Clostridium difficile Infection: Burden, Diagnostics and Recurrence

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EMORY UNIVERSITY

Emerging Infections Program GEORGIA

DEPARTMENT OF VETERANS AFFAIRS UNITED STATES OF AMERICA

Disclosures

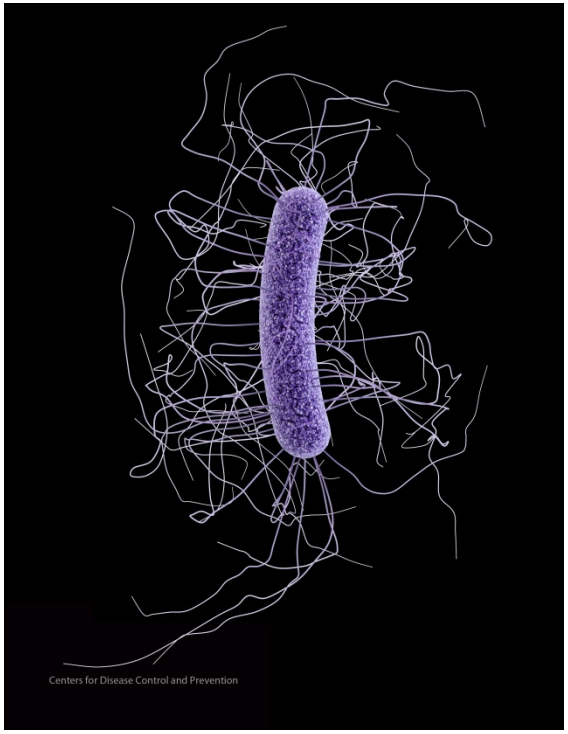
- Nothing to disclose

Outline

- Diagnostic testing for CDI
  - Change to more sensitive methods
  - Colonization vs Infection
  - Implications for providers, laboratories, and infection control
- Burden of CDI
  - National estimates
  - Multiple recurrences
- CDI trends in metro Atlanta
  - Impact of changing diagnostics on incident and recurrent case counts

C. Difficile Infection (CDI)

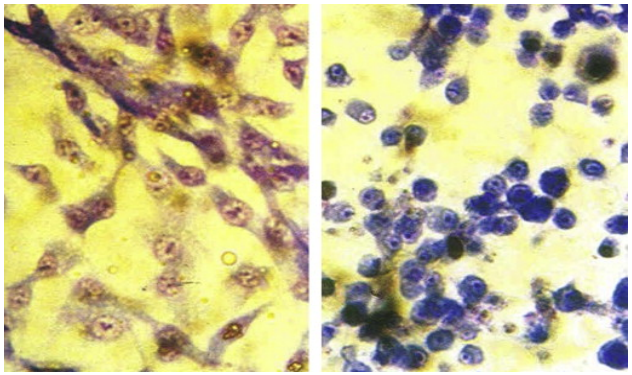
- A leading cause of healthcare-associated infections
- Clinical syndromes
  - Asymptomatic→ severe diarrhea→ death
- Recurrence
  - 15-30% of all CDI have a recurrence
- Changing diagnostics
  - More sensitive methods
  - Increased incident rates
- Public reporting
  - Soon tied to reimbursements

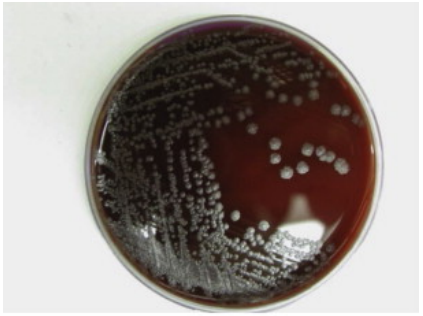


Diagnostic tests for *C. difficile* Infection

Reference tests

- **<u>Cell culture cytotoxicity neutralization assay (CCCNA)</u>**
  - Detects free toxin in feces
  - Cell culture, look for cytopathic effect, see if effect is neutralized by antibodies to toxins
- **<u>Toxigenic culture</u>**
  - Detects organisms (spores) that produce toxins
- Labor and time intensive





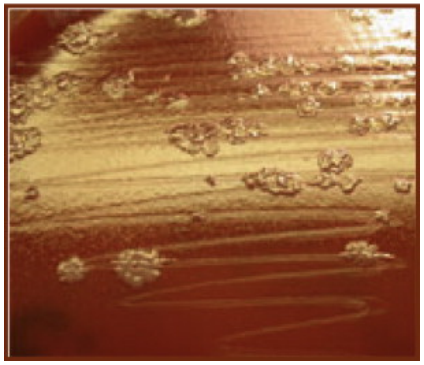


Planche T, Wilcox MH, Infect Dis Clin North Am 2015.

Diagnostic tests for *C. difficile*

- **Enzyme immunoassay (EIA):**
  - Detects toxin A and B
  - Inexpensive but low sensitivity (as low as 60%)
- **Nucleic acid amplification test (NAAT):**
  - Molecular test (PCR, LAMP) for toxin-producing gene (e.g. *tcdA* or *tcdB*)
  - High sensitivity, but expensive
  - Unable to discern carriage vs true infection
- **Glutamate dehydrogenase immunoassays (GDH)**
  - Detects conserved antigen common to toxigenic and non-toxigenic strains
  - Only used in combination with another test
- **Algorithms:**
  - GDH/EIA
  - GDH/NAAT, GDH/EIA/NAAT
  - Higher sensitivity than EIA while controlling cost

Burnham CA et al. Clin Microbiol Rev 2013.

Comparison of methods

	Sensitivity	Specificity	Cost	Comment
EIA	Low	Moderate	$	
GDH	High	Low	$	
NAAT	High	Low/moderate	$$$	Colonized vs infected?
Algorithms	Moderate/High	Moderate/High	$$	Multiple versions

Colonization ≠ Infection

- Asymptomatic colonization is common
  - 2% of community dwellers
  - 7-18% of admitted patients
    - Highest in those previously admitted
  - 20% of discharged patients
  - Up to 50% of long term care facility residents
    - Ratio of asymptomatic colonized to CDI: 7:1
- Diarrhea is common in hospitals
  - 12% of hospitalized patients have diarrhea
  - Not all diarrhea is CDI
    - *C. difficile* responsible in 4-30%

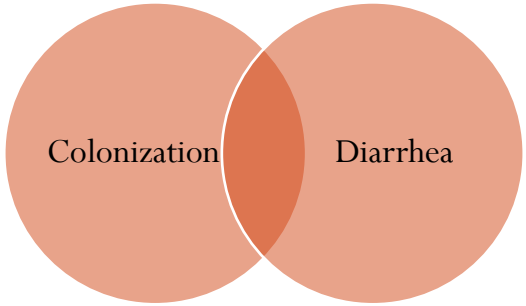
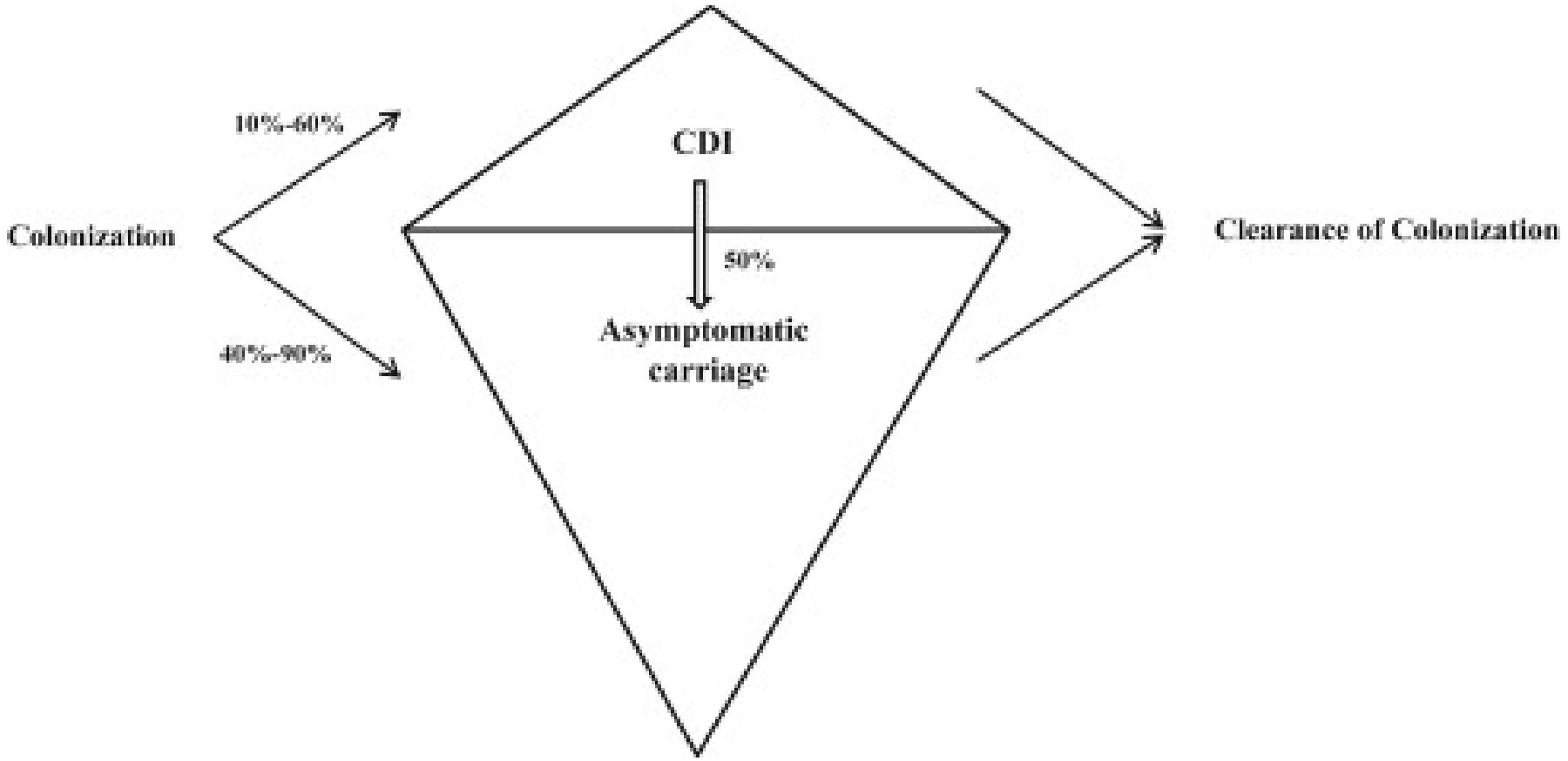


