Improving Quality of Care for Clostridium difficile Infection: Why a Better Test Means Better Care

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Illinois Campaign to Eliminate *Clostridium difficile* Webinar
April 2012

Educational Objectives

- Review some basics about microbiology & pathophysiology of *Clostridium difficile* infection (CDI)
- Outline important CDI-related epidemiologic trends
- Share Loyola's experience with management of CDI
- Review key issues in diagnostic testing & the consequences of inaccurate testing

Disclosures

- Advisory Board to Clarity PSO, Merck
- PI on Clinical Trials for Roche, Astellas, Catheter Connections (no personal/direct financial benefit)
- Speakers Bureau for France Foundation, Robert Michael Educational Institute, Optimer, Cepheid, Cubist, Merck
- Ok, I admit it…**I also take pens from displays at conferences**

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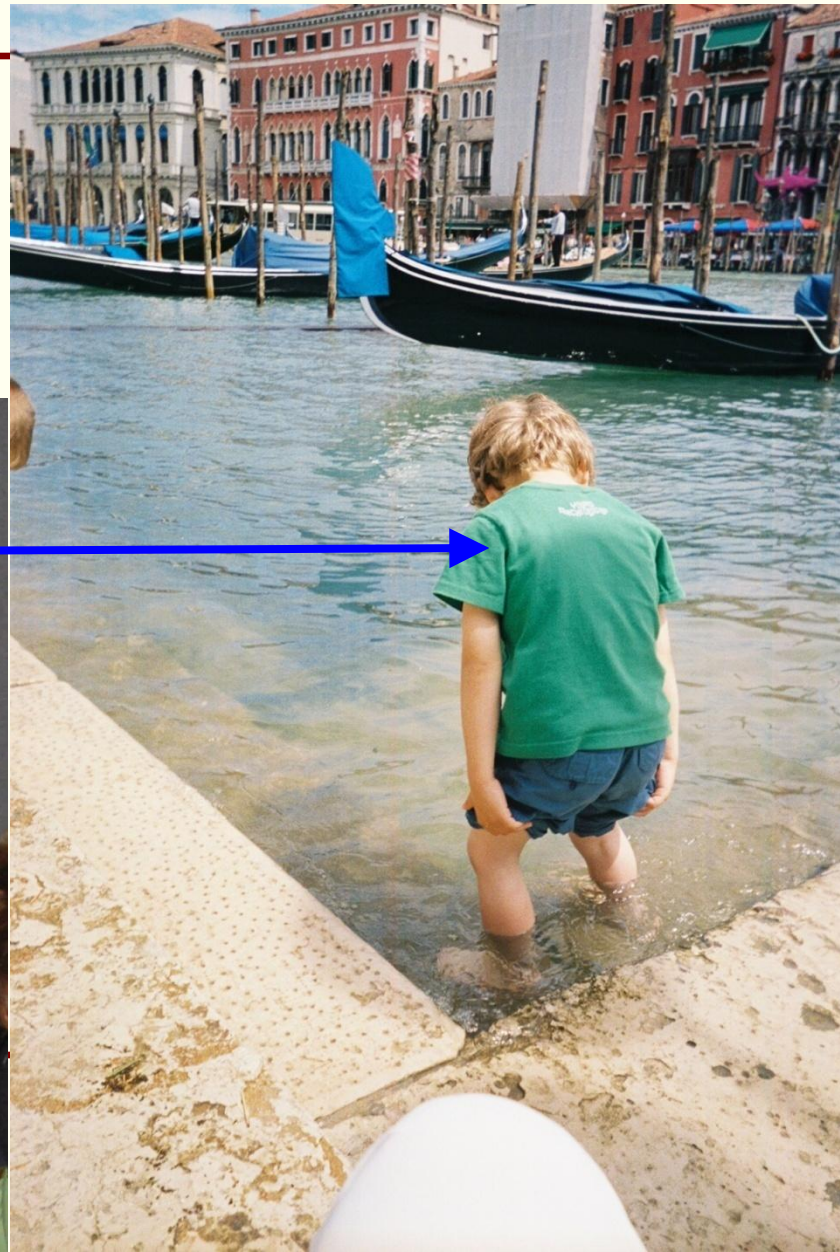
Real Conflict of Interest!

- **9-year-old son…**
  - **Broken wrist age 4**
  - **Stitches age 5**
  - **Staples age 7**



Fasten your seat belts… We're going fast!

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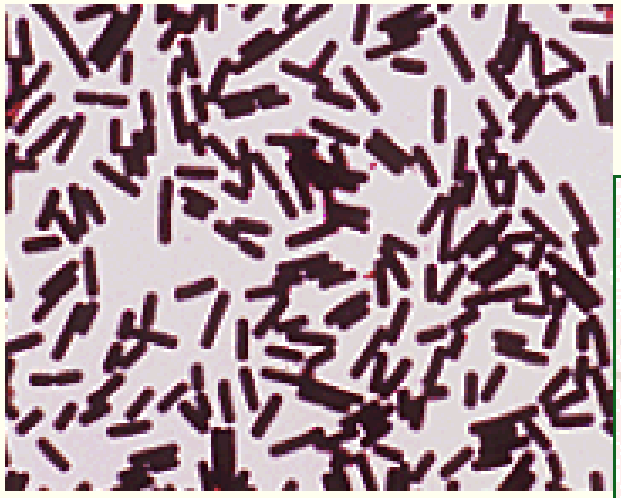
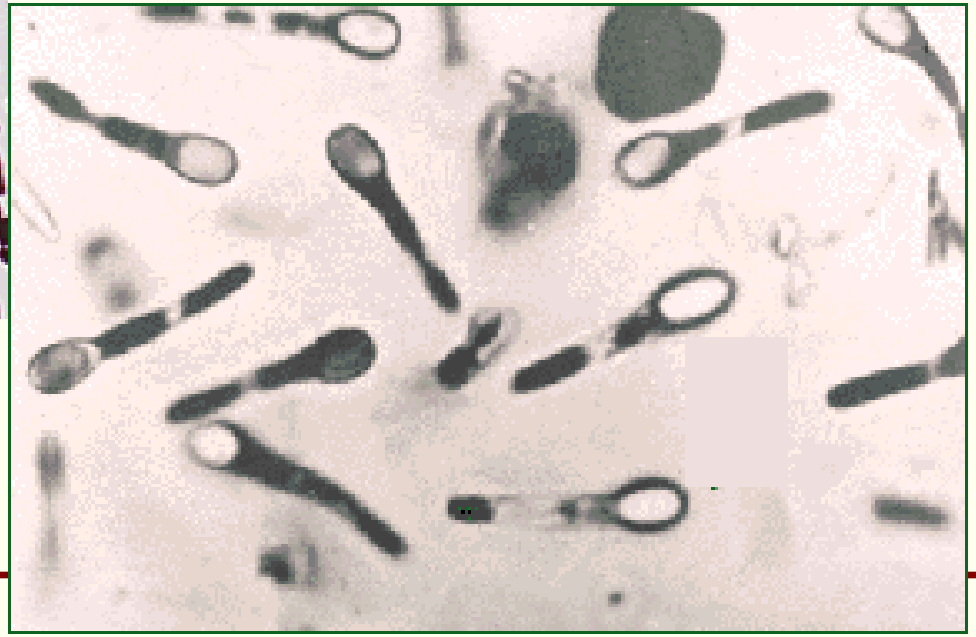
C. Difficile

Vegetative Cells & Endospores





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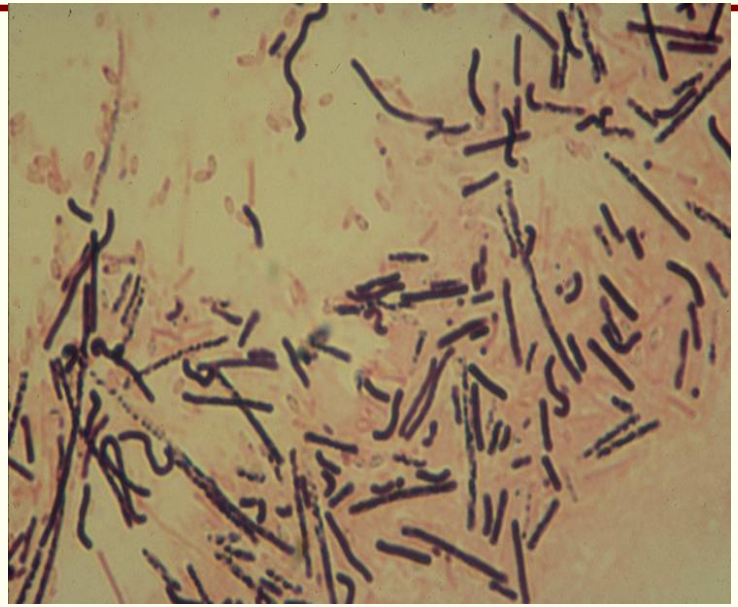
CDI Overview



- **Spore-forming**, anaerobic, gram-positive bacterium
- Causes **toxin-mediated** gastrointestinal infections resulting in diarrhea and colitis
  - Severity ranges from mild colitis to toxic megacolon and death
- Leading cause of healthcare-associated infectious diarrhea in US
- Rivals methicillin-resistant *Staphylococcus aureus* (MRSA) as the most common organism to cause healthcare-associated infections (HAI) in US

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Gerding DN, et al. *Infect Control Hosp Epidemiol*. 1995;16:459-477.

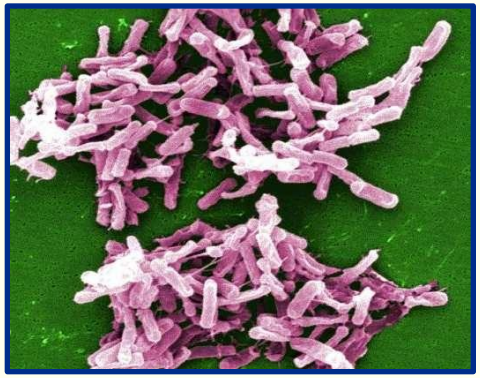
CDC. Fact Sheet, August 2004 (updated 7/22/05).

McDonald LC, et al. *Emerg Infect Dis*. 2006;12:409-415.

Microbiology of *C. difficile*

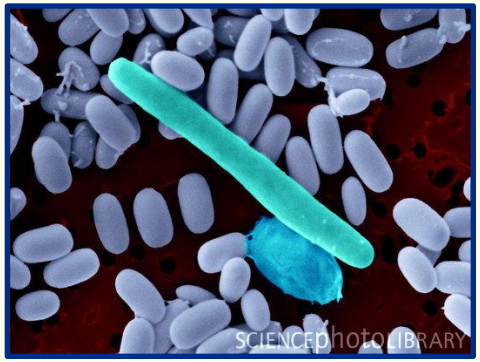
Vegetative Form

- Can survive in the environment on moist surfaces up to 6 hours[2]
- Susceptible to gastric acid, antibacterial soaps, and alcohol based hand sanitizers[3]



Spore Form[3,4]

- Can survive for months on surfaces
- Resistant to gastric acid, antibacterial soaps, alcohol-based hand sanitizers and conventional disinfectants
- Can rapidly change to vegetative form



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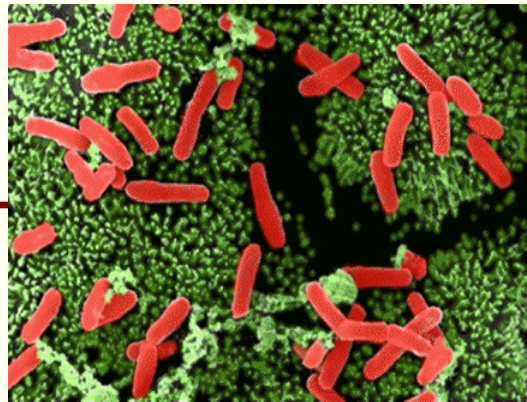
[2] Jump RLP et al. *Antimicrob Agents Chemother.* 2007;51(8):2883–2887.
[3] Fordtran JS et al. *Baylor University Medical Center Proceedings.* 2006;19(1):3–12.
[4] Cohen SH et al. *ICHE.* 2010;31(5):431–455.

Clostridium difficile: Changing Epidemiology

- Changing face of *C. difficile* infection
  - Increasing incidence
  - Increasing disease severity with substantial morbidity and mortality
  - Infection in “low-risk” populations
- Epidemic strain reported in US, Canada, and Europe



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McDonald LC, et al. *Emerg Infect Dis.* 2006;12(3):409-415.

Loo VG, et al. *N Engl J Med.* 2005;353:2442-2449.

Kuijper EJ, et al. *Euro Surveill*. 2007;12(6):E1-E2..

