortality
- 4% were outbreak associated

Significant gaps in water treatment could be seen in many outbreaks

- Especially if low levels of chlorine or other disinfectants along with warmer temperatures

Knowing now matters™ in *Clostridium difficile*

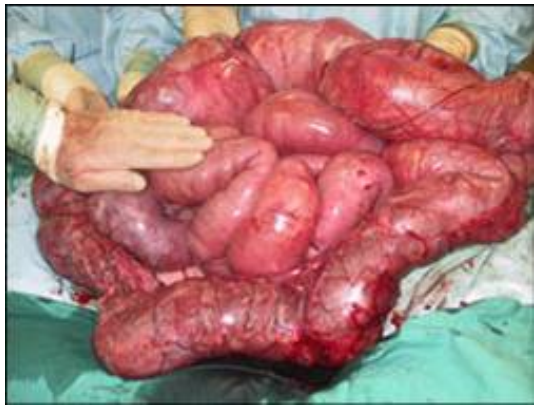
Pathogenesis of CDAD



Antibiotic-Associated Diarrhea: Life's a Beach with *C. difficile*

Clinical Manifestations of CDAD

Increasing disease severity

Asymptomatic Colonisation	Diarrheal illness	PMC Toxic megacolon
No Symptoms	• **Diarrhea- Mild to severe (explosive)** • **Abdominal Pain** • **Fever**	

What are the issues with *Clostridium difficile*?

Diarrhea is a common symptom of gastrointestinal diseases

Many patients are carriers of *C. difficile*

- Don’t need treatment but may be misdiagnosed and mistakenly treated

Overuse of antibiotics can trigger *C. difficile* infections by wiping out the natural gut flora

There is no single answer that identifies both carriers and patients with active disease

- Toxin tests won’t detect carriers
- Molecular tests can’t differentiate carriers from active infections

Consequences of Not Distinguishing Between a *C. difficile* Carrier and True Disease

May be **pulling patient off of most effective antibiotic** for the initial infection.

Treatment for *C. difficile* will **deplete the normal gut microflora**, potentially making the person more susceptible to getting a *C. difficile* infection.

Higher reportable *C. difficile* rates

Unnecessary isolation

Sample Collection & Testing

No need to collect from asymptomatic people

- Babies can have high carriage rates
- Usually 3 loose stools within 24 hour period
- Don’t use assays for test of cure

Molecular or GDH Antigen as first step

- Toxin testing not considered sensitive enough for first step
- Molecular usually targets the gene for toxin
- GDH is present in toxigenic and non toxigenic strains

Johns Hopkins – Adherence to *C. difficile* IDSA/SHEA Guidelines

Retrospective data showed adherence of only 65.7% to guidelines

- Test only loose specimens
- Repeat testing for 7 days is discouraged
- PCR positive with no diarrhea – don't treat