Planche T, Wilcox MH, Infect Dis Clin North Am 2015. Donskey CJ et al, Infect Dis Clin North Am 2015

Natural history

Colonization, Infection and Shedding

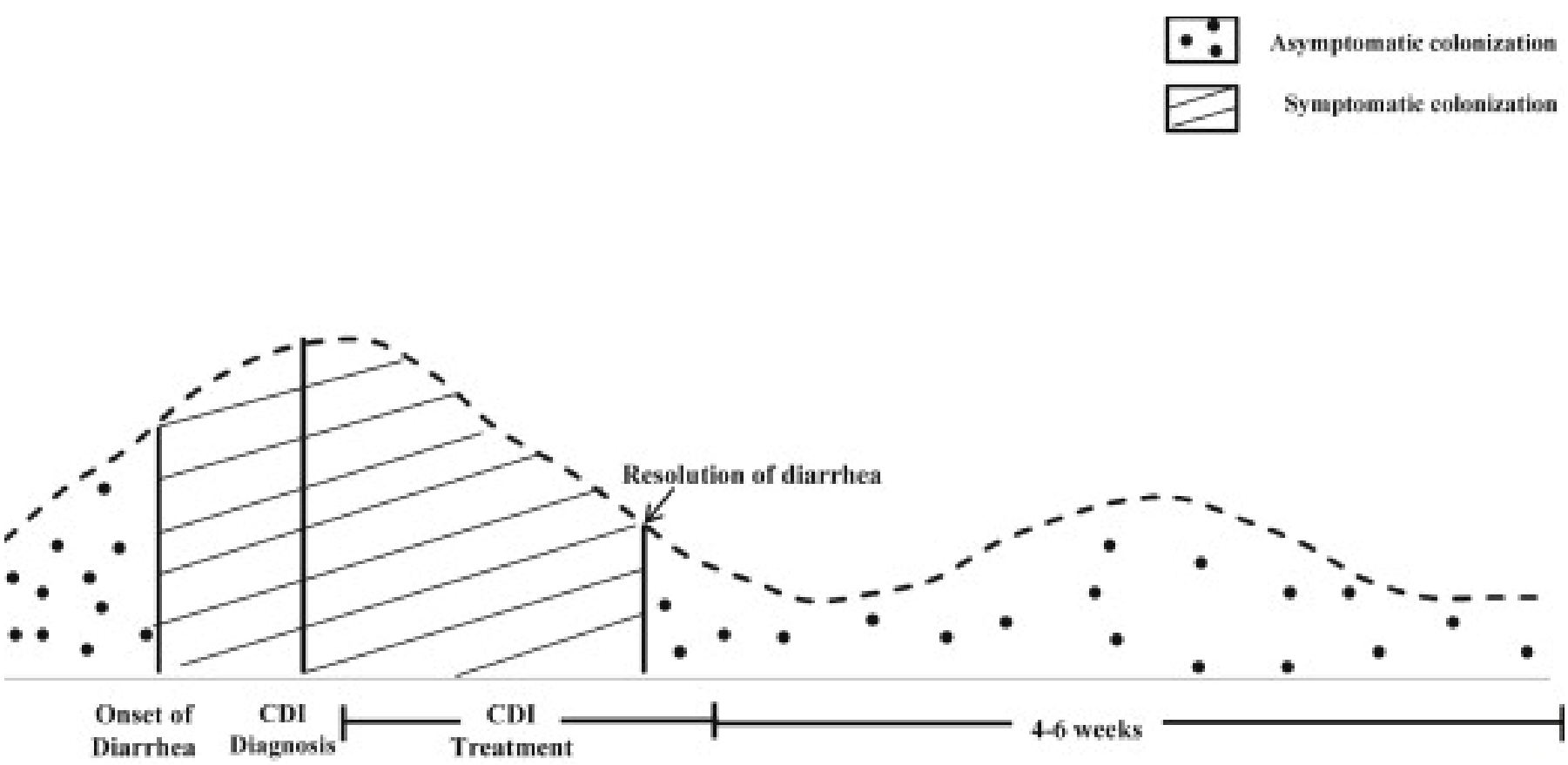
Outcomes after colonization



Donskey CJ et al, Infect Dis Clin North Am 2015

Shedding of *C. difficile*

Stool, skin and environment



Donskey CJ et al, Infect Dis Clin North Am 2015

Colonizers shed less than infected patients

	Patients with CDI contaminating:		Asymptomatic colonizers contaminating	
	Skin	Environment	Skin	Environment
Medical ward		49%		29%
LTCF residents	78%	78%	61%	61%
Acute care	83%	67%	11%	11%
Oncology unit		20%		7%

Donskey CJ et al, Infect Dis Clin North Am 2015

- Who should be tested?
- Which stool should be tested?
- Who is transmitting the bacteria?
- What should we do with asymptomatic colonizers?
- What happens next?

Who should be tested?

Providers:

- Inappropriate ordering
  - 36% of pts with CDI tests did not have clinically significant diarrhea
  - 20% were on a laxative
- TEST OF CURE IS NOT RECOMMENDED!

Laboratories:

- Stool rejection policies of formed stool
  - Often implemented with NAAT testing
  - Repeat testing limitations
    - Recent positive tests: clinical cure?
    - Recent negative test: high sensitivity of initial NAAT test

Dubberke J Clin Microbiol 2011

Which stool to test?

- 3rd loose stool in 24 hrs (IDSA/SHEA guidelines):
  - Improved diagnostic yield of true infection
  - Later isolation → increase transmission (?)
- 1st-2nd loose stool in 24 hrs (European guidelines):
  - Early isolation and treatment
  - Over diagnose colonization → over treat CDI, underdiagnose other causes

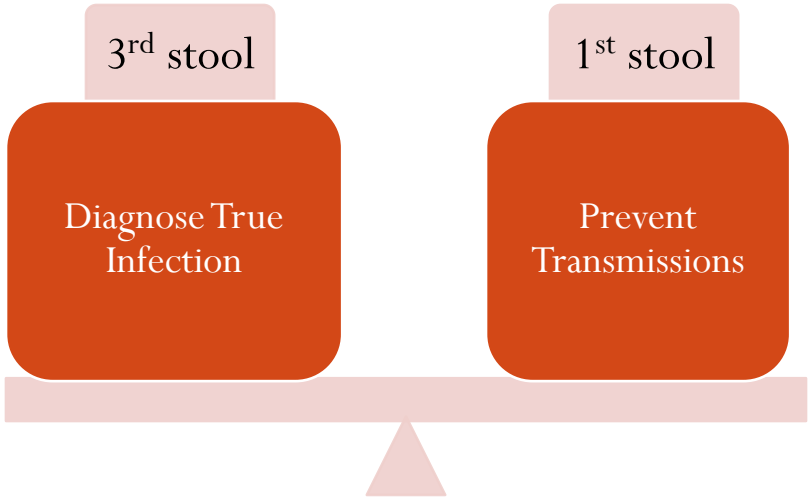


Planche T, Wilcox MH, Infect Dis Clin North Am 2015

Who is transmitting the bacteria?

- Whole genome sequencing of all CDI in Oxfordshire, England
  - 1,223 cases from 2007-2011
  - Non-outbreak setting
  - Excellent, well-established infection control measures
  - Antibiotic stewardship
- 45% of CDI cases were genetically distinct from previous cases
  - Transmission from sources other than symptomatic patients
    - Asymptomatic colonizers? The environment?