Novel Hypervirulent Strain

- Characteristics of novel epidemic strain:
  - Typed BI/NAP1/027
  - Highly virulent
    - Produces 16-fold higher levels of Toxin A and 23-fold higher levels of Toxin B
    - Produces binary toxin CDT
  - Highly resistant to fluoroquinolones

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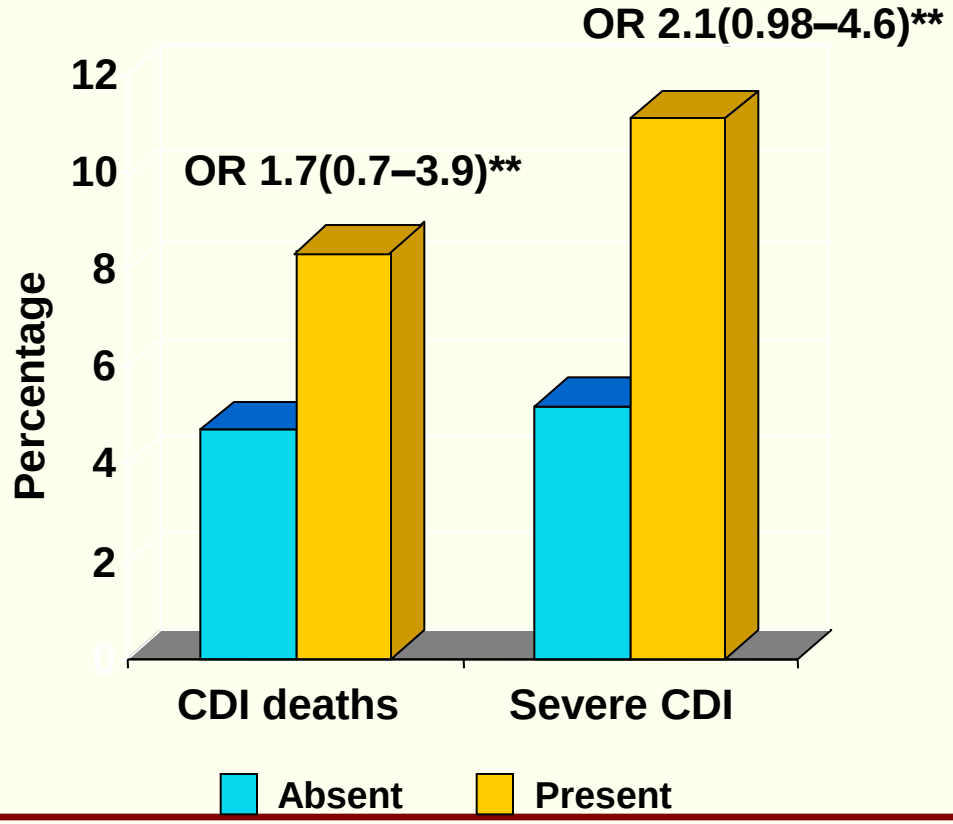
Denève C, et al. *Int J Antimicrob Agents*. 2009;33:S24-S28.

Epidemiology of CDI in Quebec

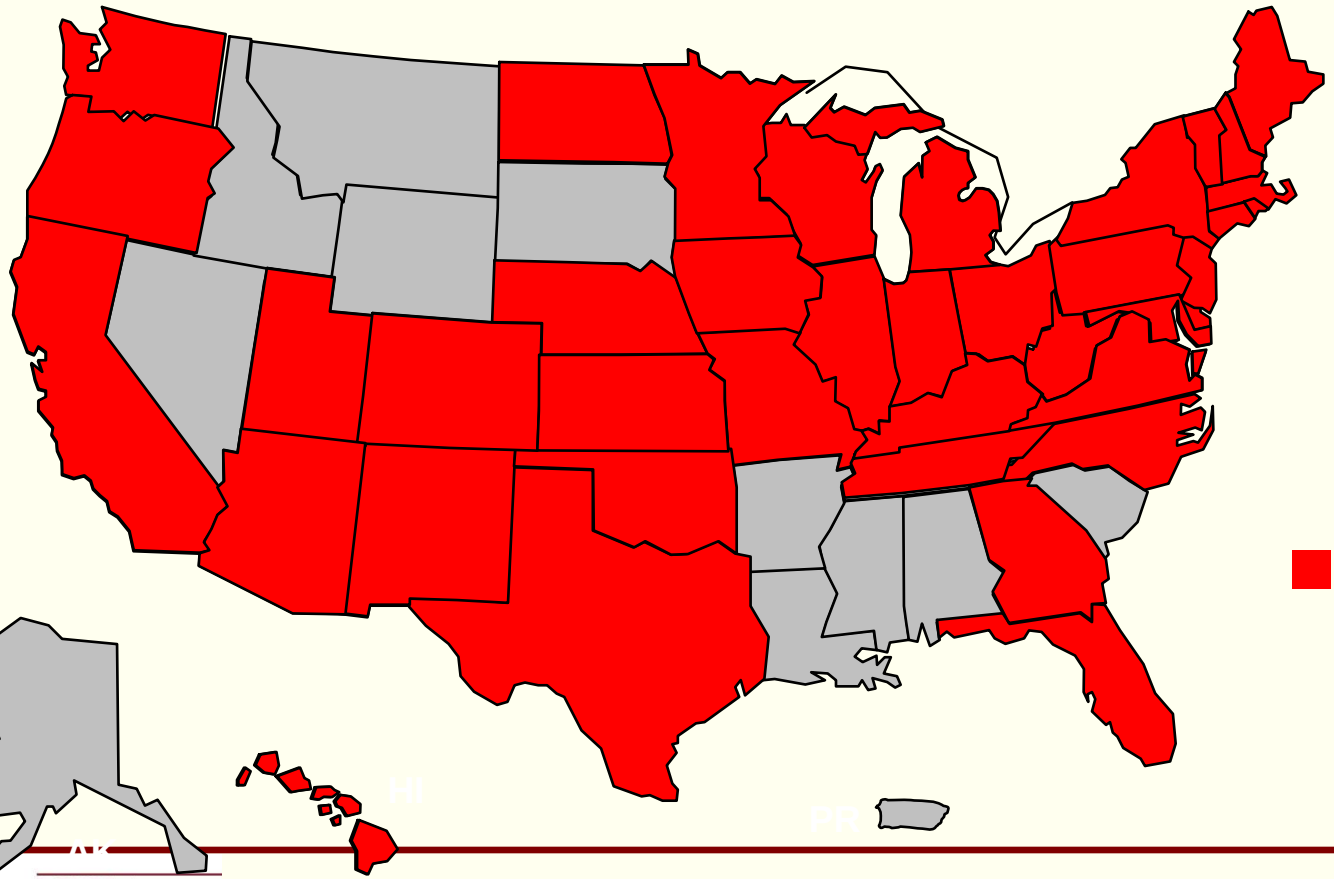
Risk for Death and Severe CDI According to Presence of "Epidemic" Strain*



*Ei[illegible]y toxin positive and partial *tcdC* deletion.
**[illegible]istically significant.
[illegible]fect Dis. 2007;44:238-244.

States with BI/NAP1/027 Strain of *C. difficile*

Confirmed by CDC (*N*=40)
January 2008



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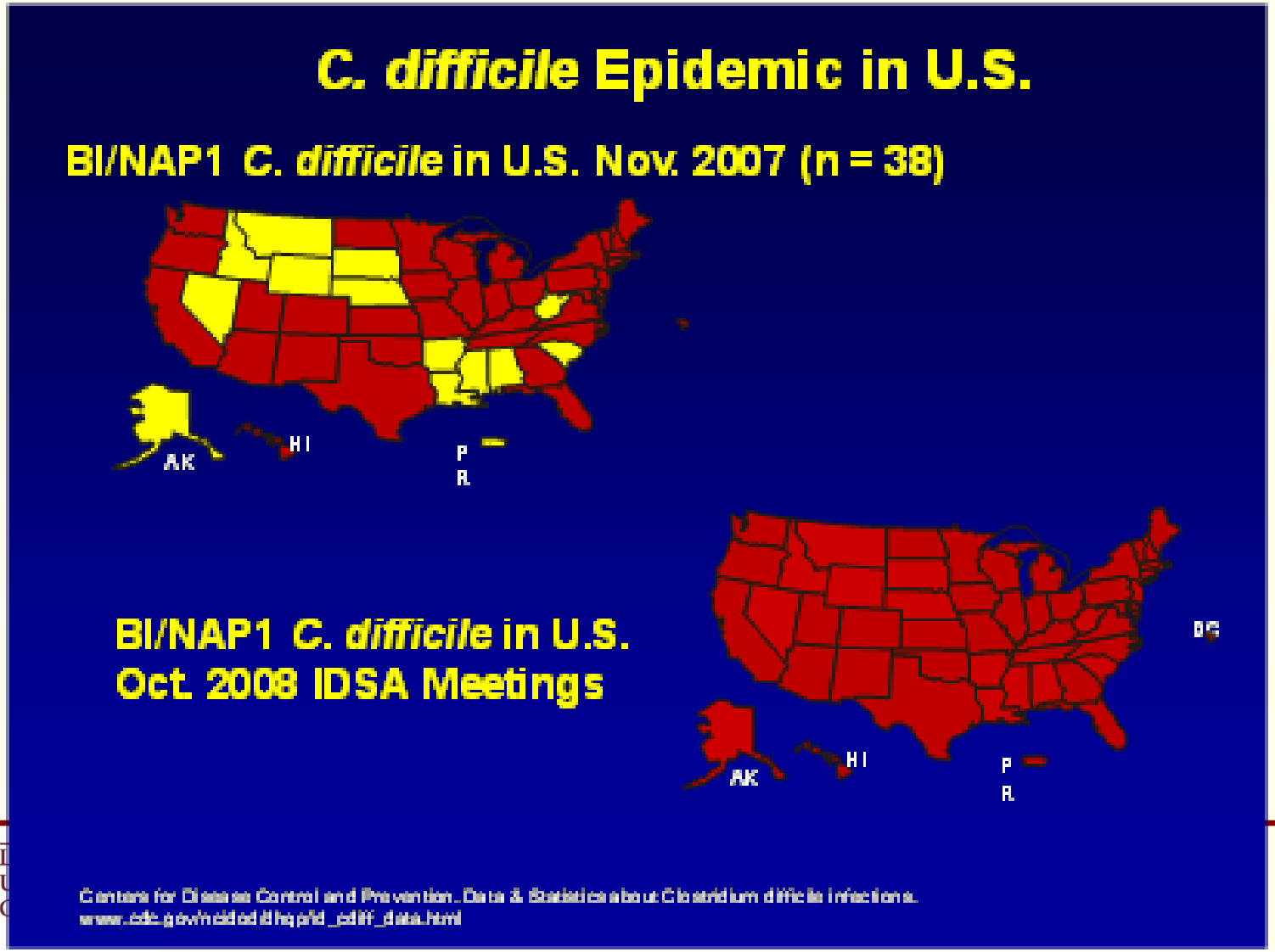
Centers for Disease Control and Prevention: www.cdc.gov/ncidod/dhqp/id_CDIff_data.html

States With BI/NAP1/027 Strain of *C. difficile* (N=50), October 2008



Impact of C diff on Healthcare Outcomes and Costs

- **C diff has repeatedly been documented to cause:**
  - Increased length of hospitalization
  - Increased morbidity and mortality
  - Increased costs
  - Lost revenue-blocked beds
- **Lawsuits…**

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$1-3 BILLION

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Economic Burden of CDI

Study	Patient Population	Per-Episode Costs	Increase in Length of Stay	US Cost
Kyne 1998[1]	-2 medical wards -40 cases	**$3,669**	**3.6 days**	**$1.1 billion**
O'Brien 2000[2]	-MA discharge database -3,692 cases	*Primary diagnosis:* **$10,212** *Secondary diagnosis:* **$13,675**	**3.0 days**	**$3.2 billion**
Dubberke 2003[3]	-Nonsurgical patients -439 cases	**$2,454 – $3,240**	**2.8 days**	**$1.3 billion**

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1. Kyne L, et al. *Clin Infect Dis*. 2002;34:346-353.
2. O'Brien JA, et al. *Infect Control Hosp Epidemiol*. 2007;28:1219-1227.
3. Dubberke ER, et al. *Clin Infect Dis*. 2008;46:497-504.

Cost of Recurrent CDI

- Patients enrolled into recurrent CDI trial
- Direct costs on outpatient visits, inpatient admissions, labs, and treatments
- 209 patients
  - 2.6 ± 1.9 prior episodes of CDI
- **Mean $10,970 per patient**
- **Mean $3,103 per episode**

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McFarland LV, et al. Infect Control Hosp Epidemiol. 1999;20:43-50.

Additional CDI Cost Issues

- **CDI as a "Never Event"???**
- CDI currently short-listed for Medicare/Medicaid future "non-reimbursable diagnoses"
- Cost of bed-days lost <=> contact precautions
- Non-acute care facility costs not known
  - Outpatient costs
  - Long-term care facilities
- Increasing CDI severity
- Impact of treatment on CDI costs
  - Does duration of symptoms affect length of stay?