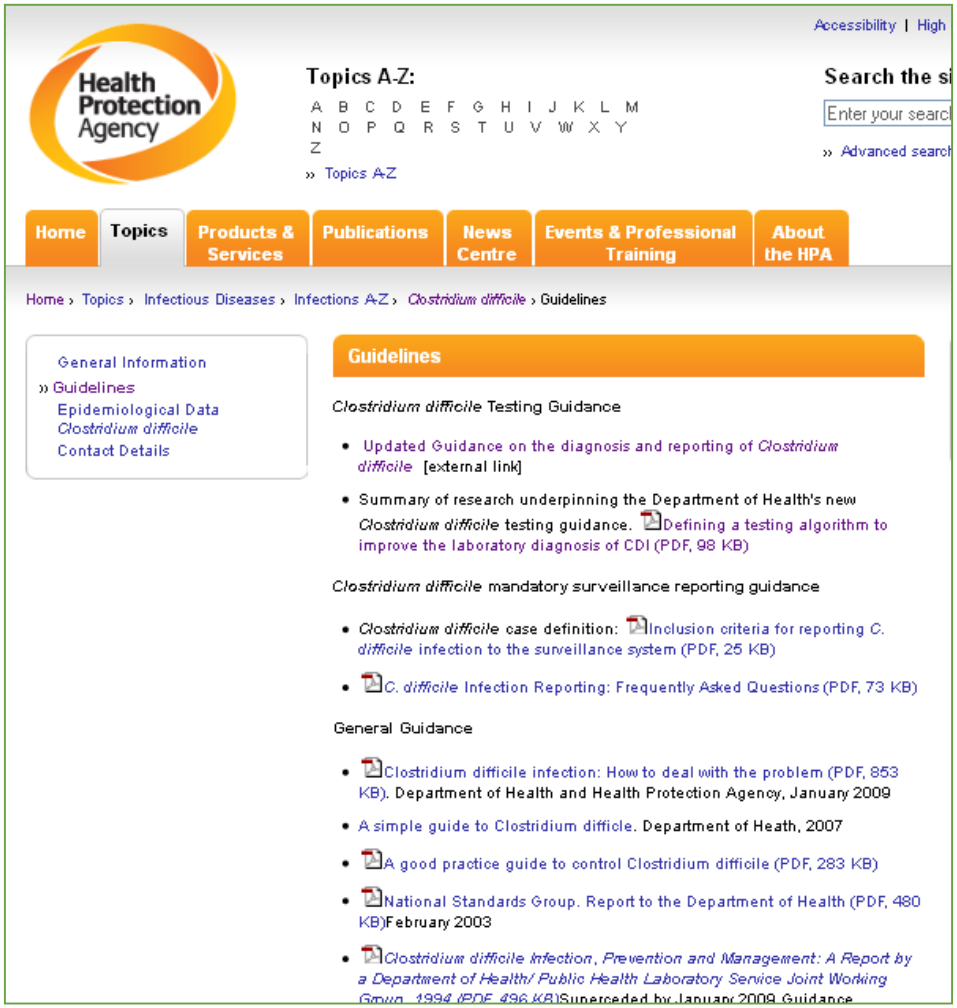
43% of pre-intervention patients were taking a laxative within 48 hours of test

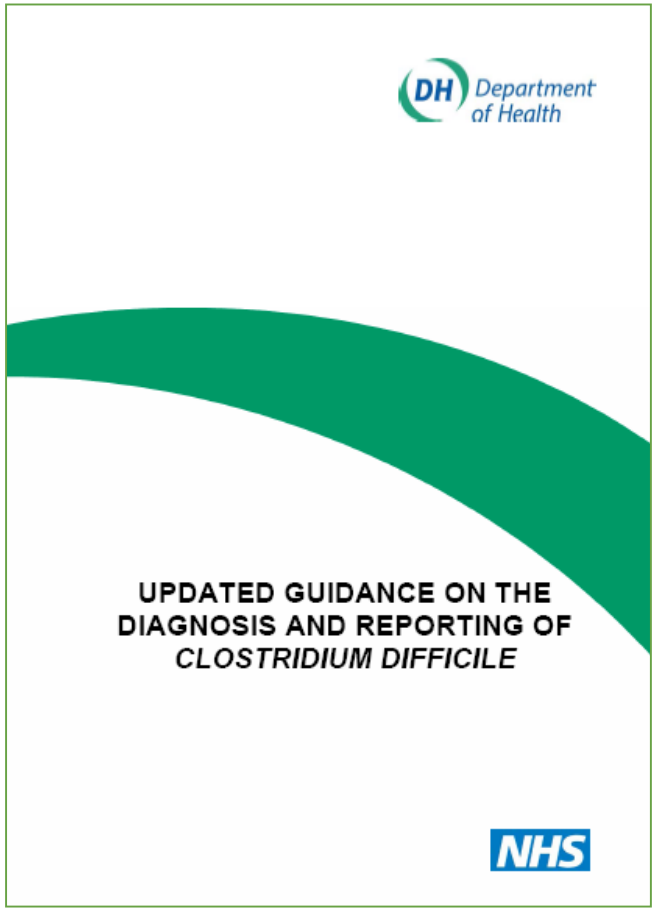
Table 3. Sensitivity and Specificity of individual assays and algorithms compared with cell cytotoxin assay – Training dataset (n = 6761)