Eyre et al. NEJM 2013

Potential interventions for asymptomatic colonization

- Screening and isolation
  - Expensive (NAAT testing) or delayed (cultures)
  - Resource intensive with unknown benefit
  - Can we identify the super-shedders?
- Decolonization
  - Treatment does not eradicate colonization
  - CDI treatment contributes to dysbiosis→ patient harm
- Skin and environmental disinfection
- Antibiotic stewardship interventions

Donskey CJ et al, Infect Dis Clin North Am 2015

Future directions in diagnostics

- Canines?
- Biomarkers
  - Lactoferrin
  - Calprotectin
  - Cytokine analyses

- Reverse algorithms

  National Health Service (England)
  - NAAT or GDH first (screen)
    - If positive then EIA
  - NAAT+ and EIA+ = *C. difficile* infection
  - NAAT+ and EIA- = "potential fecal excretor"
    - Do not need CDI treatment, other causes should be considered
    - But may consider isolation precautions

- Diagnostics will evolve:
  - Relies on lab-provider-epidemiologist communication

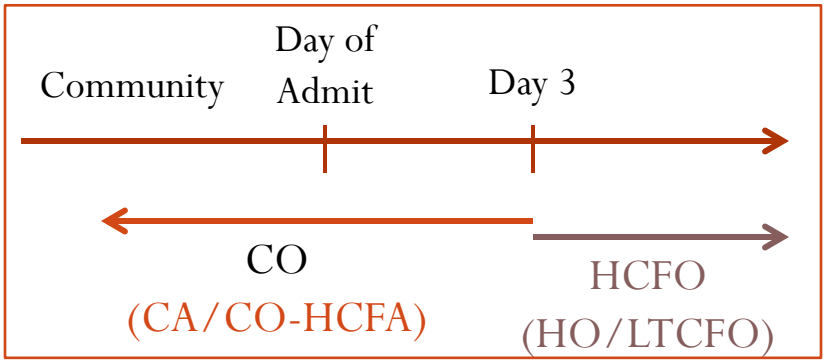
Burden of CDI

In the United States and in Atlanta

Epidemiological Classification

HCFO (Healthcare Facility Onset)

- CDI ≥ three days after admission to hospital,
- Stool collected at LTCF or LTACH,
- Or admitted from LTCF
  - **HO** (Hospital Onset):
    - CDI in acute care setting
  - **LTCFO** (Long-term Care Facility Onset):
    - Stool collected in LTCF
    - Or admitted from LTCF



CO (Community Onset):

- CDI in outpatient setting,
- Or within first 3 days of hospitalization
  - **CO-HCFA** (Community Onset-Healthcare Facility Associated):
    - Healthcare exposure 12 weeks prior to CDI
    - Overnight stay in healthcare facility or resident of LTCF
  - **CA** (Community Associated):
    - No healthcare exposure 12 weeks prior to CDI
    - No overnight stay nor resident of LTCF

LTCF: long term care facility/skilled nursing facility
LTACH: long-term acute care hospital

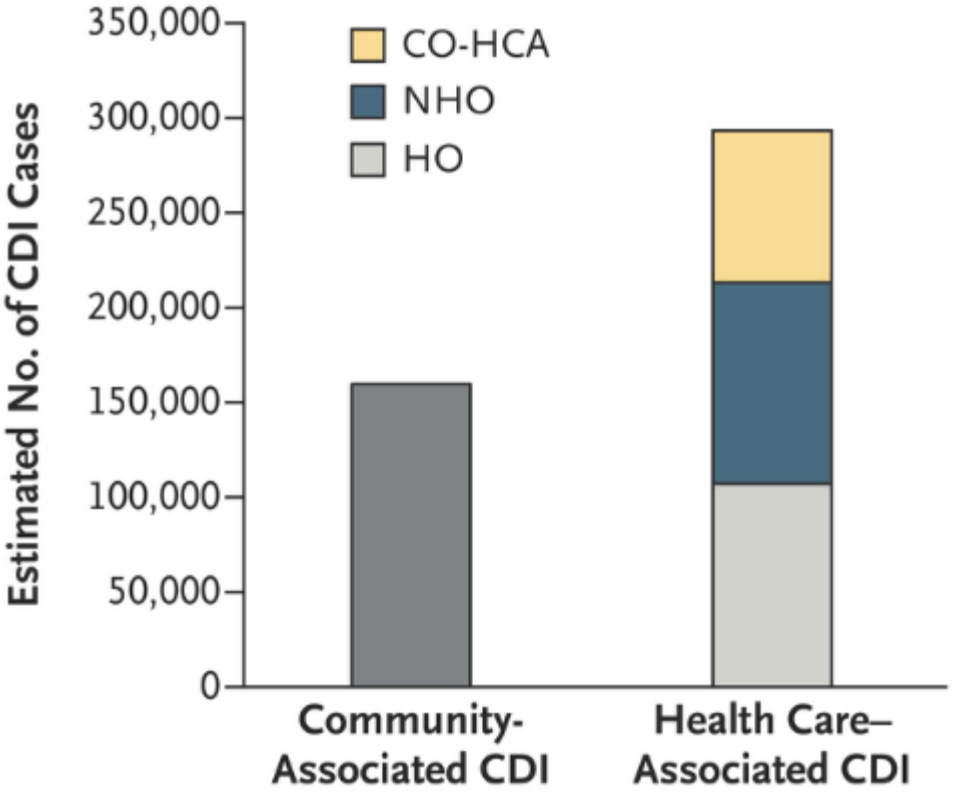
CDI in the US in 2011

- Incident cases: ~453,000 cases in US
  - 65% health care-associated
  - 24% health care onset
  - NAP1 more common in healthcare associated disease than community associated
- First recurrences: ~ 83,000 cases
- Deaths after CDI: ~29,300 cases
- CDI rates:

All CDI:	147 cases/100,000 persons
> 65 yo:	627 cases/100,000 persons
Females:	163 cases/100,000 persons
White:	162 cases/100,000 persons
First recurrences	27 cases/100,000 persons
Deaths	10 cases/100,000 persons

Lessa F et al, NEJM 2015

National estimates of CDI



CO-HCA: community onset- health care associated; NHO: nursing home onset; HO: hospital onset

Lessa F et al, NEJM 2015

Survey of health care associated infections (HAI) in acute care facilities

- One day survey of 183 hospitals; 11,282 patients
- 4% (452 patients) had 1 or more HAI
- Most common pathogen:
  - *C. difficile* (12%)
  - *S. aureus* (11%)
  - *Klebsiella* (10%), *E. coli* (9%), *Enterococcus* (9%), *Pseudomonas* (7%), *Candida* (6%)
- Types of infection:
  - Pneumonia (22%)
  - Surgical site infections (22%)
  - Gastrointestinal infections (17%)
    - 71% due to CDI
- Device-associated infections: 25%
- Estimated 648,000-721,800 HAI in US hospitals in 2011

Magill S et al, NEJM 2014

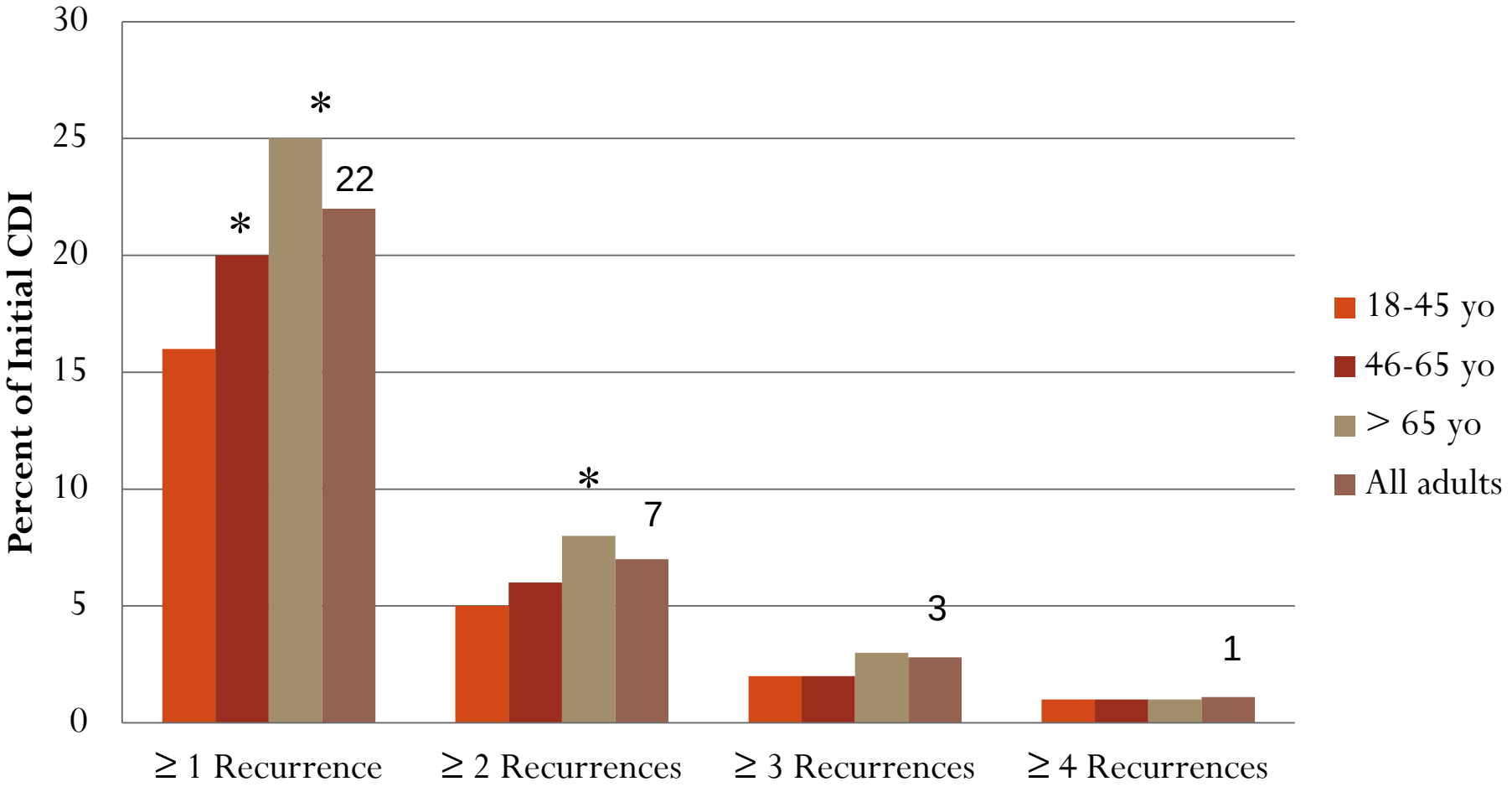
Multiple CDI Recurrences

Risk for multiple recurrences in metro Atlanta 2010-2013

- Initial cases
  - No history of previous positive
  - Age >18 years old
  - Followed minimum 3 months. Average 24.5 months
- Initial episode:
  - 11,945 initial cases
  - 60% female
  - 49% >65 years old
- Recurrence:
  - Any subsequent positive >14 days from initial (or a recurrent test)