Recurrent CDI

- CDI recurrence is a significant challenge

- Rates of recurrent CDI:
  - 15-25% after first episode
  - 30-45% after first recurrence
  - 40-65% after two or more recurrences

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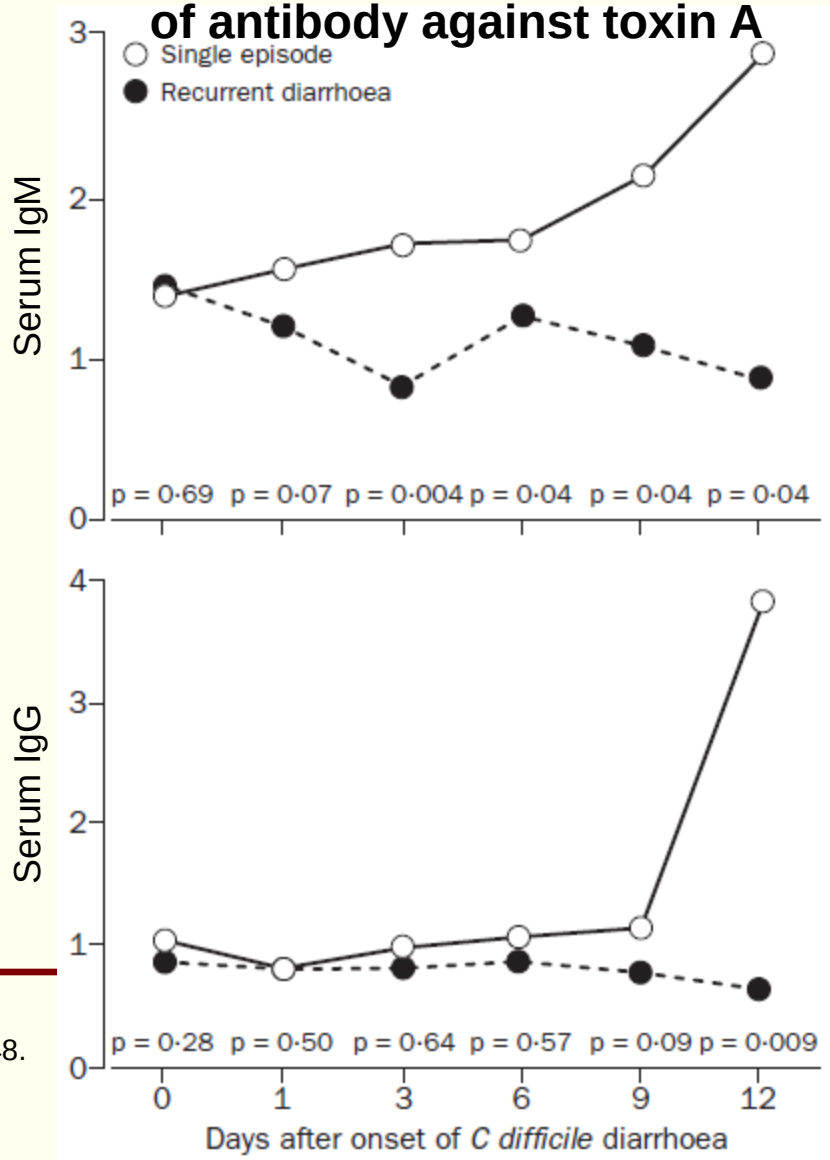
Cohen SH, et al. *Infect Control Hosp Epidemiol.* 2010;31(5):431-455.
Johnson S. *J Infect*. 2009;58(6):403-410.
Pépin J, et al *Clin Infect Dis* 2006;42:758–764.

Defective immune response to toxin A

- Generation of an antibody response to toxin A is associated with protection against symptomatic disease and asymptomatic carriage of *C. difficile*
- Following symptomatic infection, many individuals develop anti-toxin A and B antibodies
- Inability to acquire immunity to toxin A increases risk for recurrent disease
  - Individuals with recurrent CDI mount poor anti-toxin responses



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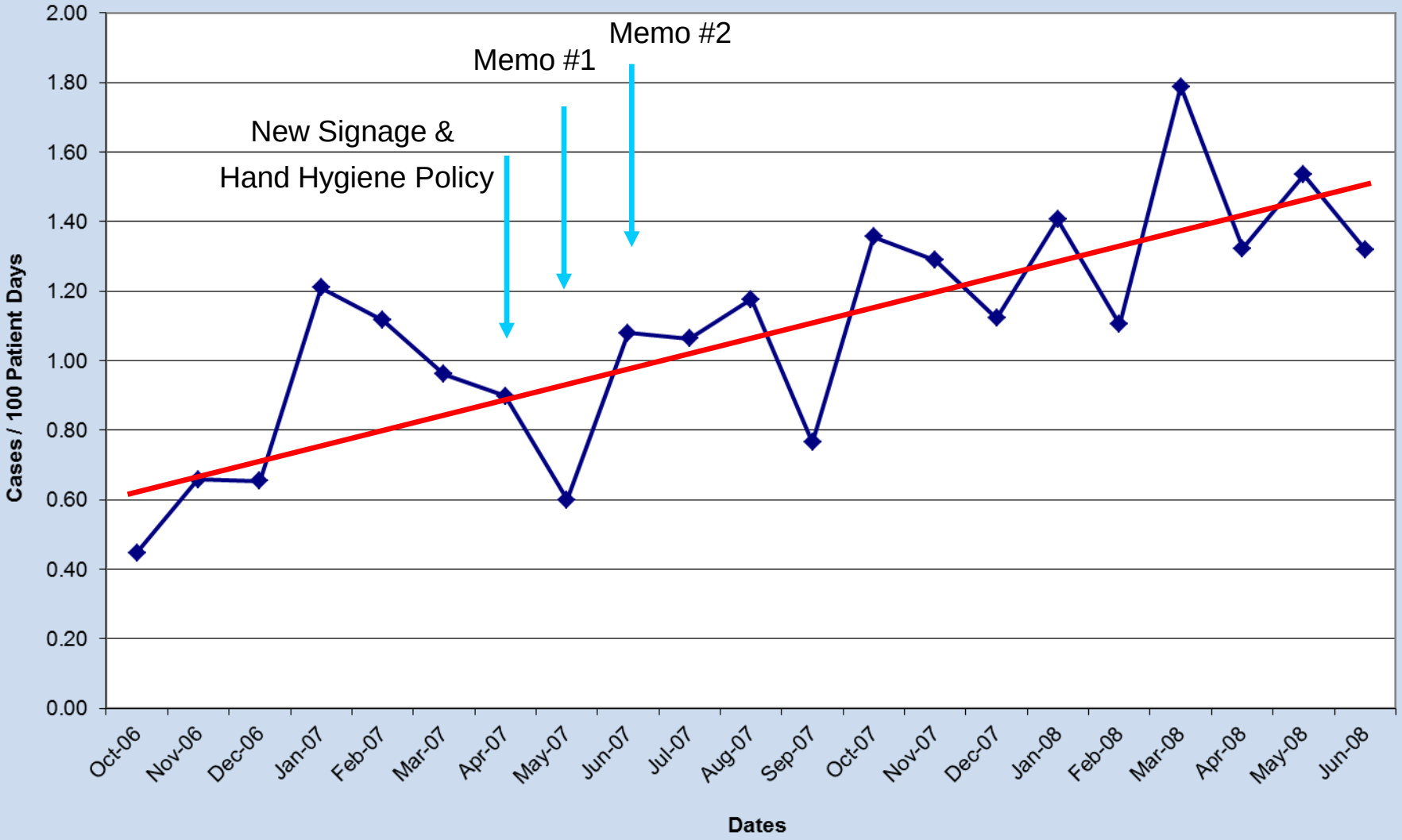
Giannasca PJ, Warny M. *Vaccine*. 2004;22:848.

Kyne L, et al. *Lancet*. 2001;357:189

C diff Epidemiology

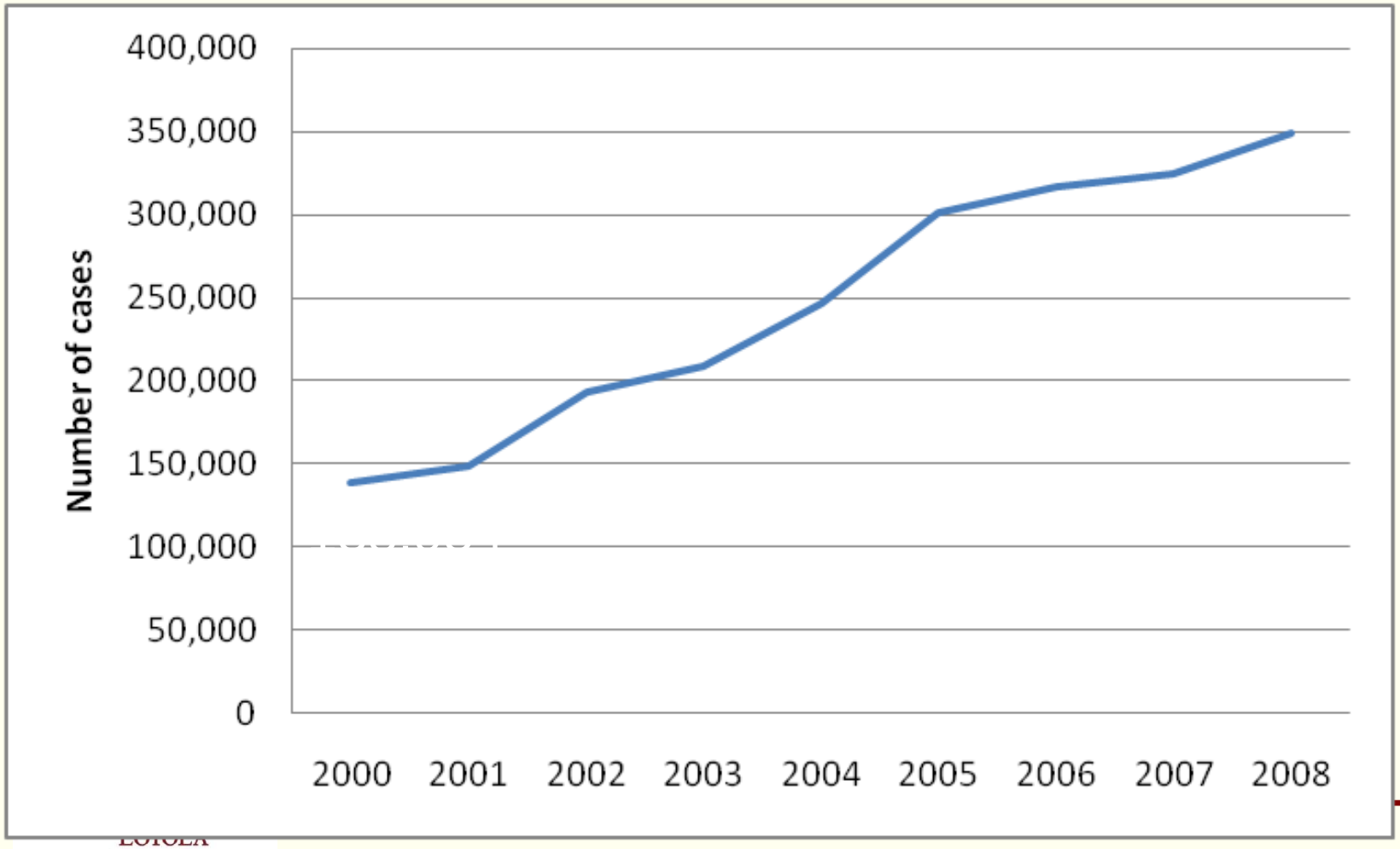
MORE...
MORE...
MORE!

C. Difficile Rates Oct 2006 to June 2008



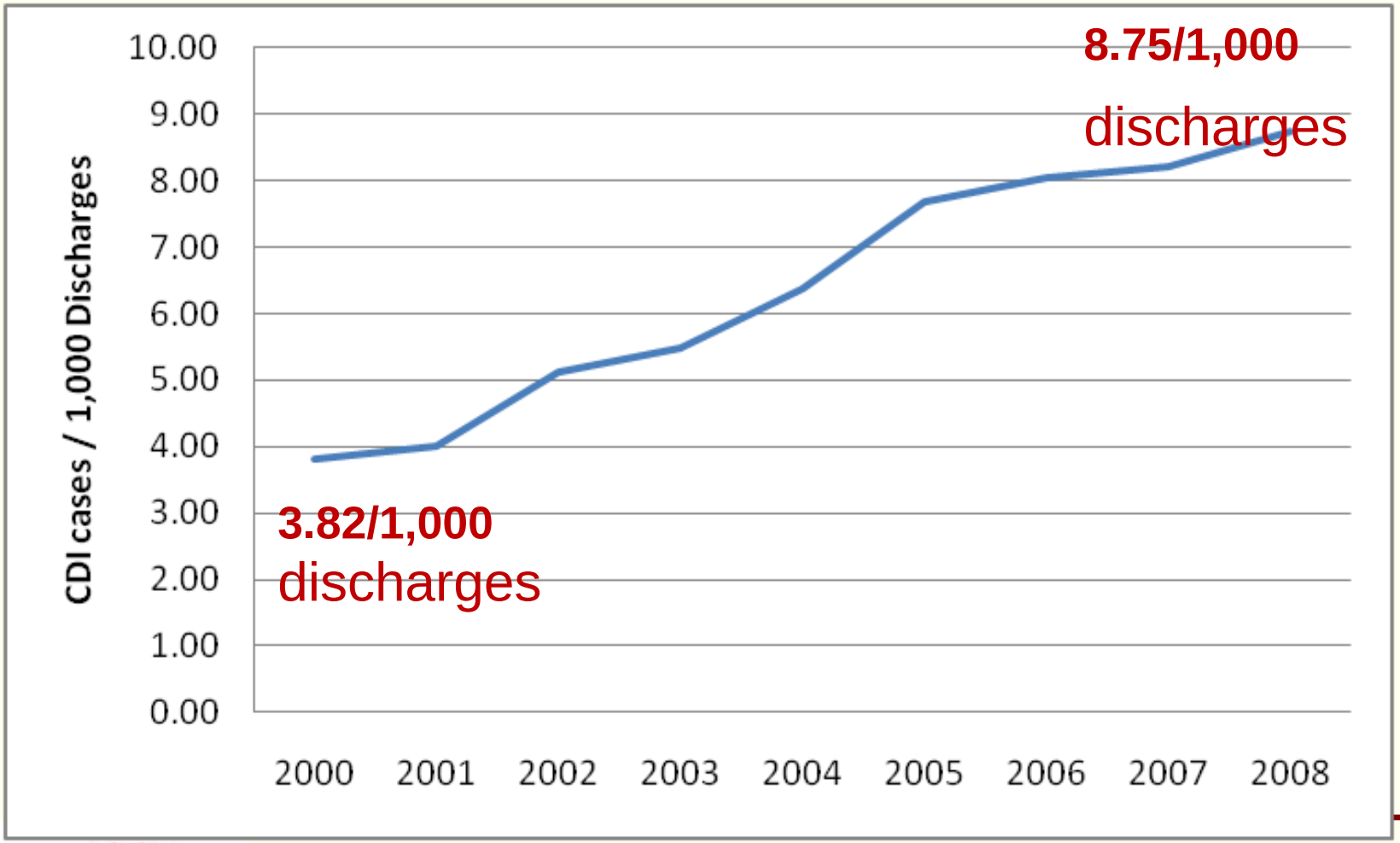
CDI Epidemiology

- Total number of cases of is increasing in the US



Healthcare Cost and Utilization Project (HCUP). http://hcupnet.ahrq.gov.