	Single assays-Manufacturers' cut-offs				Two stage assays-Manufacturers' cut-offs				
	GDH EIA	NAAT	Toxin EIA 1	Toxin EIA 2	GDH EIA	GDH EIA	GDH EIA	Toxin EIA 1	Toxin EIA 2
					Toxin EIA 1	NAAT	Toxin EIA 2	NAAT	NAAT
Sensitivity % (95% CI)	95.9 (93.4-97.6)	96.9 (94.7-98.4)	69.2 (64.3-73.8)	82.3 (78.9-85.9)	67.4 (62.4-72.1)	94.6 (91.9-96.6)	80.4 (76.2-84.3)	68.9 (64.0-73.6)	82.0 (77.8-85.7)
Specificity % (95% CI)	92.1 (91.4-92.8)	94.9 (94.3-95.4)	99.4 (99.2-99.6)	98.8 (98.5-99.1)	99.7 (99.5-99.8)	95.6 (95.5-96.5)	99.6 (99.4-99.7)	99.7 (99.6-99.8)	99.6 (99.4-99.8)
PPV% (95% CI)	42.7 (39.4-46.1)	54.0 (50.2-57.7)	87.4 (83.0-91.0)	80.8 (76.5-84.5)	93.1 (89.2-95.7)	59.3 (55.3-63.1)	91.8 (88.2-94.4)	93.9 (90.2-96.3)	93.0 (89.6-95.4)
NPV% (95% CI)	99.7 (99.5-99.8)	99.8 (99.6-99.9)	98.1 (97.8-98.5)	98.9 (98.6-99.1)	98.1 (97.7-98.4)	99.7 (99.5-99.8)	98.8 (98.5-99.1)	98.1 (97.8-98.5)	98.9 (98.6-99.1)

Davies KA et al. The largest ever study to define a testing algorithm to optimise the laboratory diagnosis of *C. difficile* infection. 22nd ECCMID, 2012. http://registration.akm.ch/einsicht.php?XNABSTRACT_ID=151898&XNSPRACHE_ID=2&XNKONGRESS_ID=161&XNMASKEN_ID=900;

http://www.hpa.org.uk/Topics/InfectiousDiseases/InfectionsAZ/ClostridiumDifficile/Guidelines/





http://www.dh.gov.uk/prod_consum_dh/groups/dh_digitalassets/@dh/@en/documents/digitalasset/dh_133016.pdf

Wilcox, Planche, Crook, Shetty, Davies, Coen, et al. 2012.

GDH EIA (or NAAT) positive, toxin EIA (or cytoxin) positive:
CDI is likely to be present
→ **for mandatory reporting to HPA**

or

GDH EIA (or NAAT) positive, toxin EIA negative:
C. difficile could be present i.e. potential *C. difficile* excretor
→ **not for mandatory reporting**
(but may have transmission potential and be suitable for local reporting)

or

GDH EIA (or NAAT) negative:
C. difficile or CDI is very unlikely to be present
→ **not for mandatory reporting**
but may have transmission potential (other pathogens)

Refer to the following local policies:
- Remember the **SIGHT** list
- *Clostridium difficile* Policy
- *Clostridium difficile* Treatment Guideline
- Source Isolation Policy
- Source Isolation Cleaning Policy

Consider other causes of diarrhoea
Consider continuation of single room isolation and other measures to reduce risk of CDI

Consider other causes of diarrhoea; if not infective may consider ending single room isolation

IDSA/SHEA Guidelines

From the guidelines:

Are there pre-agreed institutional criteria for patient stool submission?