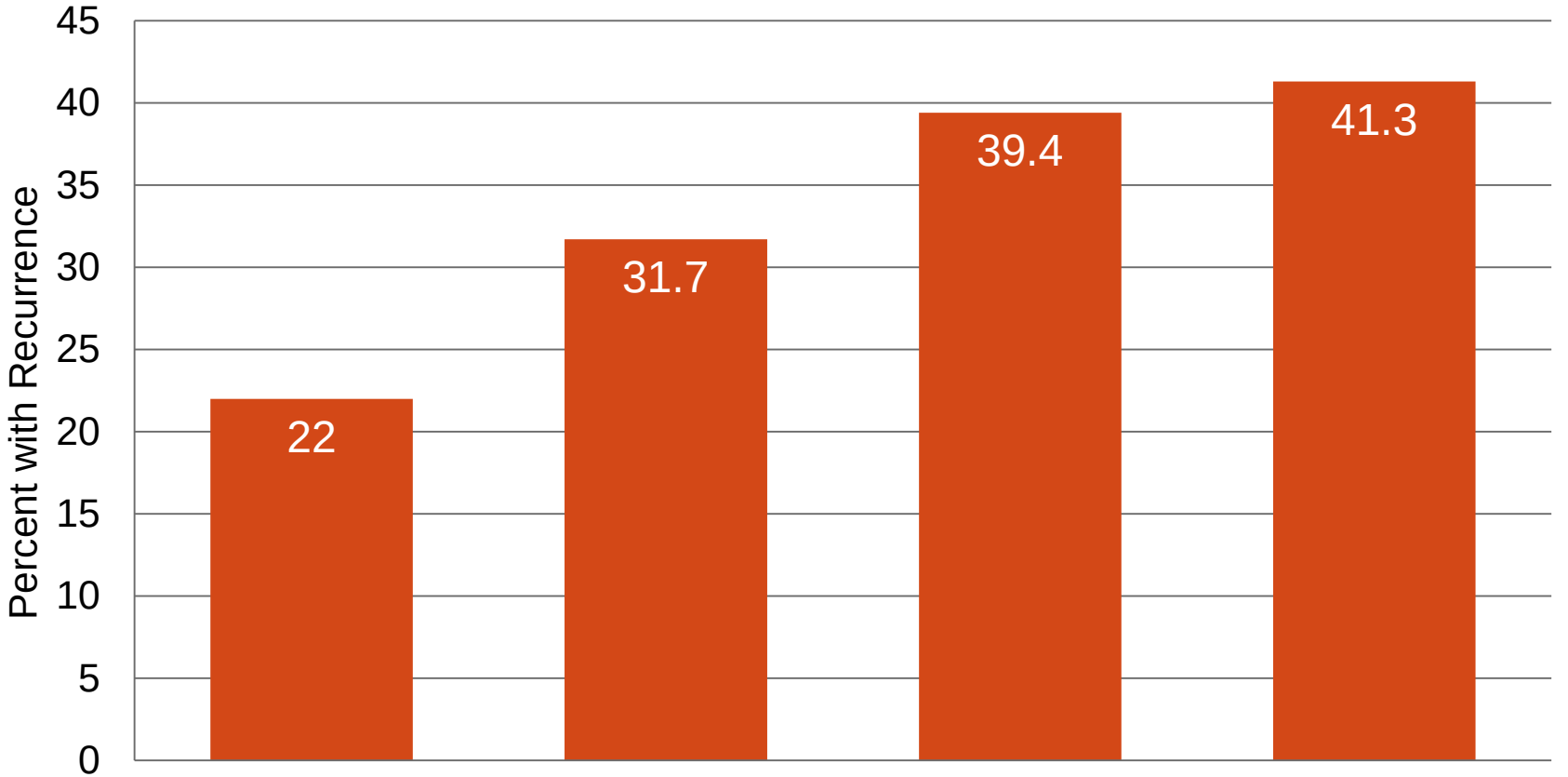
Reddy SC et al, ID Week 2014

Risk of Recurrent CDI By Age (n=11,945)



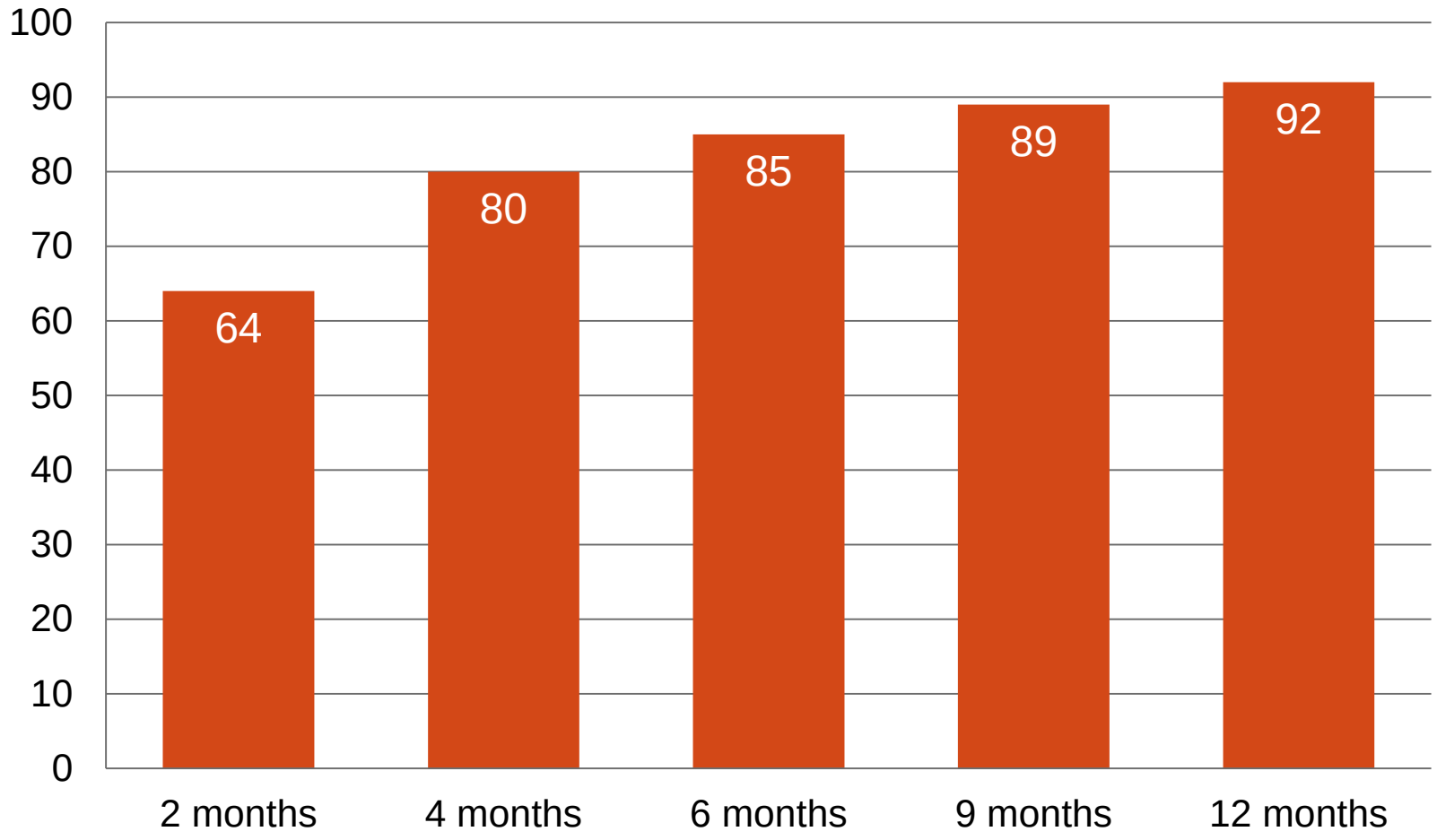
* Compared to 18-45 yo: p<0.05

Increased Risk for Subsequent Recurrences



	≥ 1 Recurrence	≥ 2 Recurrences	≥ 3 Recurrences	≥ 4 Recurrences
# at risk	11,945	2,629	834	329
# with subsequent recurrence	2,629	834	329	136

When do Recurrences Occur?
Cumulative Proportion of 1st Recurrence by Time from Initial
In patients with >1 year of follow up (n=9,745)



The median number of days to 1st recurrence was 39 days (IQR: 24-85)