US: Overall Incidence



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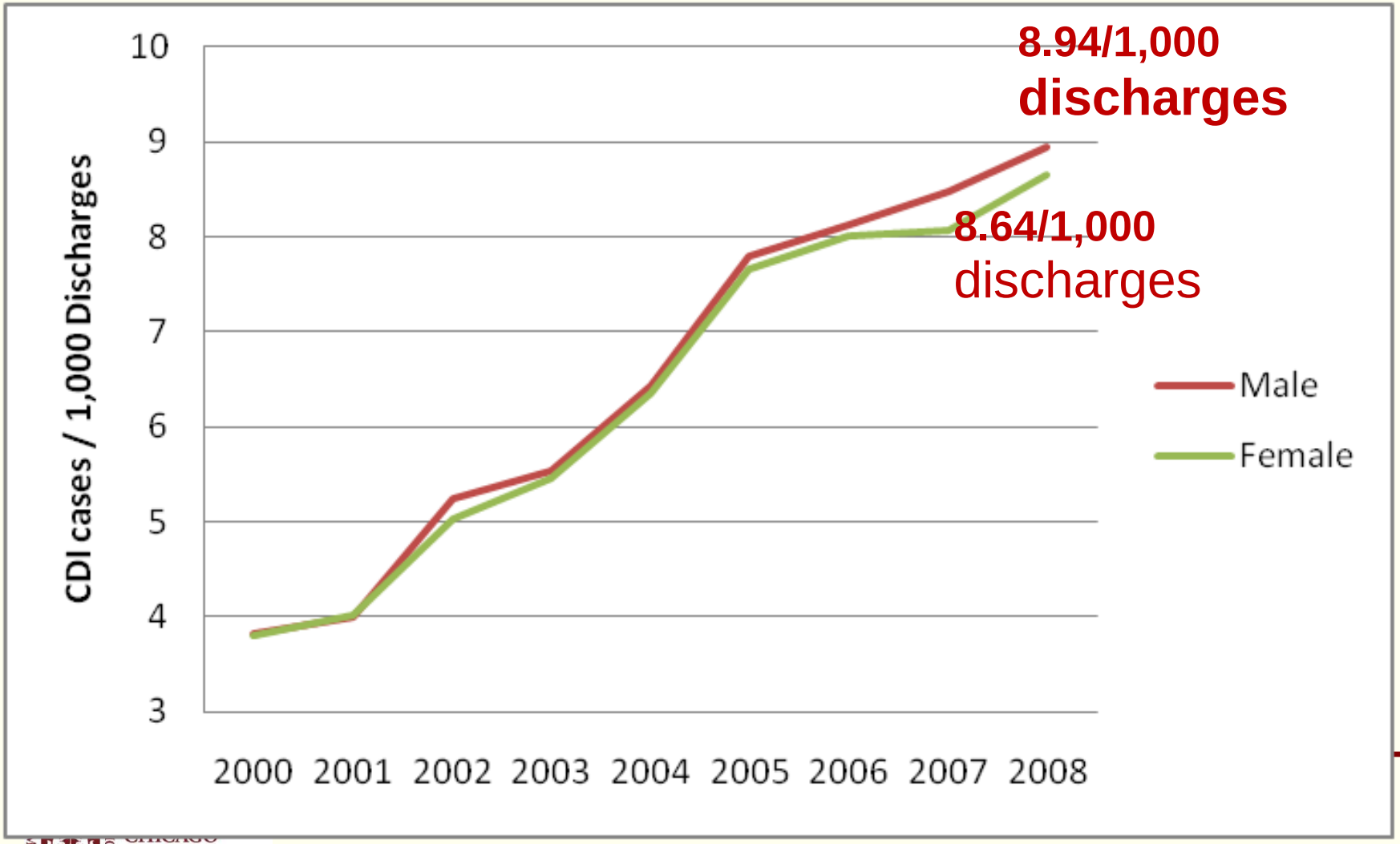
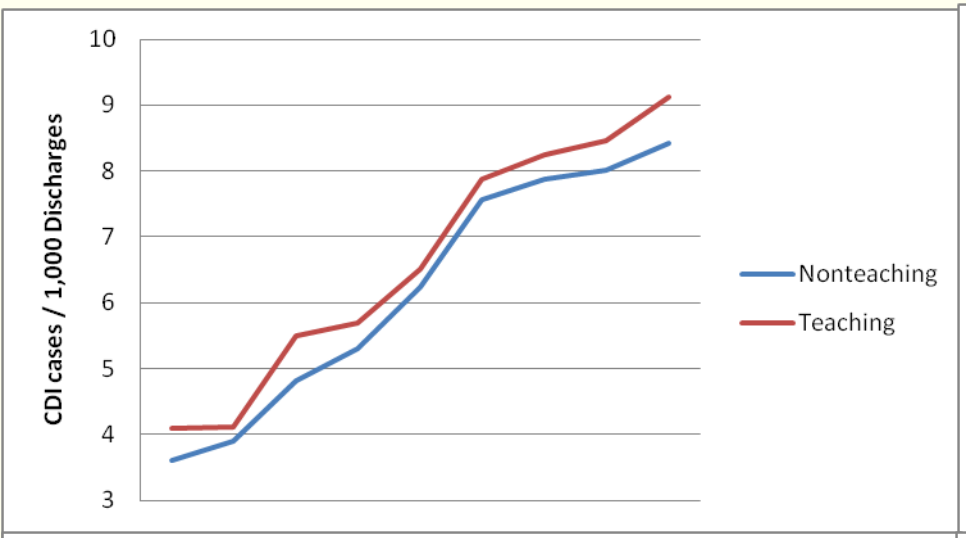
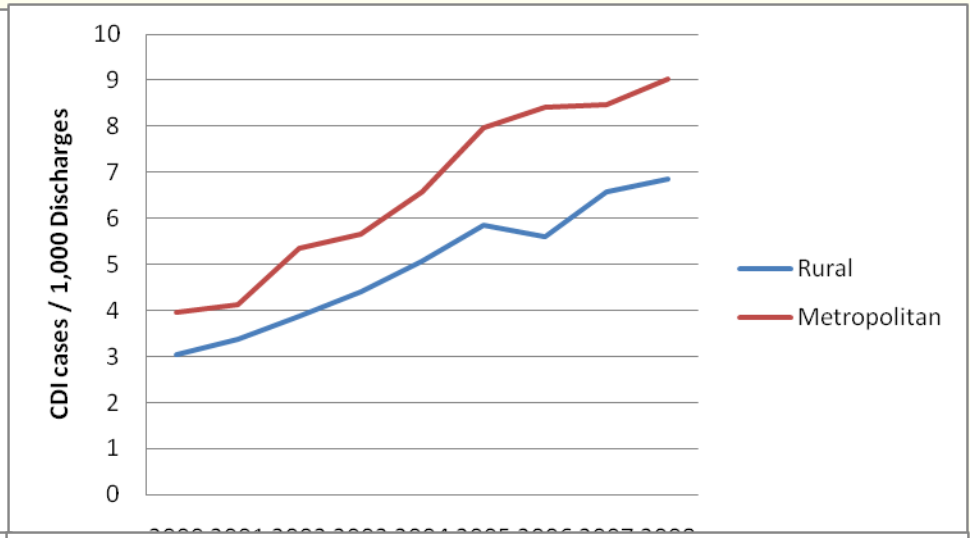
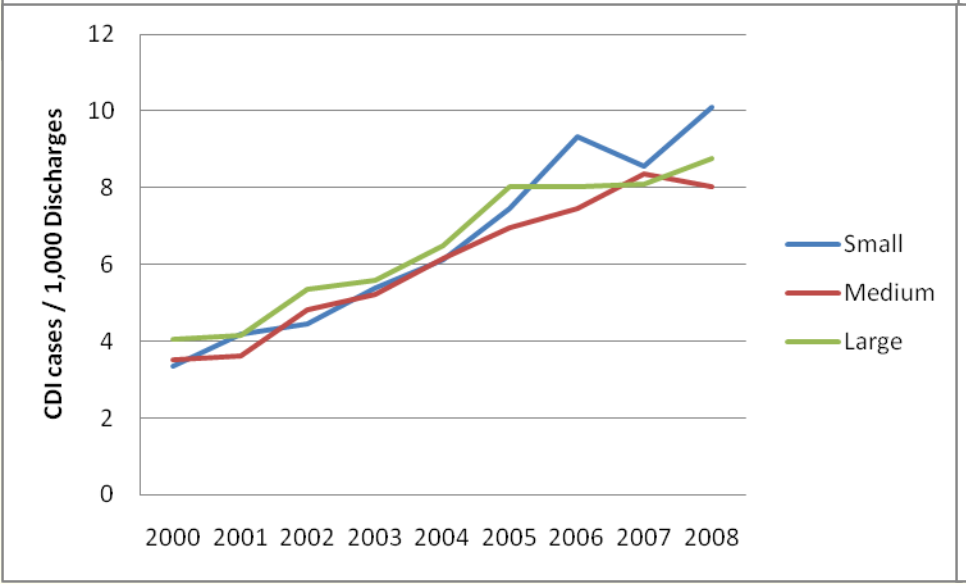
US: CDI Incidence by Gender