NO

Best performing method:

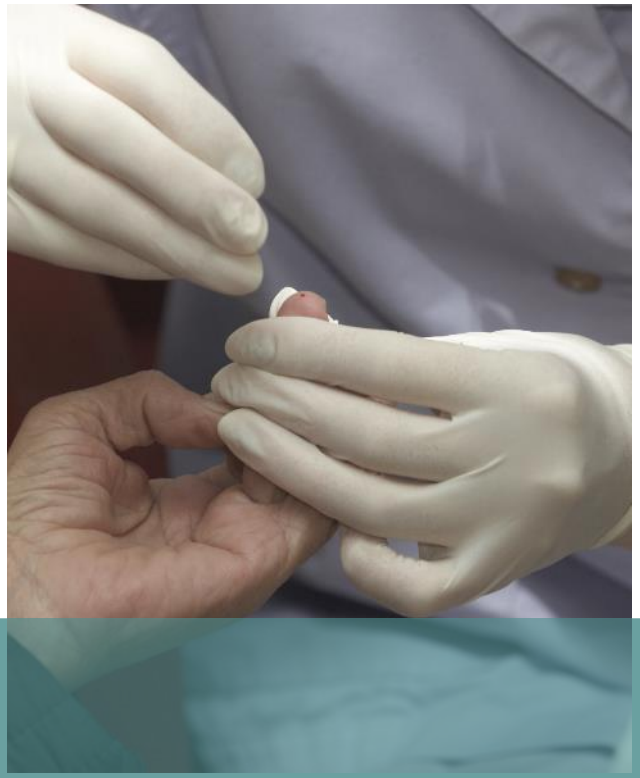
Use a stool toxin test as part of a **multistep algorithm *rather than* a NAAT alone** for all specimens received in the clinical laboratory

YES

Most sensitive method:

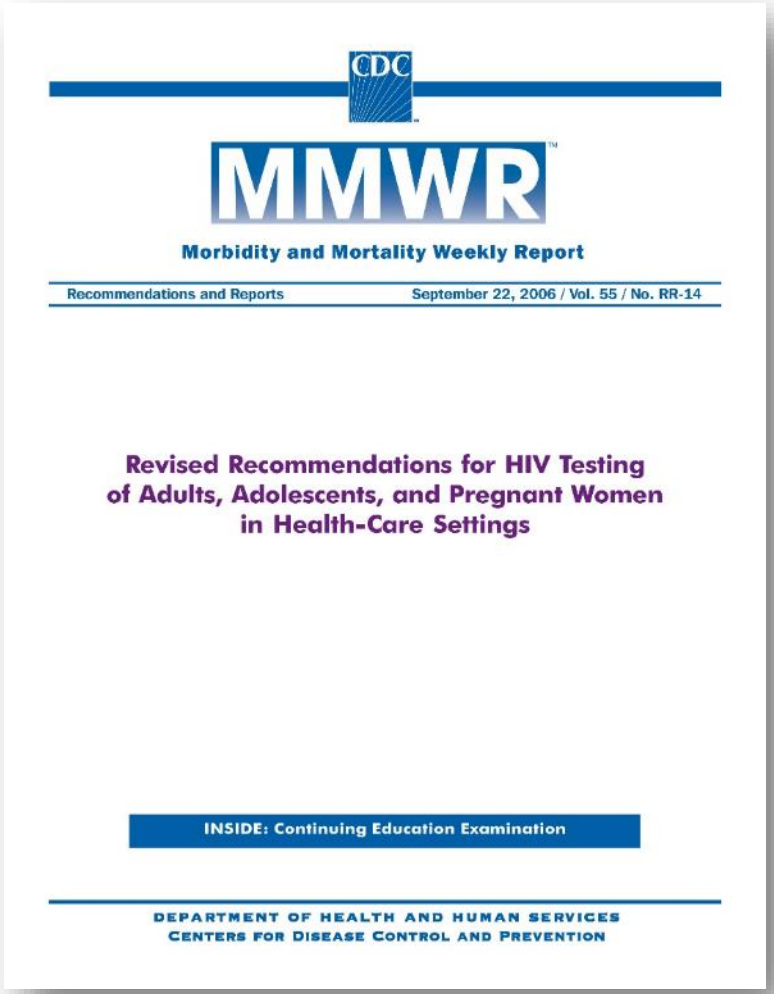
Use a **multistep algorithm or NAAT alone** for testing rather than a toxin test alone

McDonald et al. *Clin Infect Dis* 2018; cix1085, https://doi.org/10.1093/cid/cix1085



Knowing now matters™ in HIV testing

Summary of the Recommendations



- Routine screening in all healthcare settings with undiagnosed prevalence ≥0.1% for patients aged 13 to 64 years
- Repeat testing should be performed at least annually for those determined to be high-risk
- Routine screening for all pregnant women
- Screening should be voluntary using opt-out consent