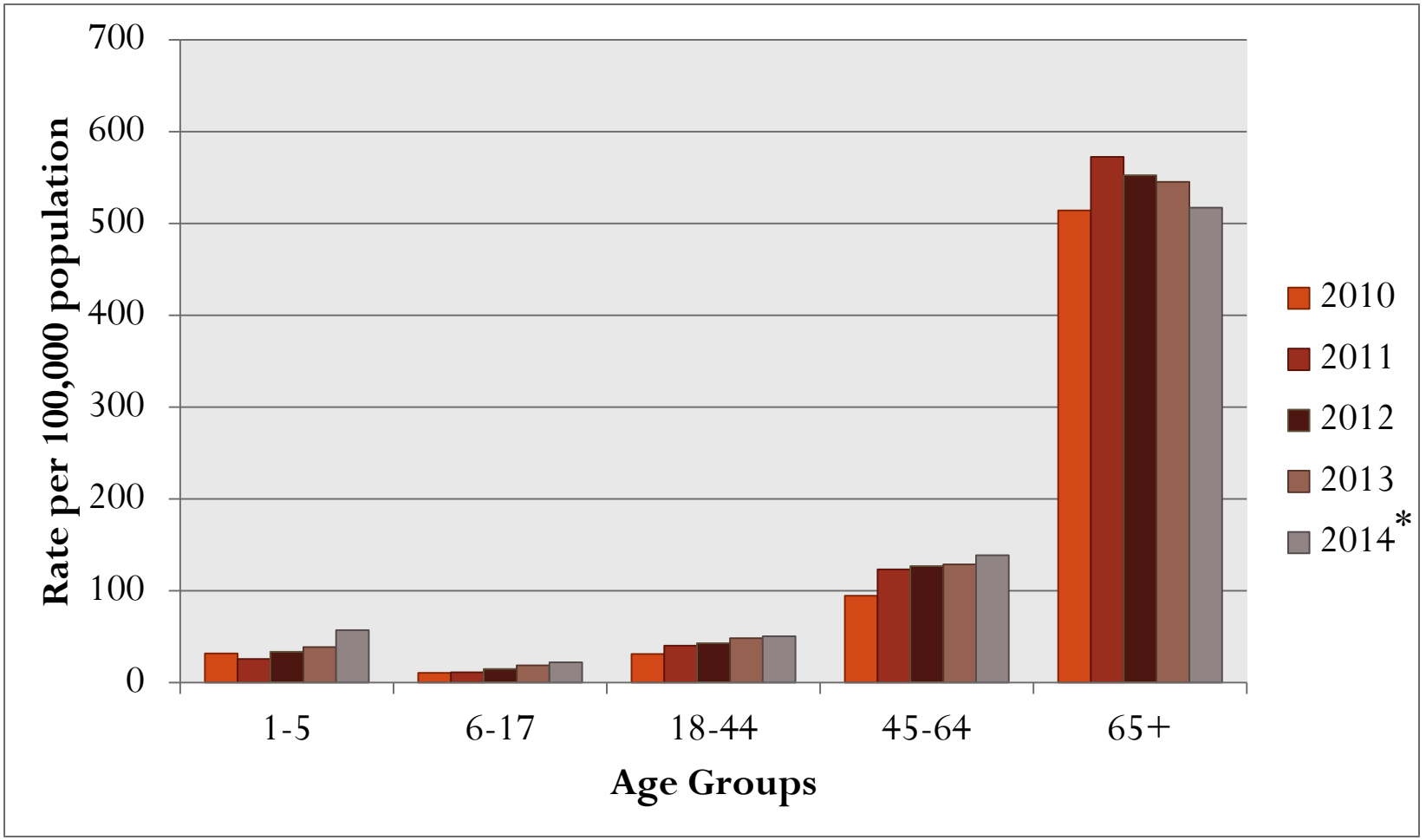
Patients go to different labs!

- >30% of 1st recurrences were diagnosed at a different lab than the initial episode
- Single laboratory site analyses could underestimate risk of recurrent disease