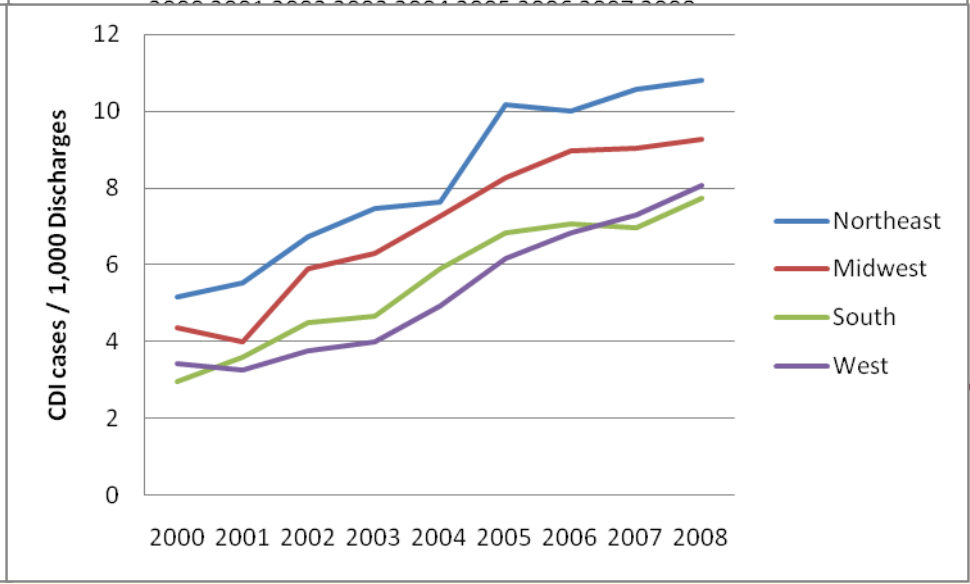


US: CDI Incidence by Hospital Type and Location

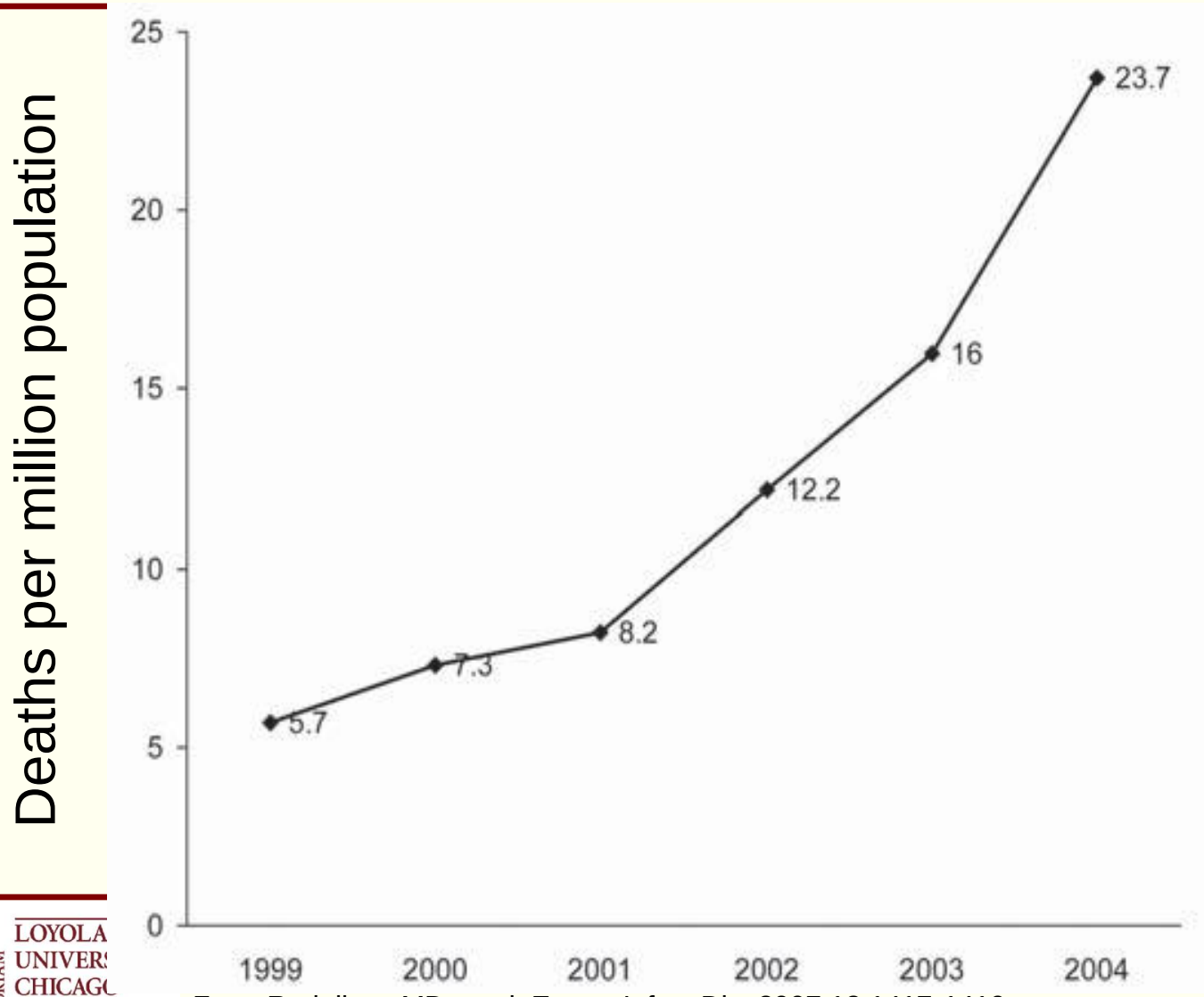








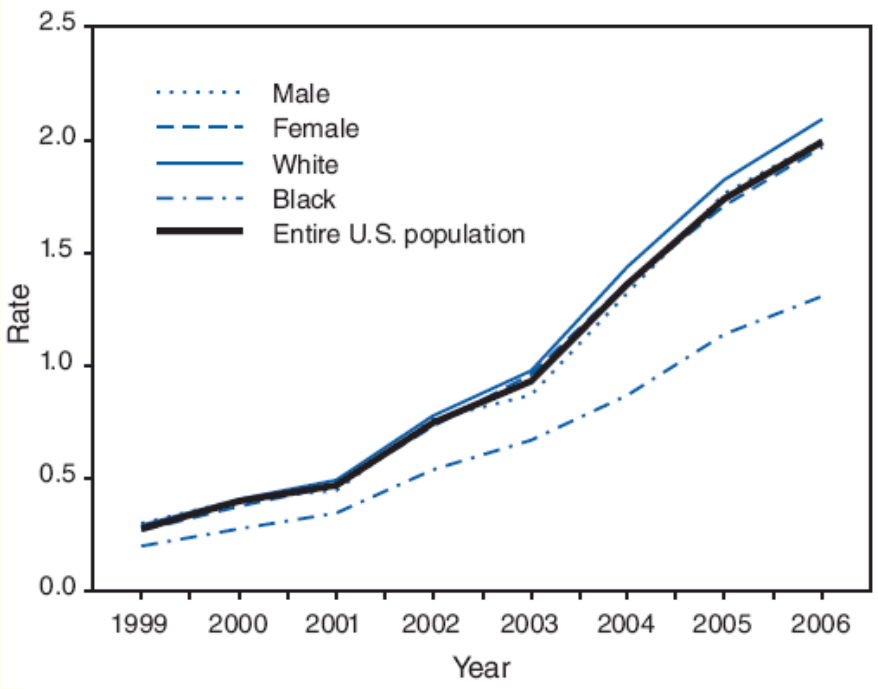
US: Increasing Case Fatality Rate



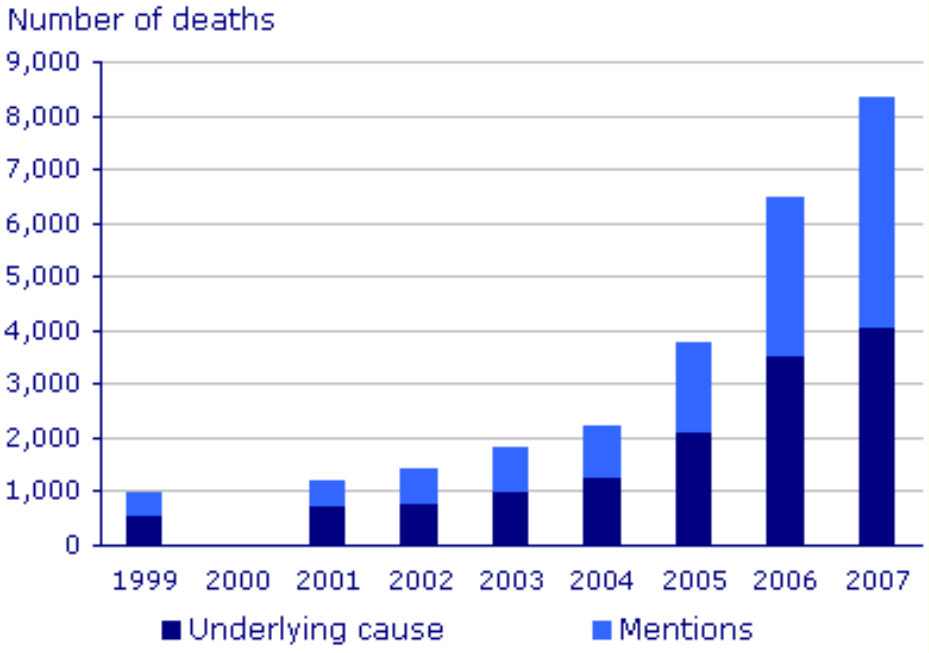
From Redelings MD, et al. Emerg Infect Dis. 2007;13:1417-1419.

Increase in *C. difficile*-Related Deaths

US Age-Adjusted CDI Death Rates



United Kingdom CDI Age-Adjusted Death Rates*

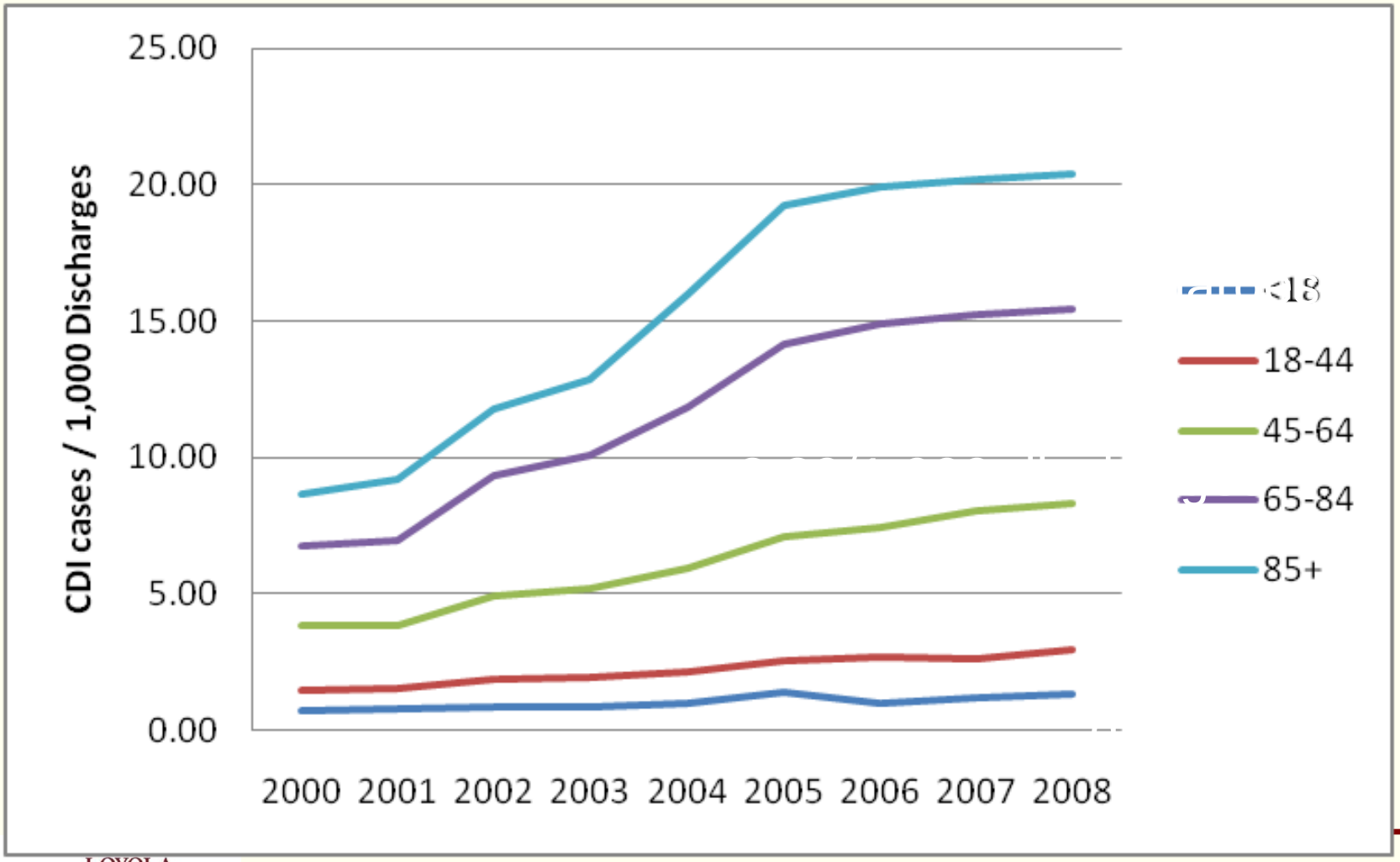


SOURCE: Heron MP, Hoyert DL, Murphy SL, Xu JQ, Kochanek KD, Tejada-Vera B. Deaths: final data for 2006. Natl Vital Stat Rep 2009;57(14). Hyattsville, MD: US Department of Health and Human Services, CDC; 2009. Available at http://www.cdc.gov/nchs/data/nvsr/nvsr57/nvsr57_14.pdf.

***Death certificates mentioning *Clostridium difficile* and recording *C. difficile* as the underlying cause of death (England and Wales).**

UK Office of National Statistics. www.statistics.gov.uk/pdfdir/mrsa0208.pdf.