Centers for Disease Control and Prevention. MMWR 2006;55(No. RR-14)

ACEP 2014 Policy Statement

Early diagnosis and treatment of HIV	Candidates for HIV screening	ED HIV screening programs are best when
▪ Prolongs life ▪ Reduces transmission ▪ Is a cost-effective public health intervention	▪ All from 15-65 years old ▪ High risk adolescents and elderly ▪ All pregnant women with unknown HIV status	▪ Local prevalence of HIV is ≥ 0.1% ▪ Procedures are practical and feasible ▪ Integrated with resources of the healthcare system (linkage to care)

Ann Emerg Med. (2014) **64:**563

Is Rapid Testing in the ED Feasible?

PROS

- High-risk populations use the ED as their sole source for medical care
- Seroprevalence is relatively high (≥ 0.1% per CDC guidance) and this affords an outstanding opportunity to determine risk and to test for HIV
- Rapid tests are quick and accurate
- Growing experience and body of literature demonstrating clinical and cost effectiveness

CONS

- Perceptions regarding ED-based prevention efforts vary
- Program implementation will vary depending on resources and site
- Limited comparative data
- Funding

Benefits of Early Diagnosis of HIV Infection

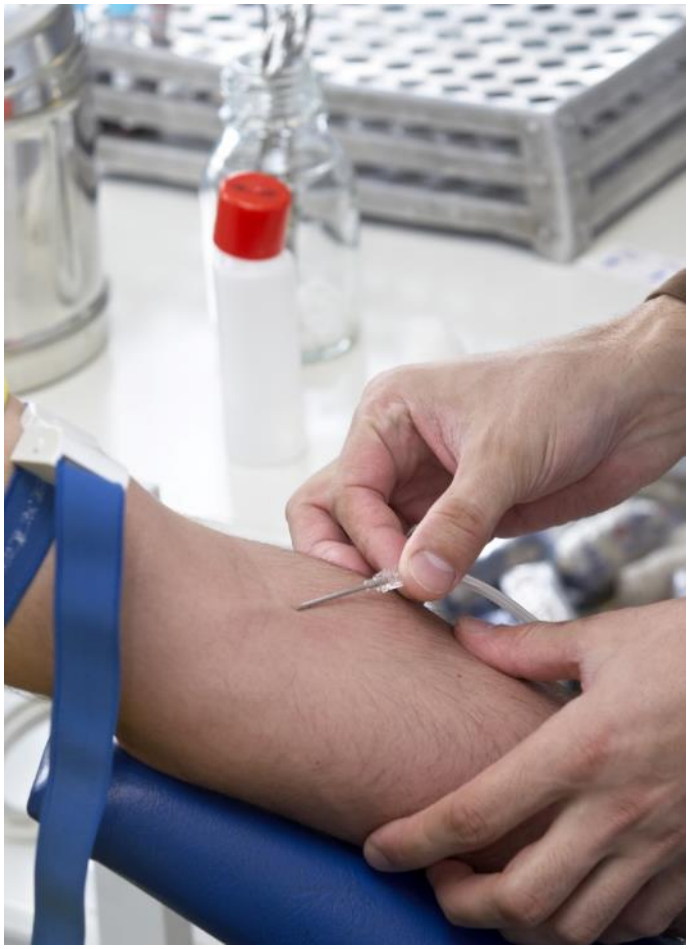
Reduction of high-risk behavior[1]

Reduces the risk of forward transmission:

Individuals with acute HIV infection are 43 times more contagious than chronically infected HIV patients[2]

Allows individuals with HIV to seek treatment earlier which:[3,4,5]

- Will improve their health
- Reduces the risk of premature death
- Reduces their viral load, reducing the risk of forward transmission