C. Difficile Infection in Metro Atlanta

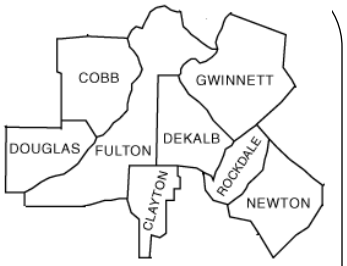
Impact of Changing Diagnostics

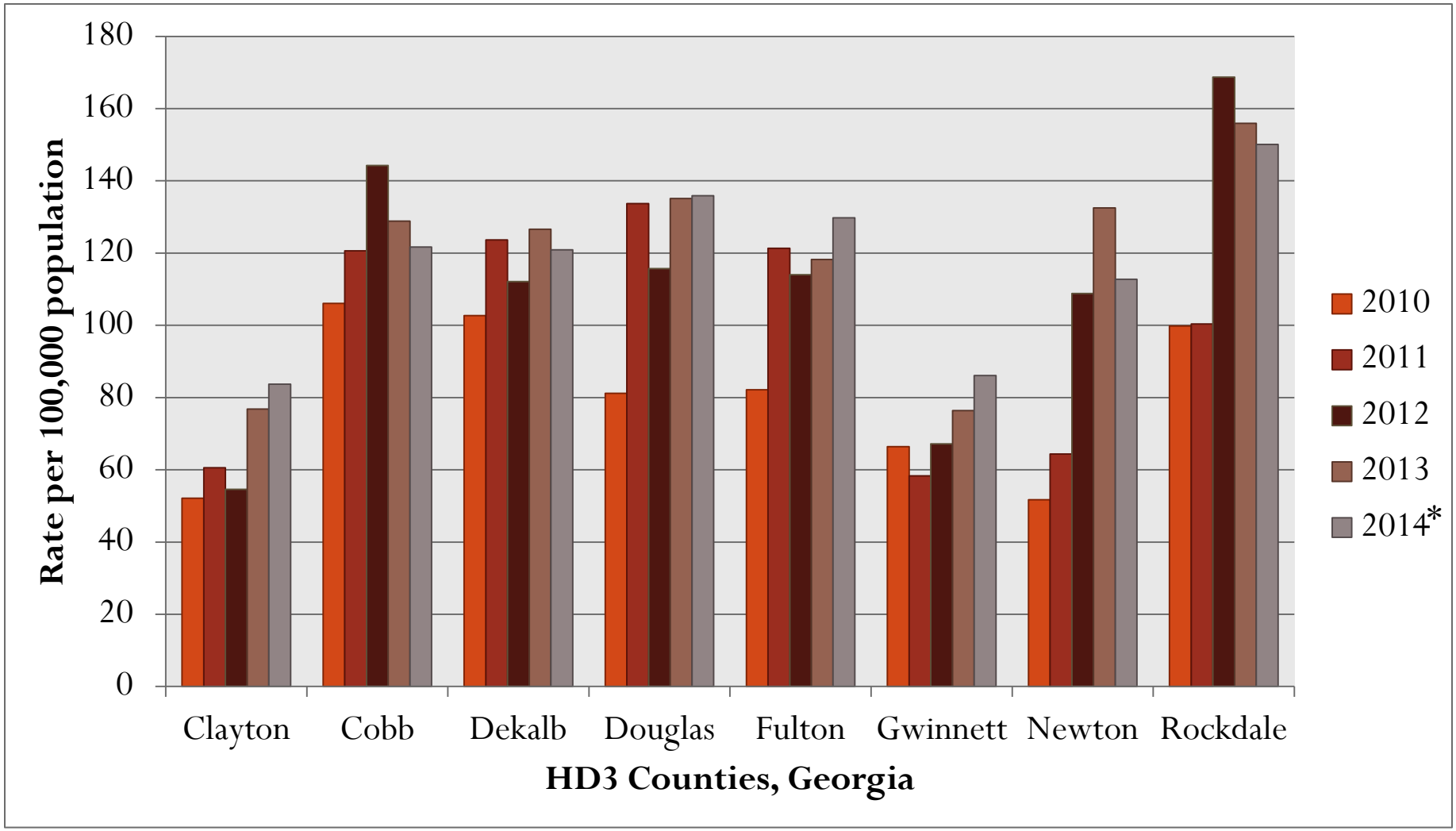
CDI Rates by Age Group 2010-2014*



*2014 data incomplete and uses 2013 population estimates

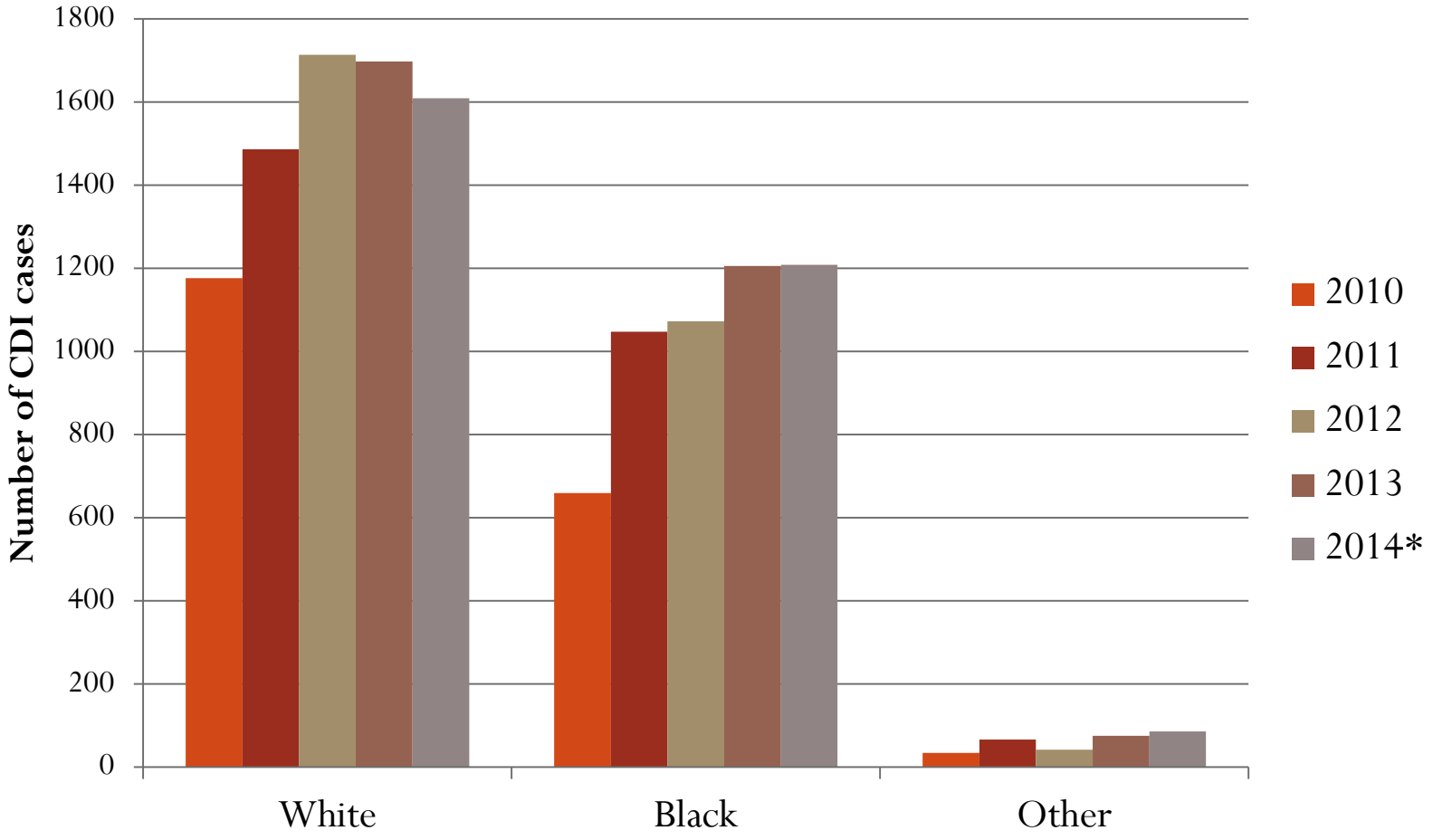
Rates by County 2010-2014*





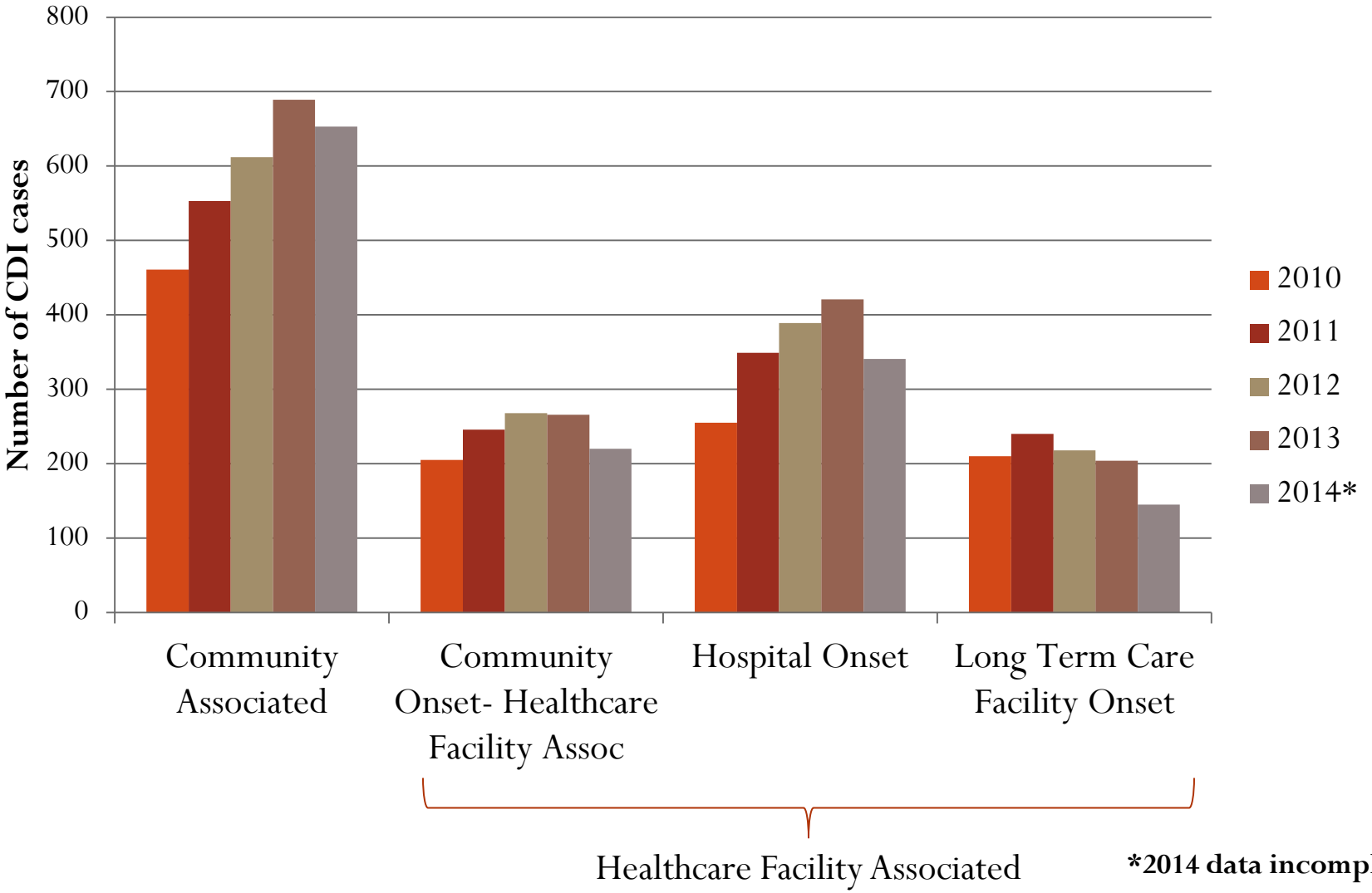
***2014 data incomplete and uses 2013 population estimates**