Elderly – CDI Incidence & Age



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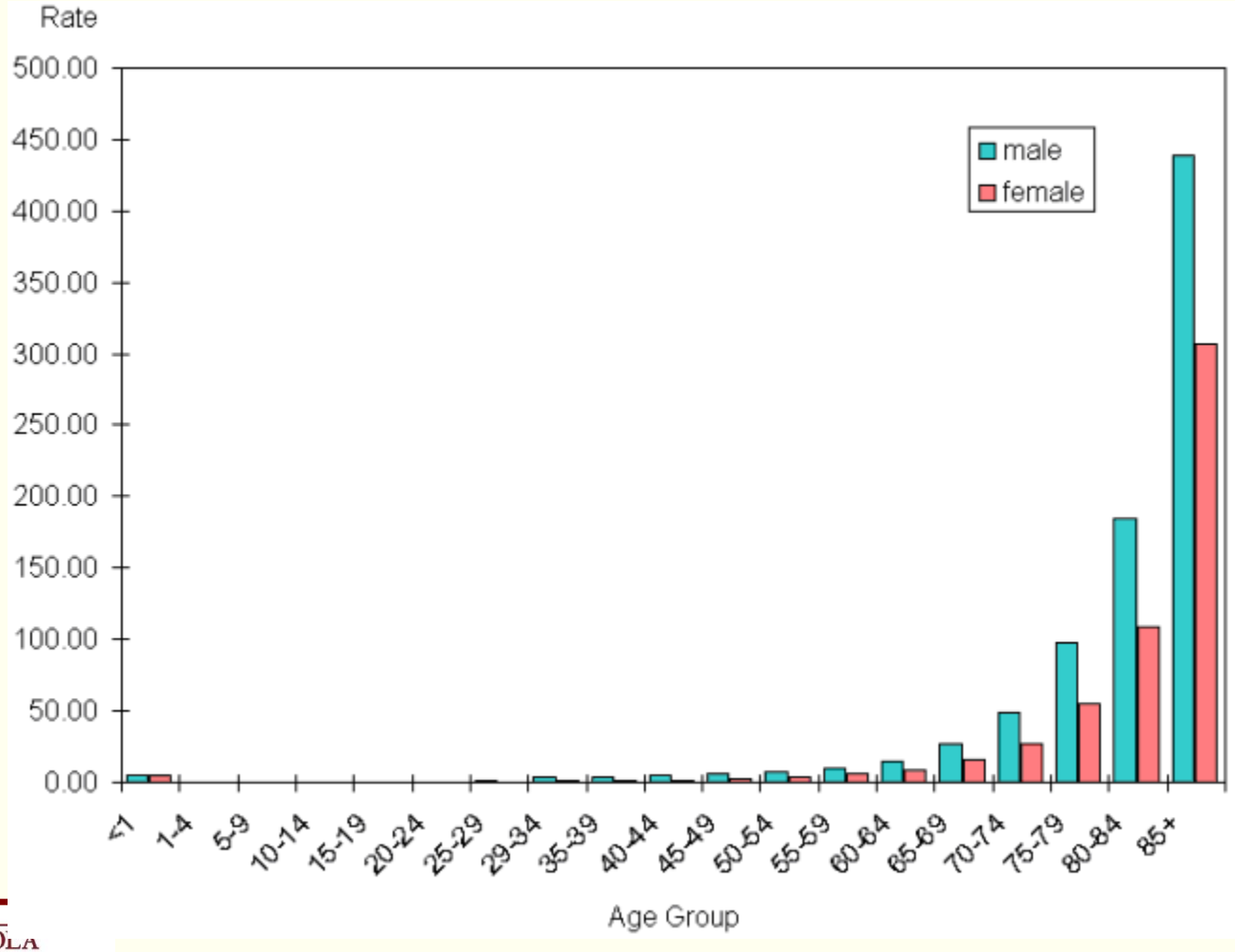
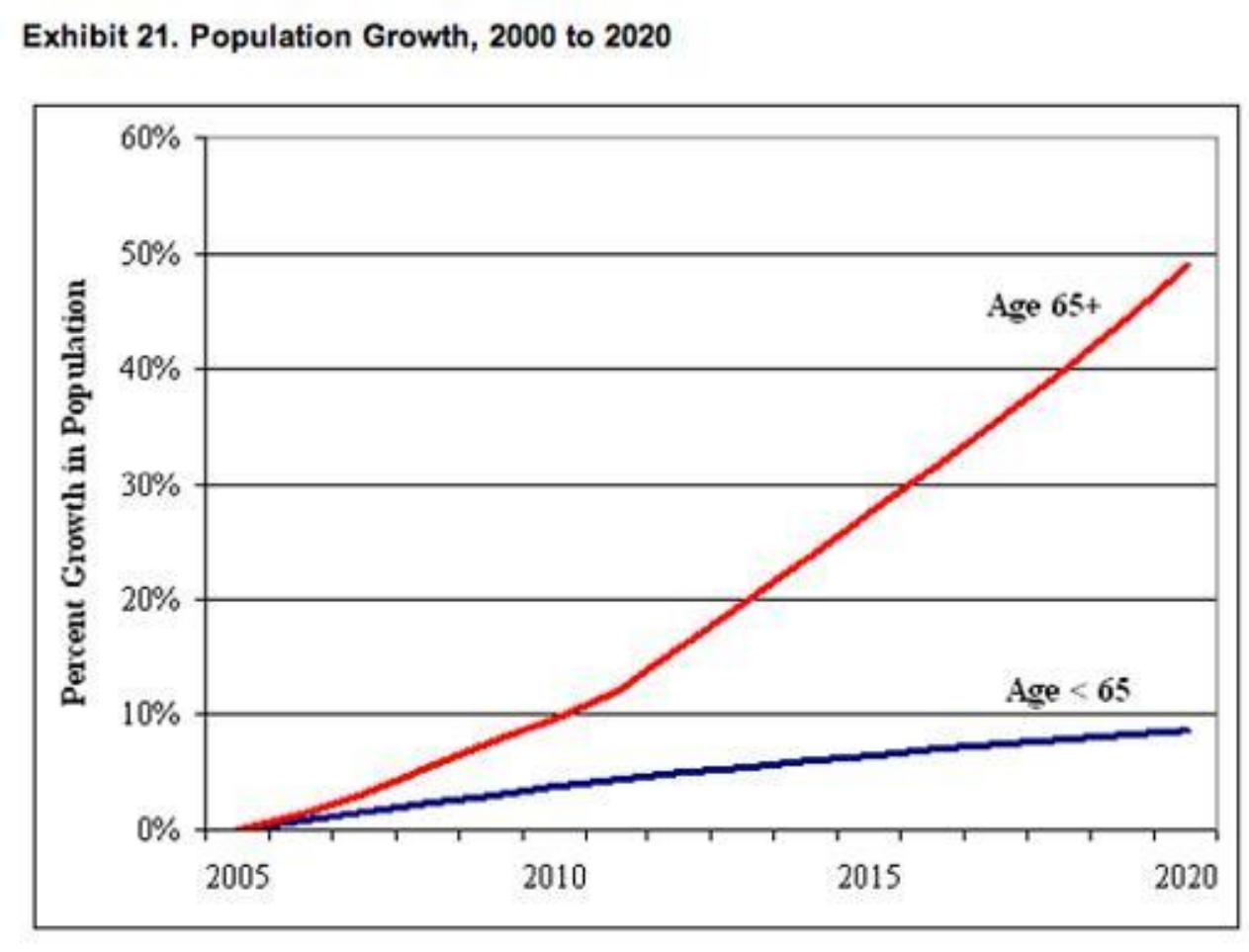
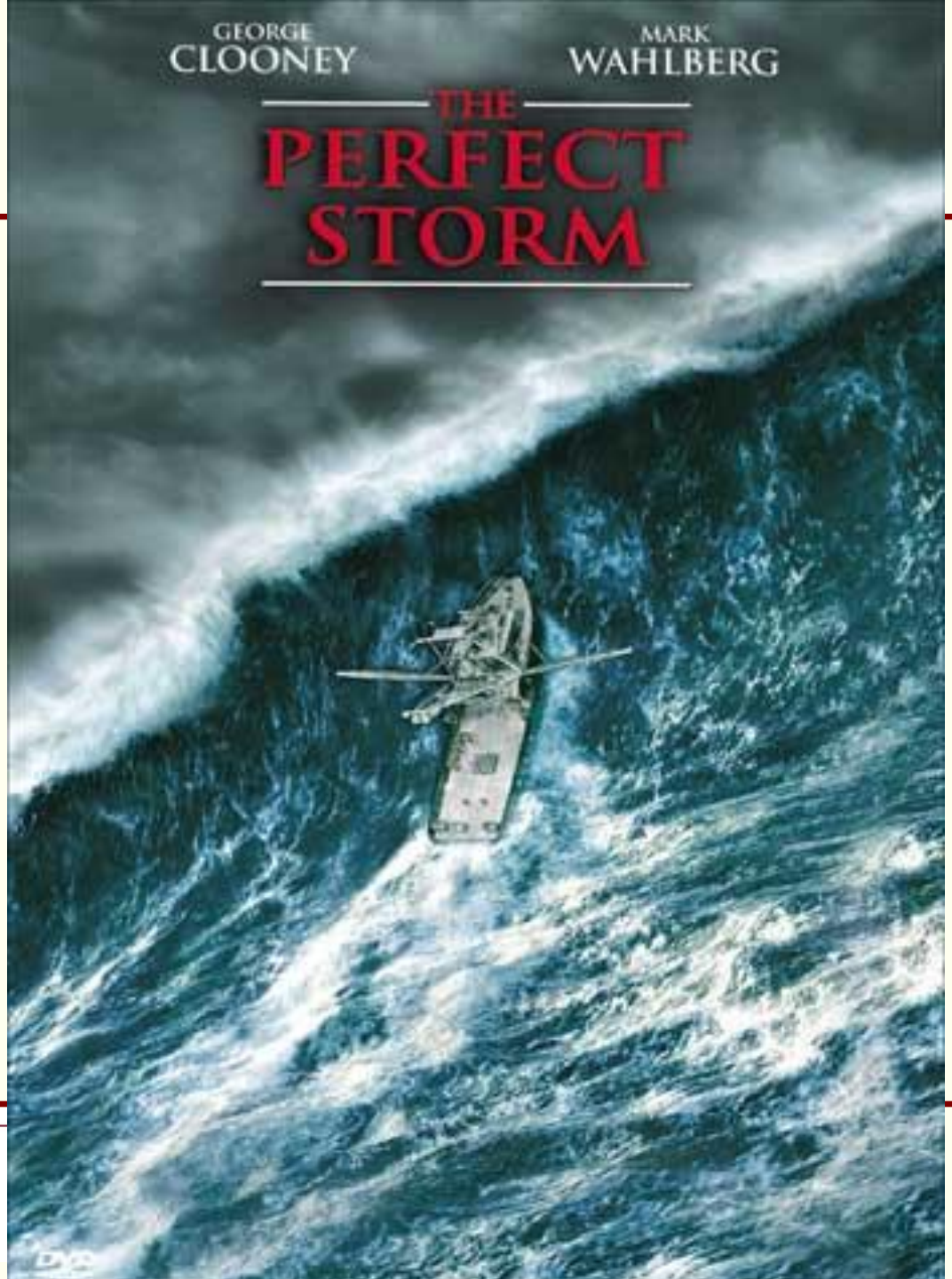
Healthcare Cost and Utilization Project (HCUP). http://hcupnet.ahrq.gov.

Elderly – CDI Mortality & Age



US Population & Age





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With this in mind…

We formed the:

The **C Diff** (reduction) **Task Force**…

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On the Importance of Planning…

Multidisciplinary TEAM

- Medical champion
- Nursing champions
- Infection preventionists
- Housekeeping
- Laboratory services
- IT services

- Staff & patient education

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Infection Control Strategies

- Diagnosis
- Hand hygiene
- Isolation and contact precautions
- Environmental disinfection
- Antimicrobial stewardship

SYSTEMS APPROACH

- Not run around yelling at mistakes…
- **MAKE IT EASY TO DO THE RIGHT THING**

- Empower employees
- Technology: Rapid PCR diagnostic testing
- Develop pathways / systems for early specimen collection & flagging results…
- Better IT – leverage emr / informatics

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Engaged Surveillance

Dr. Parada

Infection Control Team

C difficile Quality Improvement Collaborative

4/29/2010

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LOYOLA UNIVERSITY HEALTH SYSTEM
Loyola University Chicago

DAILY C DIFF BUNDLE

Clostridium difficile Infection

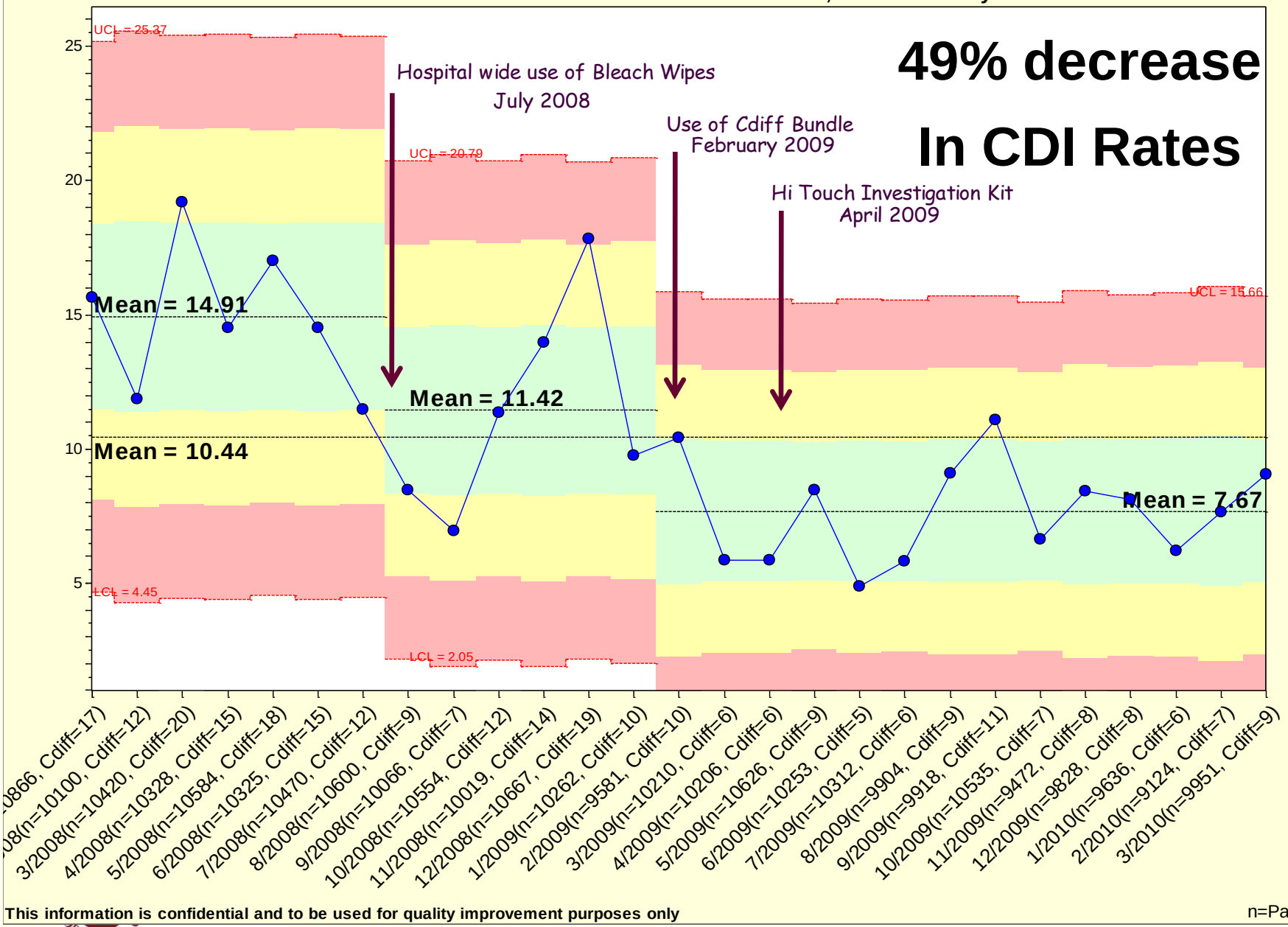
Cross-transmission minimization bundle

UNIT		NAME completing the C diff bundle		DATE completed	

Fax Daily to # 63476					
CDIFF STATUS: SUSPECTED (rule out) = S **CONFIRMED = C**					
BUNDLE CRITERION	**YES = Y** **NO = N**	**YES = Y** **NO = N**	**YES = Y** **NO = N**	**YES = Y** **NO = N**	**YES = Y** **NO = N**
1. CONTACT ISOLATION A. CDI& r/o CDI **patient is in contact isolation** in a single room with **"Contact Isolation" sign is on door**.					
B. CDI **patient has "Use Soap & Water"** sign on door. (NOTE: Two confirmed C. diff positive patients can be co-horted in a double room)					
3. EVERYONE USE PPE Checking all **healthcare workers and visitors don PPE** (gloves and gowns) before entering CDI & r/o CDI room and remove PPE after CDI patient care activity.					
4. DAILY BLEACH WIPES / SCRUB Service assistants cleaned and disinfected equipment, high touch areas and environment of CDI & r/o CDI patient today with a chlorine based wipe/solution with scrubbing motion.					
5. HAND WASHING Ensuring HCW's and visitors perform hand washing with liquid soap and water after leaving a CDI & r/o CDI patient's room.					