[1]Marks G, et al. JAIDS (2005) 39:446-453

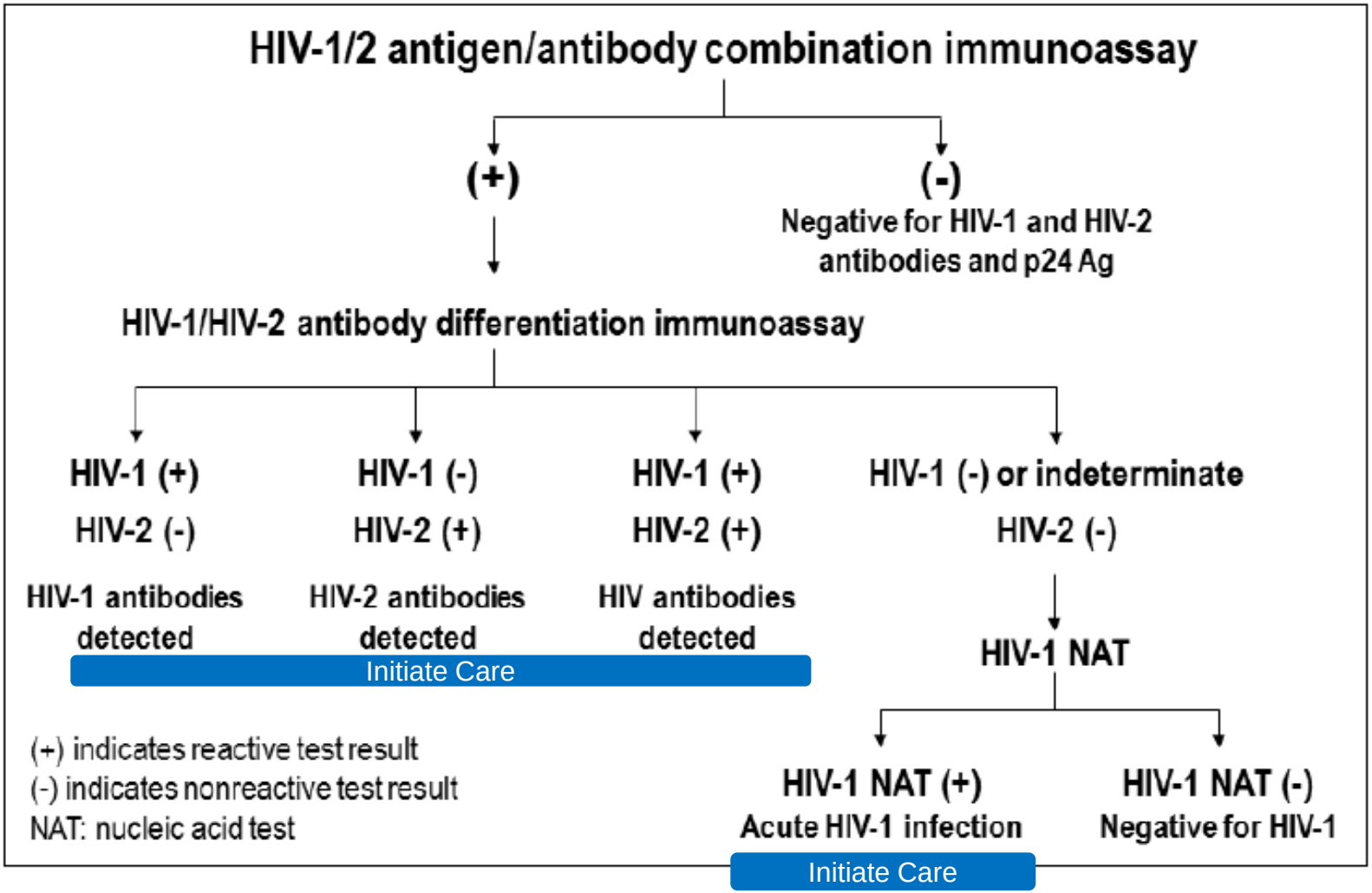
[2]Pinkerton, S.D. AIDS Behav. 2008 September ; 12(5): 677–684. doi:10.1007/s10461-007-9329-1.

[3]Moyer VA, et al. Ann Intern Med. 2013 Jul 2;159(1):51-60.

[4]CDC. MMWR 2011;60(47):1618–23.