Case counts by Race 2010-2014*



***2014 data incomplete**

Case counts by Epidemiologic classification 2010-2014*

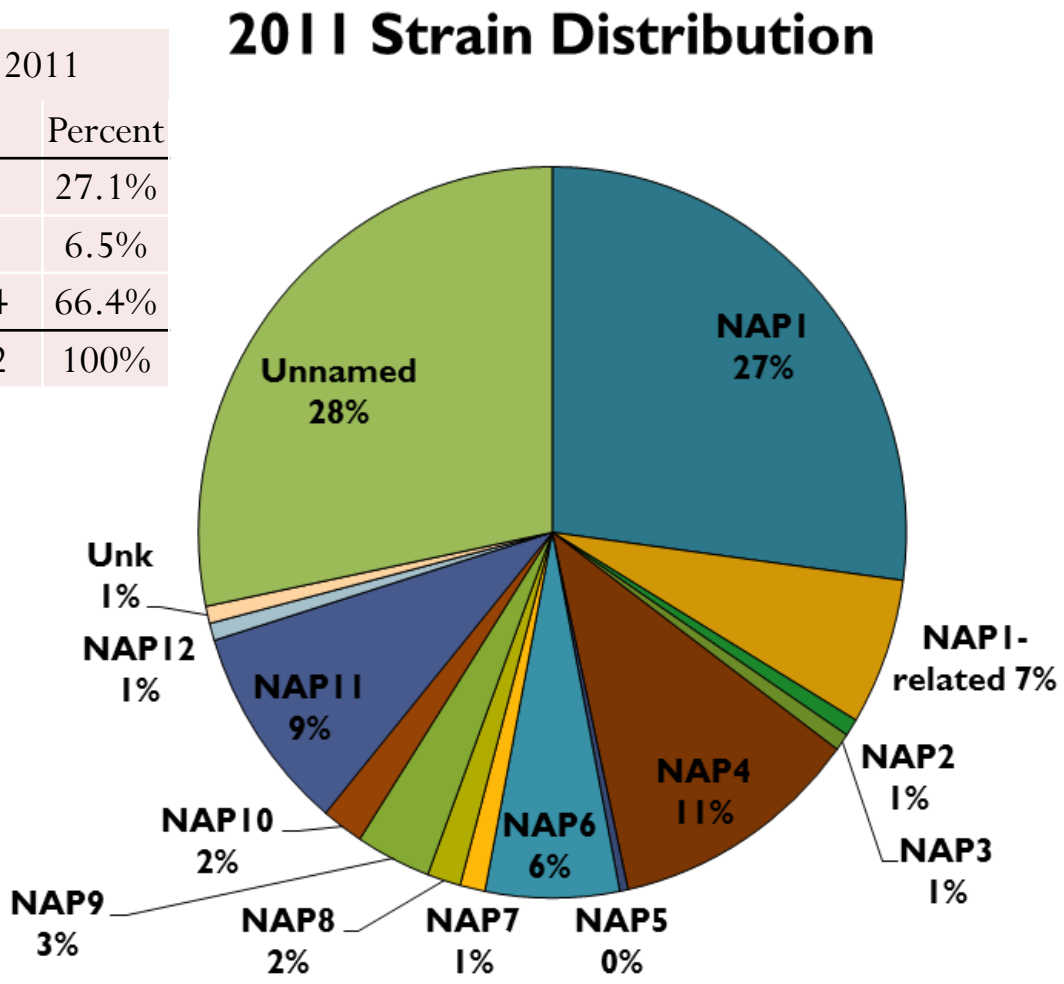


*2014 data incomplete

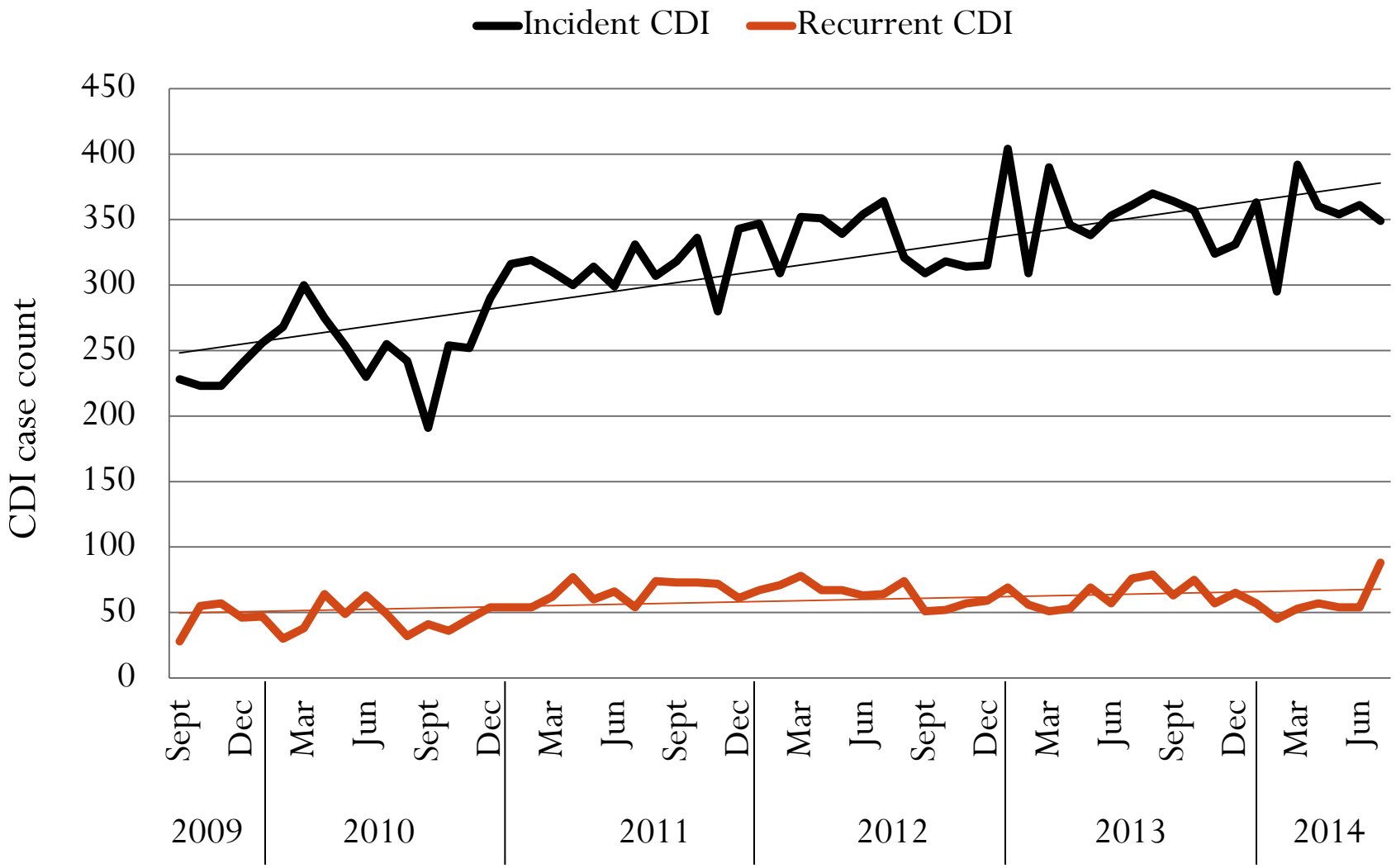
GA Specimen Strain Typing Data

2010 – 2011 NAP 1 Strain Distribution

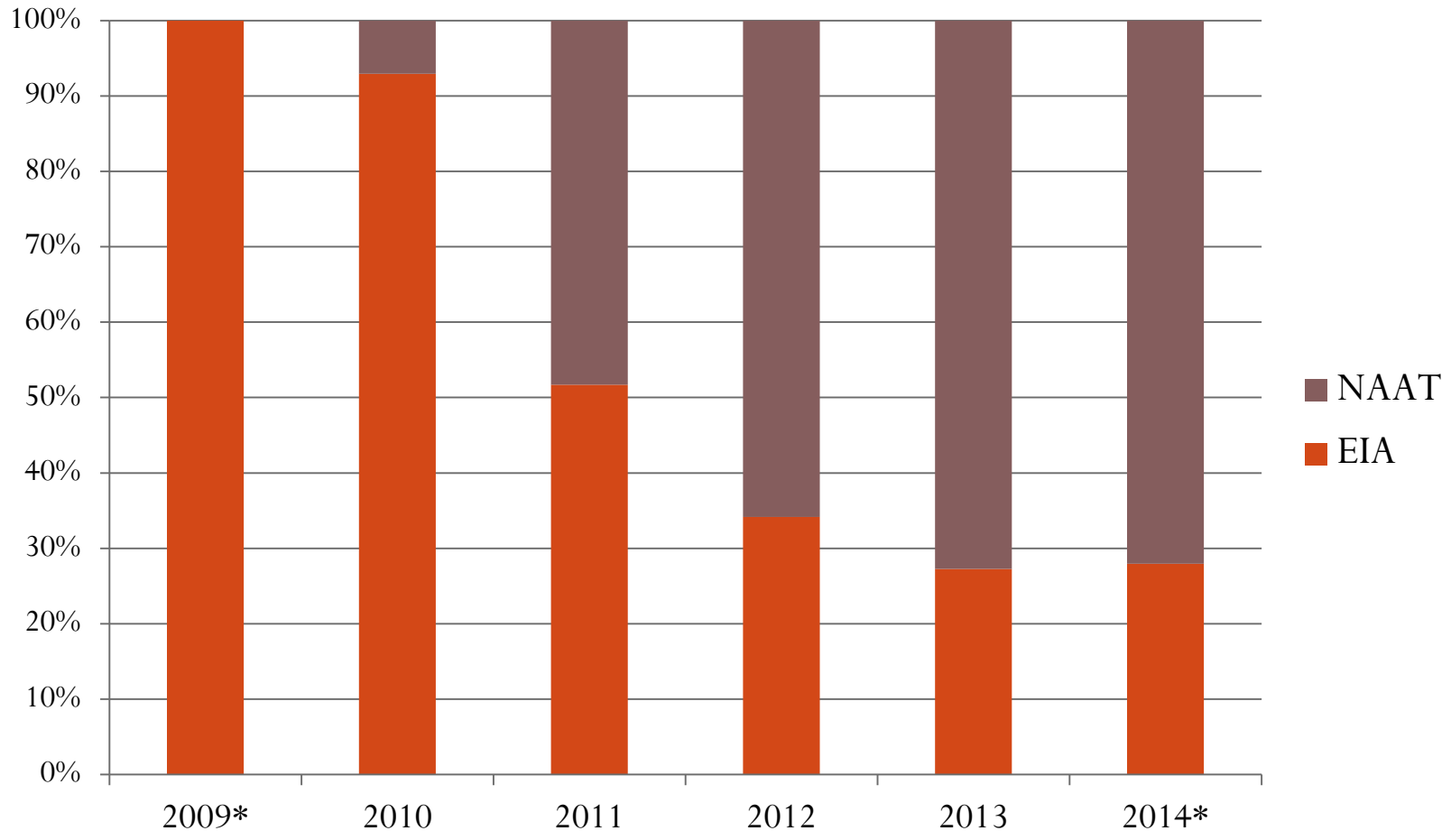
	2010		2011	
	N	Percent	N	Percent
NAP 1	11	26.3%	71	27.1%
NAP 1-related	2	4.7%	17	6.5%
Other	29	69%	174	66.4%
Total	42	100%	262	100%