How did we do on the final?

Loyola University Medical Center
Infection Prevention and Control Program
Nosocomial C Difficile Infection Rates Per 10,000 Patient Days



This information is confidential and to be used for quality improvement purposes only

n=Patient Days

Some Words About C Diff Testing

SHEA/IDSA 2010 Guidelines for Diagnosis

- Testing for *C. difficile* or its toxins should be performed only on unformed stool (unless ileus is suspected)[1]

  ***Brecher rule:* *"If it ain't loose, it's of no use"*[2]**

- Testing asymptomatic patients is not clinically useful[1]

- Test of cure is not recommended[1]

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1.Cohen SH, et al. *Infect Control Hosp Epidemiol.* 2010;31(5):431-455.
2. Dr. Stephen Brecher, verbal communication.

CDI Current Diagnostic Options

Test	Advantage(s)	Disadvantage(s)
Toxin testing		
Enzyme immunoassay	Rapid, simple, inexpensive	Least sensitive method
Tissue culture cytotoxicity	More sensitive than enzyme immunoassay	Labor intensive; requires 24–48 hours for a final result, special equipment
Organism identification		
Detection of glutamate dehydrogenase (GDH)	Rapid, sensitive, may prove useful as a triage or screening tool	Not specific, toxin testing required to verify diagnosis; may not be optimally sensitive
PCR	Rapid, sensitive, detects presence of toxin gene	Cost, special equipment, does not necessarily indicate the presence of toxin; indiscriminant testing with PCR is a particular concern
Stool culture	Most sensitive test available when performed appropriately	Like GDH, may be associated with false-positive results if isolate is not tested for toxin; labor-intensive; not practical for most laboratories

C. difficile Testing in the US

- 95% of USA testing is not cytotoxin or culture

  - LC McDonald et al, EID 12, 409-24, 2006

- 101 microbiology laboratories surveyed
  - 4 (4%) routinely culture for *C. difficile*
  - 20 culture for special reasons (not as a diagnostic test)

  - P Gilligan, ClinMicroNet, October 31st, 2008

CDI TESTING…JUST MATH

- **CDI (ELISA A + B) Toxin Assay**
- Sensitivity: (65-85%) 70%
- Specificity: (80-95%) 90%
- Prevalence: (15-25%) 20%

	1000 Diarrhea			
	200 CDI	800 non-CDI	1000 Diarrhea	
Test #1	140	80	220 dx	780 no dx
Test #2	42	72	334 dx	666 no dx
Test #3	11	65	410 dx	490 no dx
TOTAL	193	217		½ patients!

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The Lessons of History

"Only a crazy person would do the same thing over and over and expect different results."

Albert Einstein

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What is the Consequence of a Low Sensitivity Test?

Goal: Find All Positive

- EIA (Sensitivity = 73.3%; Specificity = 97.6%)
  - 5 repeat tests
  - Total true positive = 100
  - Total false positive = 107
- PCR (Sensitivity = 93.3%; Specificity = 97.4%)
  - 2 repeat tests
  - Total true positive = 100
  - Total false positive = 49

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L Peterson and A Robicsek, Ann Int Med 151:176-9, 2009

Loyola Data

TABLE 2. Comparison of performance results for Xpert *C. difficile*, EIA, and two GDH algorithms compared to toxigenic culture with enrichment by site[a]

Site no.	Site assay	*n*	Sensitivity (%)		Specificity (%)		PPV (%)		NPV (%)	
			Xpert	Site	Xpert	Site	Xpert	Site	Xpert	Site
1[b,c]	Toxin A/B EIA	1,023	94.1	67.5	93.7	92.0	74.6	62.6	98.8	93.5
2[d]	GDH-EIA	268	91.4	74.3	93.6	94.8	68.1	68.4	98.6	96.1
3[e]	Toxin A/B EIA	293	92.3	53.8	94.5	97.6	72.0	77.8	98.8	93.2
4[f]	Toxin A/B EIA	312	91.4	54.3	94.2	95.7	66.7	61.3	98.9	94.3
5[g]	GDH-EIA-PCR	114	92.3	61.5	96.0	94.1	75.0	57.1	99.0	95.0
6[b]	Toxin A/B EIA	173	97.0	33.3	93.6	93.6	78.0	55.0	99.2	85.6
7[h]	Cytotoxin	110	90.9	54.5	94.9	98.0	66.7	75.0	98.9	95.1

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Tenover et al. Journal of Clinical Microbiology, October 2010, p. 3719-3724, Vol. 48, No. 10

Extrapolation of Loyola Data

- EIA (Sensitivity = 33%; Specificity = 94%)
  - 13 repeat tests **$1,430.00**
  - Total true positive = 100
  - Total false positive = **222**
- PCR (Sensitivity = 97%; Specificity = 94%)
  - 2 repeat tests **$70.00**
  - Total true positive = 100
  - Total false positive = **47**

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Consequences
(of an Unreliable EIA)

- Many patients withOUT C diff on Rx and in isolation
  - 1 test: 42% on isolation are false +
  - Costs & Patient Safety
- Many patients WITH C diff NOT on Rx and nor in isolation
  - 1 test: 67% cases not detected
  - Cost & Patient Safety

Consequences

- Undermines confidence in test
  - Physicians will leave test negative patients on isolation and treat them anyway
  - Increased LOS
- Undermines buy-in for use of PPE
- Increased environmental contamination
- Increased C diff transmission
- Increased C diff

Persistent Problem…

Research article

Open Access

How long do nosocomial pathogens persist on inanimate surfaces? A systematic review

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Type of bacterium	Duration of persistence (range)
Acinetobacter spp.	3 days to 5 months
Bordetella pertussis	3 – 5 days
Campylobacter jejuni	up to 6 days
Clostridium difficile (spores)	5 months
Chlamydia pneumoniae, C. trachomatis	≤ 30 hours
Chlamydia psittaci	15 days

Email – June 6, 2010

- "Quite literally, flipping a coin is more accurate then EIA testing"
- "We are not talking about spending more money for a marginally better test. We are talking about continuing to spend money on a useless test (EIA) vs spending money on a very good test."
- "Nobody questions the need for a CT scanner or MRI, simply because they provide so much better diagnostic information…like CT and MRI, PCR is an order of magnitude better test"

Stool Testing for C diff by PCR

Started July 1, 2010

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ASM Practical Guidelines for Toxigenic C. diff - Sept 21, 2010

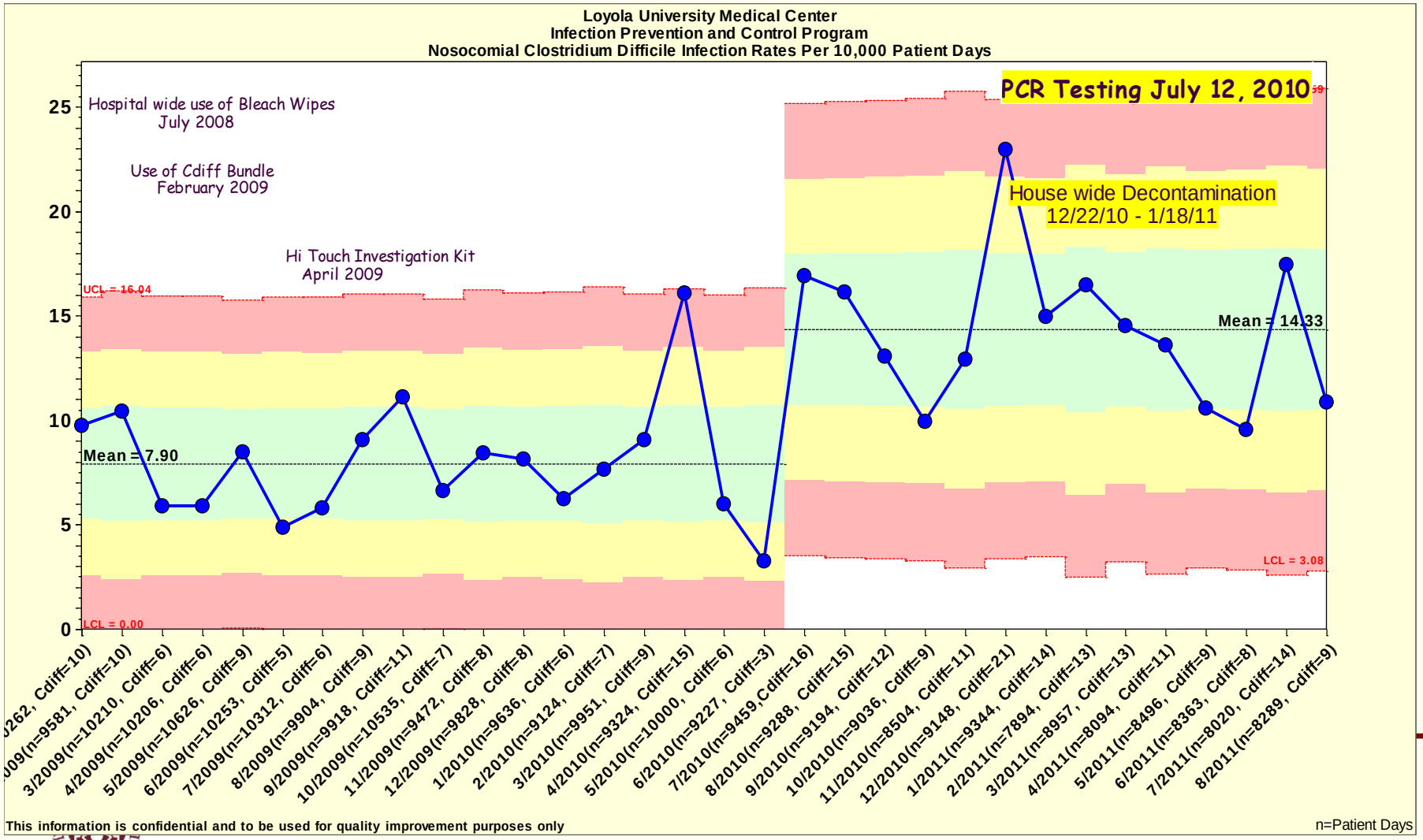
- Utilizing toxin A/B EIA for C. diff toxin diagnosis is insensitive and *not* recommended as a stand alone test
- Positive A/B EIA for C diff toxin must be confirmed with a positive cytotoxin test or Nucleic Acid Amplified Test (PCR)
- PCR may be used as a stand alone test

Early Experience with PCR

- CDI rates initially increase because of increased sensitivity (true prevalence detection)
- Test volume goes down by 50%
- Test materials cost offset by appropriate utilization of antibiotics and infection control protocols