[5]Starting antiretroviral treatment early improves outcomes for HIV infected individuals. http://www.nih.gov/news/health/may2015/niaid-27.htm

CDC/APHL HIV Diagnostic Algorithm[1]



Advantages of the new CDC HIV Diagnostic algorithm

More Accurate Diagnosis of acute/early HIV-1 infection

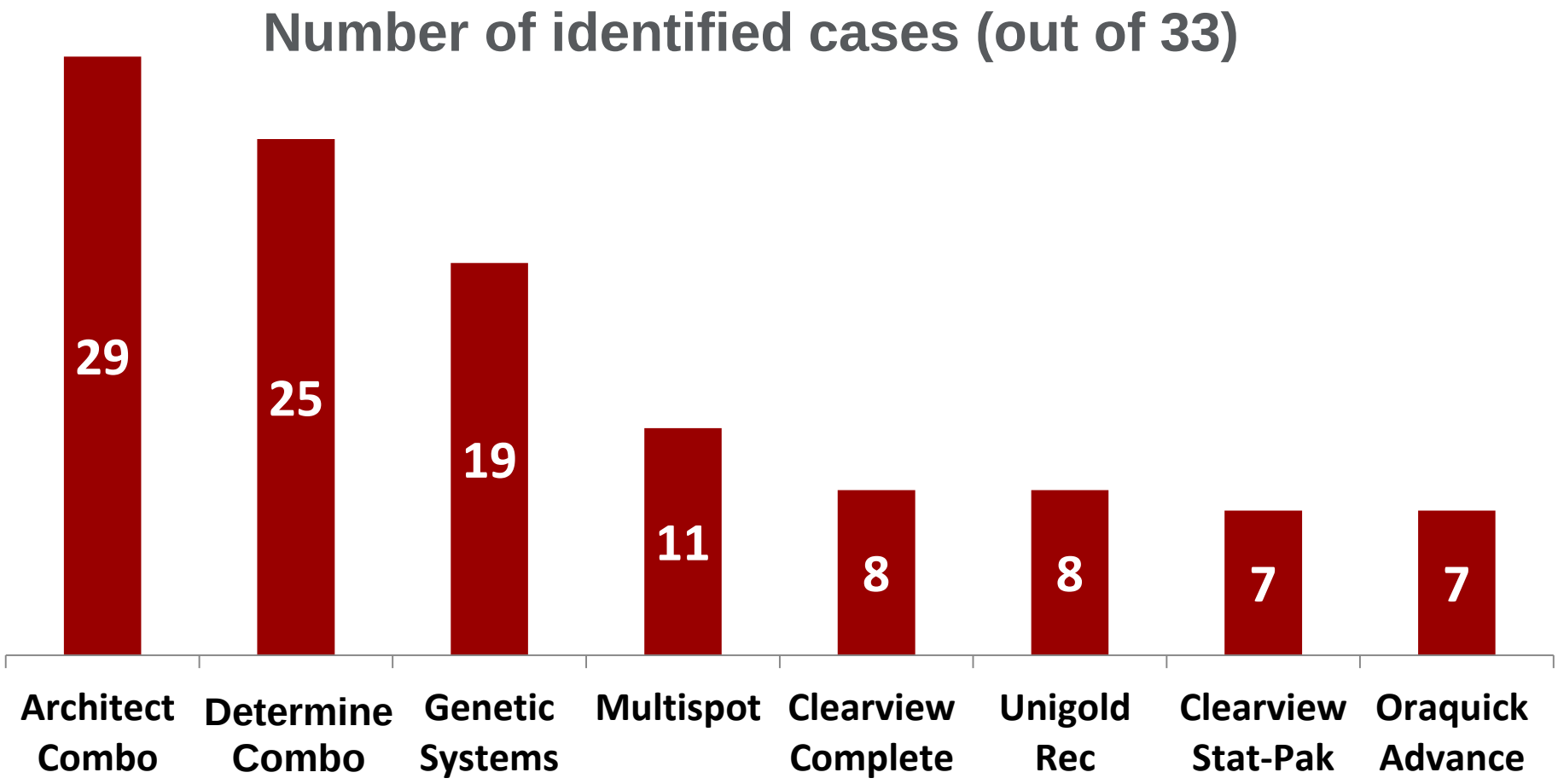
Equally accurate laboratory diagnosis of established HIV-1 infection

More accurate laboratory diagnosis of HIV-2 infection

Fewer indeterminate results

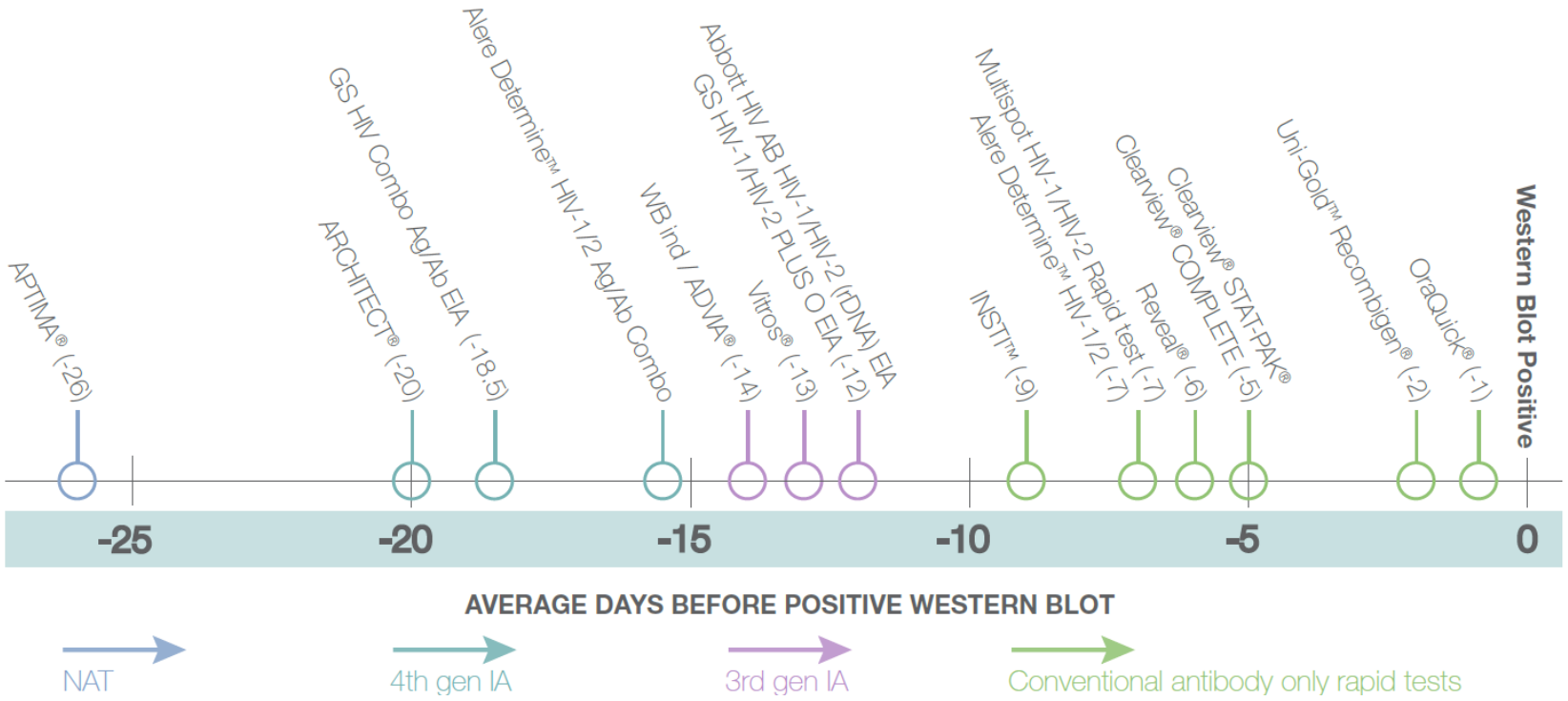
Faster turnaround time for most test results

CDC Study: Early HIV screening



Modified from Patel et al. JCV May 2012

Performance of Tests Compared to Western Blot



Thank you

Questions?