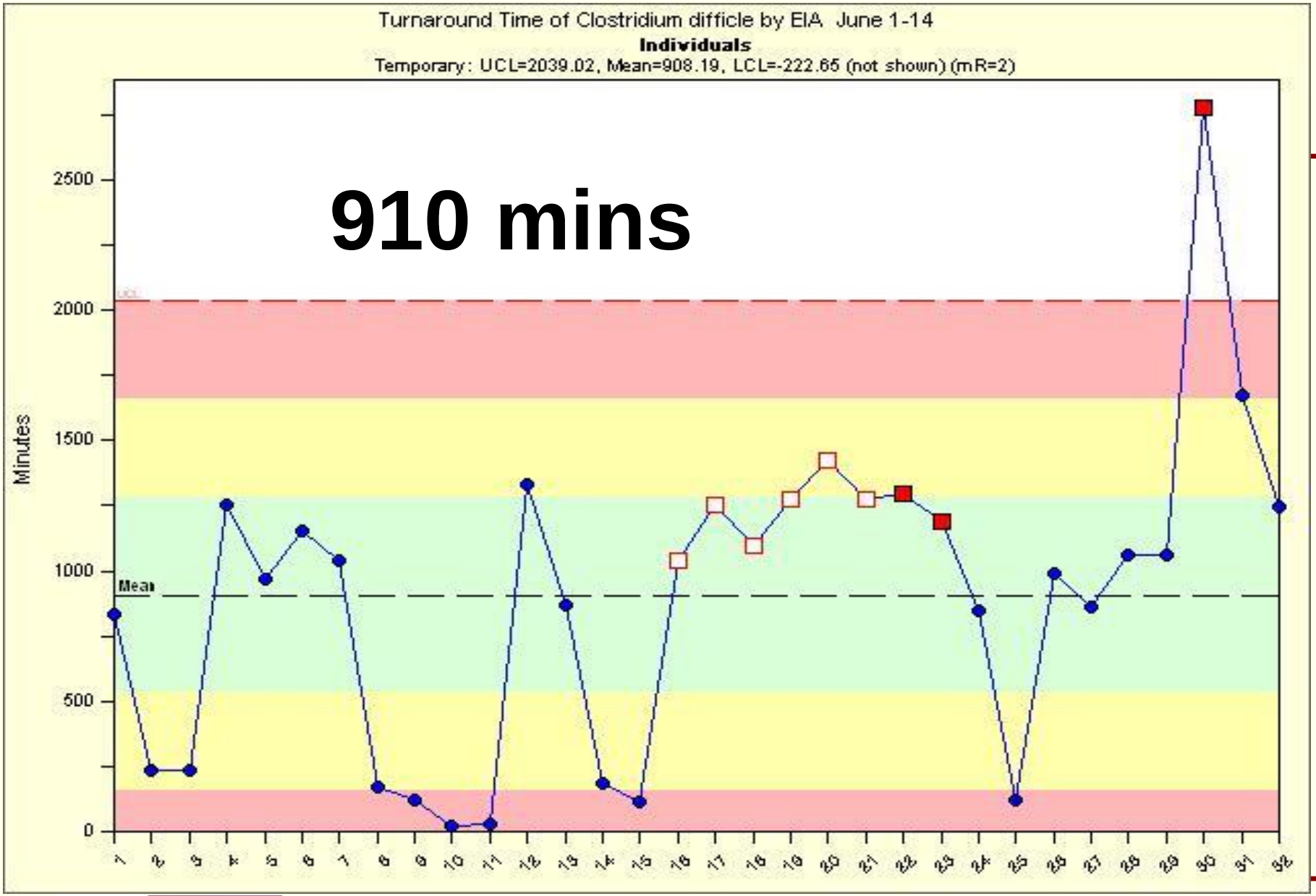
Belmares J, et al. SHEA 2011; Abstract #150.

Post PCR "Jump" in C diff Rates!



Micro Lab Opportunity Statement

- Decrease Turn Around Time (TAT) for C difficile toxin detection with PCR testing
- Increase sensitivity for the detection of patients with C. diff infections with PCR
- BETTER QUALITY OF CARE



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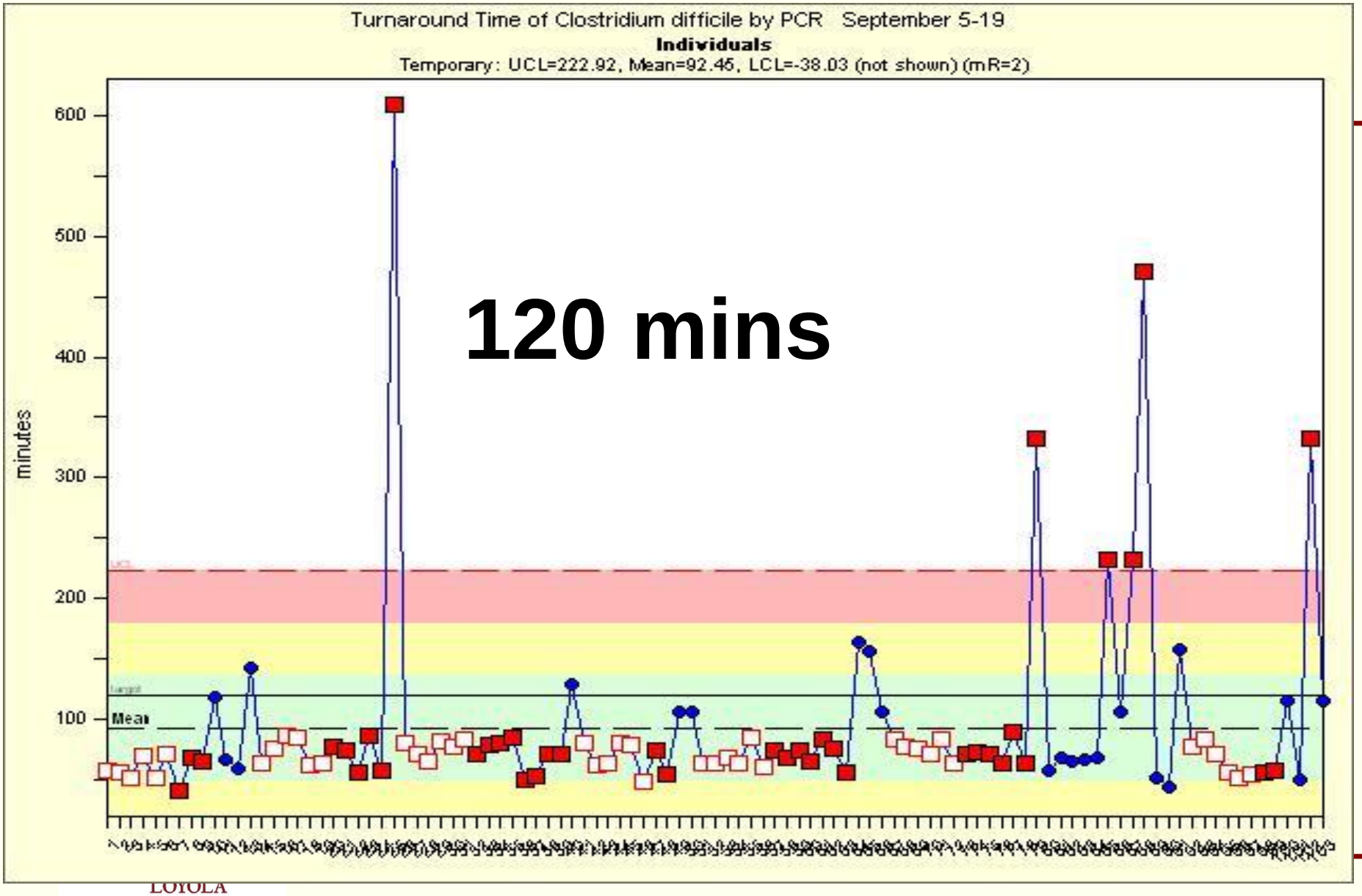

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Loyola Data

- The mean C diff testing TAT dropped 90%
  - (C diff PCR = 93 min vs EIA Assay = 909 min)

- C diff PCR assay detected 3/4 more positives (19% PCR vs 11% EIA)

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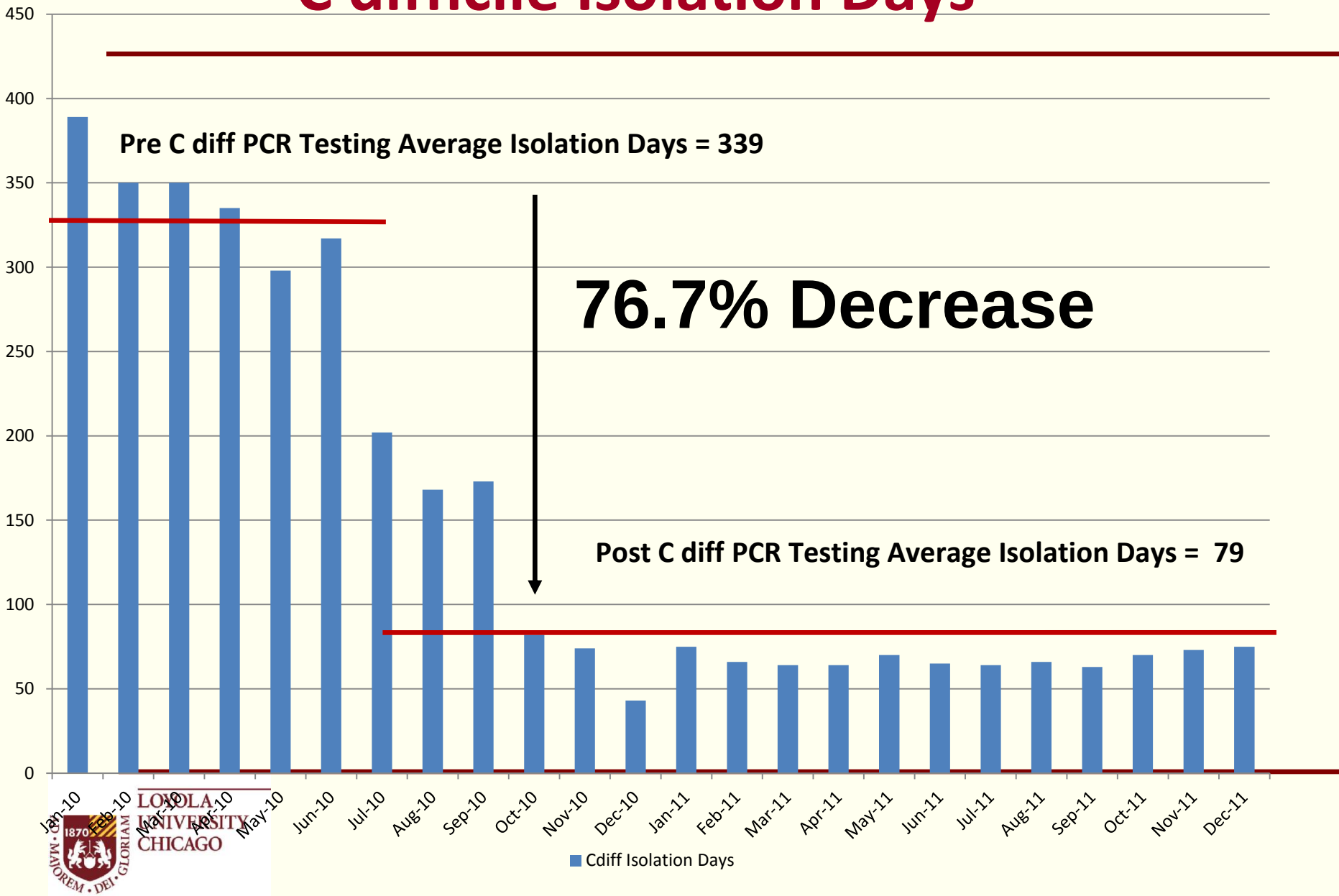
TAT = Turn Around Time

C difficile Isolation Days



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ID WEEK – National Meeting of IDSA-SHEA 2012

- "Impact of real time PCR testing for Clostridium difficile on antimicrobial use and patient management"
- Patients tested negative PCR vs EIA (2009 vs 2012)
  - Fewer C diff tests sent & less repeat testing ($p<0.001$)
  - Less meteroidazole & vancomycin use ($p=0.007$)
  - Fewer C diffile antimicrobial treatment days ($p=0.004$)
  - Less diagnostic radiology testing (Abd X-ray, $p=0.013$ & CT scan, $p=0.002$)
  - Fewer Infectious Diseases consultations ($p=0.033$)
  - Less Sigmoidoscopy/colonoscopy ($p=0.006$)
  - Lower LOS (21% decrease)

Impact of Rapid C diff PCR at LUMC

- Decreased C diff testing
- Decreased C diff isolation days
- Decrease PPE use
- Decreased blocked beds
- Decreased ancillary testing & ID consultation
- Decreased LOS
- Better antibiotic stewardship
- Plus…decreased anxiety from false + diagnosis

Not Just Wishful Thinking…

Contents lists available at ScienceDirect

American Journal of Infection Control

journal homepage: www.ajicjournal.org

Major article

Real-time polymerase chain reaction testing for *Clostridium difficile* reduces isolation time and improves patient management in a small community hospital

Mary Catanzaro RN, BSMT, CIC*, Justin Cirone BS

From the Infection Prevention Department, Pocono Medical Center, East Stroudsburg, PA

Key Words:
Isolation reduction
Accurate testing
Health care associated infection
Nosocomial infection

Background: The impact of a switch from a toxin A/B enzyme immunoassay (EIA) to a polymerase chain reaction (PCR) method for detection of toxigenic *Clostridium difficile* was assessed for *C difficile* infection (CDI) rates, patient isolation-days, and CDI-related treatment.
Methods: A 6-month retrospective study was done on symptomatic patients tested by the toxin A/B EIA and PCR assays. Data on the number of *C difficile* tests ordered, patient isolation-days, and treatment with metronidazole or vancomycin were collected. CDI rates were reported as cases per 10,000 patient-days, and differences between both groups were compared by χ^2 and Z-test analysis.
Results: The CDI incidence was 11.2 and 12.7/10,000 patient-days in the EIA and PCR test periods, respectively (P .36). Health care-associated CDI decreased from 4.4 per 10,000 patient-days during EIA testing to 0.9 per 10,000 patient-days during PCR testing (P .02). A significant decrease in patient isolation-days ($P < .00001$), tests ordered (P .002), and metronidazole treatment for patients with a negative *C difficile* test (P .02) was observed with PCR testing.
Conclusion: PCR testing is a viable option for small community hospitals, providing accurate and timely results for patient management and infection control. This can potentially lead to improved outcomes, increased patient satisfaction, and significant hospital cost savings.

3 C. difficile Testing Take Home Rules

1. Don’t use EIA as a stand alone test
   - Two-step or PCR as stand alone test

2. Don’t test formed stool
   - (only test symptomatic patients = diarrhea)

3. No test of cure
   - (only test symptomatic patients = diarrhea)

Economic Burden of CDI

MORE...
MORE...
MORE!

THE END