Incident and Recurrent CDI
Sept 2009- July 2014

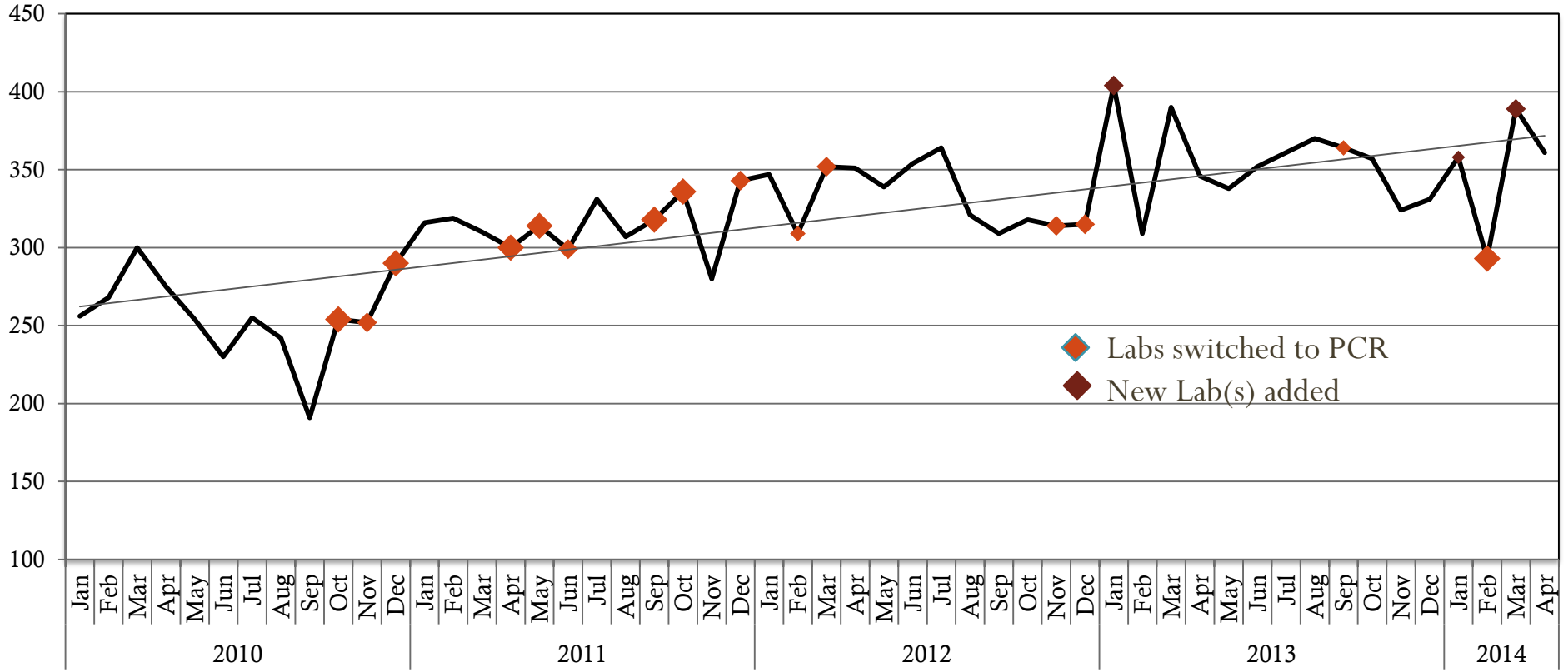


% Incident cases by diagnostic method



***Sept-Dec 2009; Jan-July 2014**

Are Changes in Diagnostic Testing Associated with Increased Incident and Recurrence Rates?



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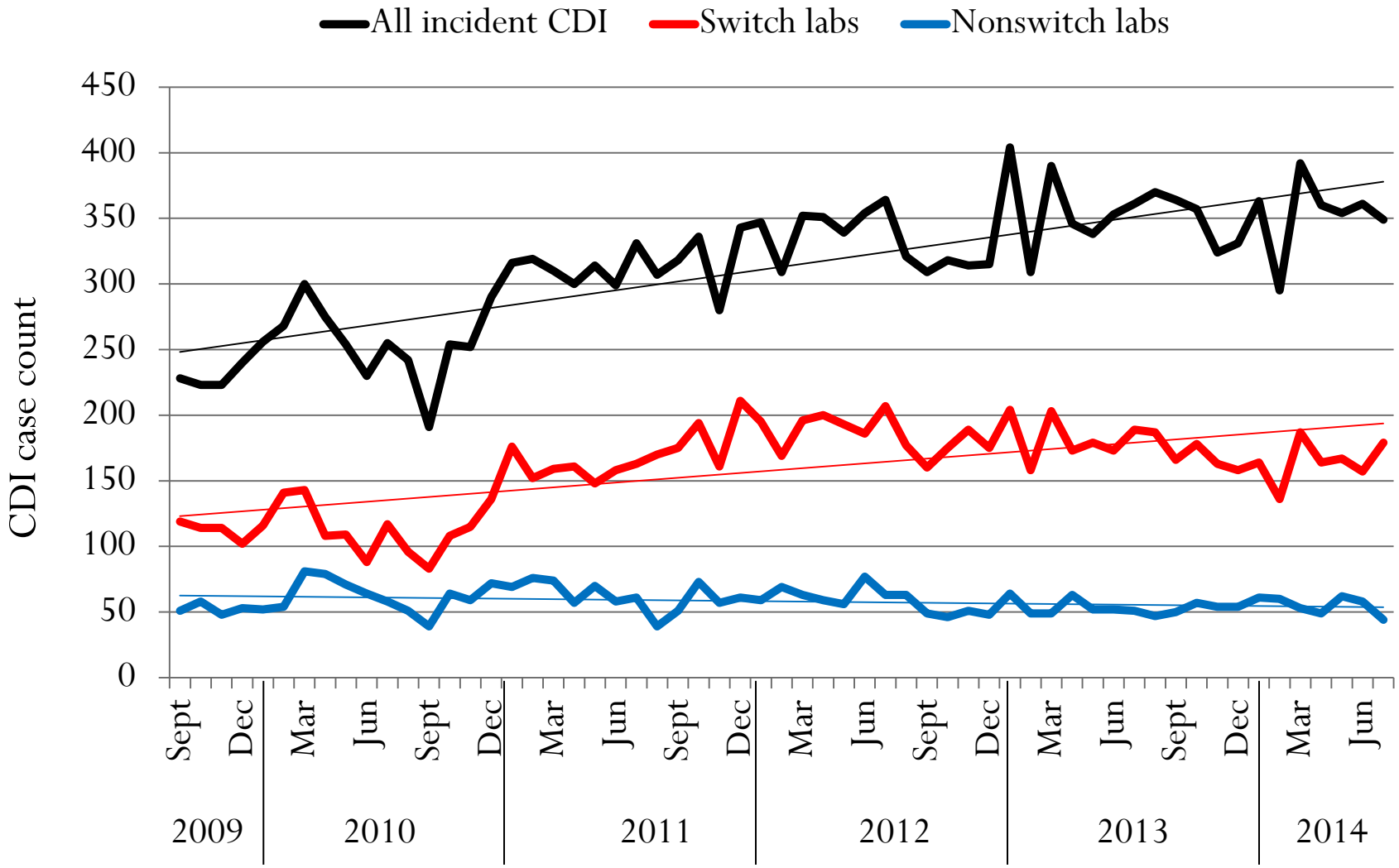
Incident CDI by laboratory classification
Sept 2009- July 2014

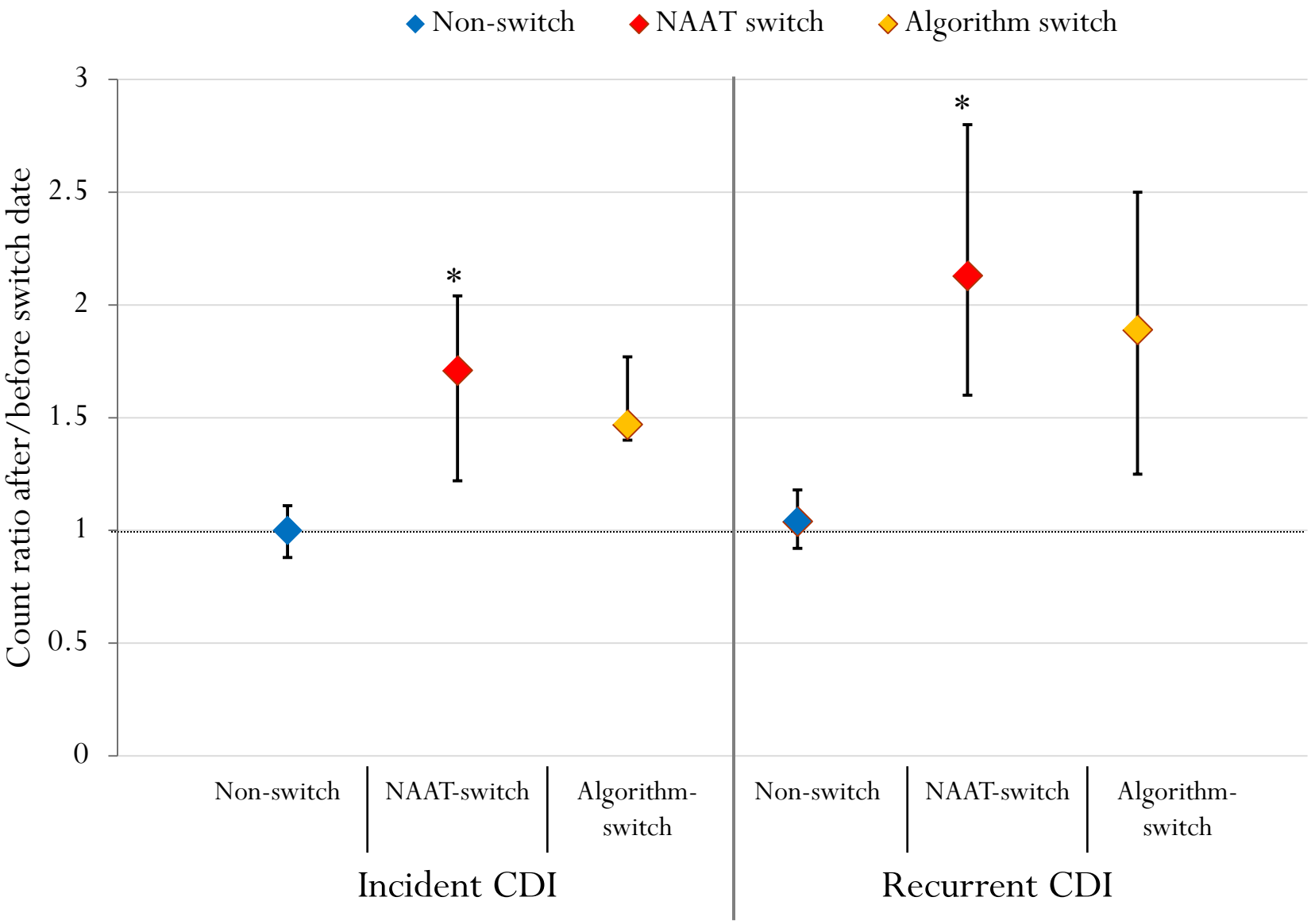


Characteristics of switch/non-switch labs

Characteristic	NAAT switch n=12	Algorithm switch n=4	Non-switch n=5
Facilities that labs serve			
Hospital-affiliated lab	12	4	2
Reference labs	0	0	3
Stool rejection policies			
Reject formed stool	11	4	0

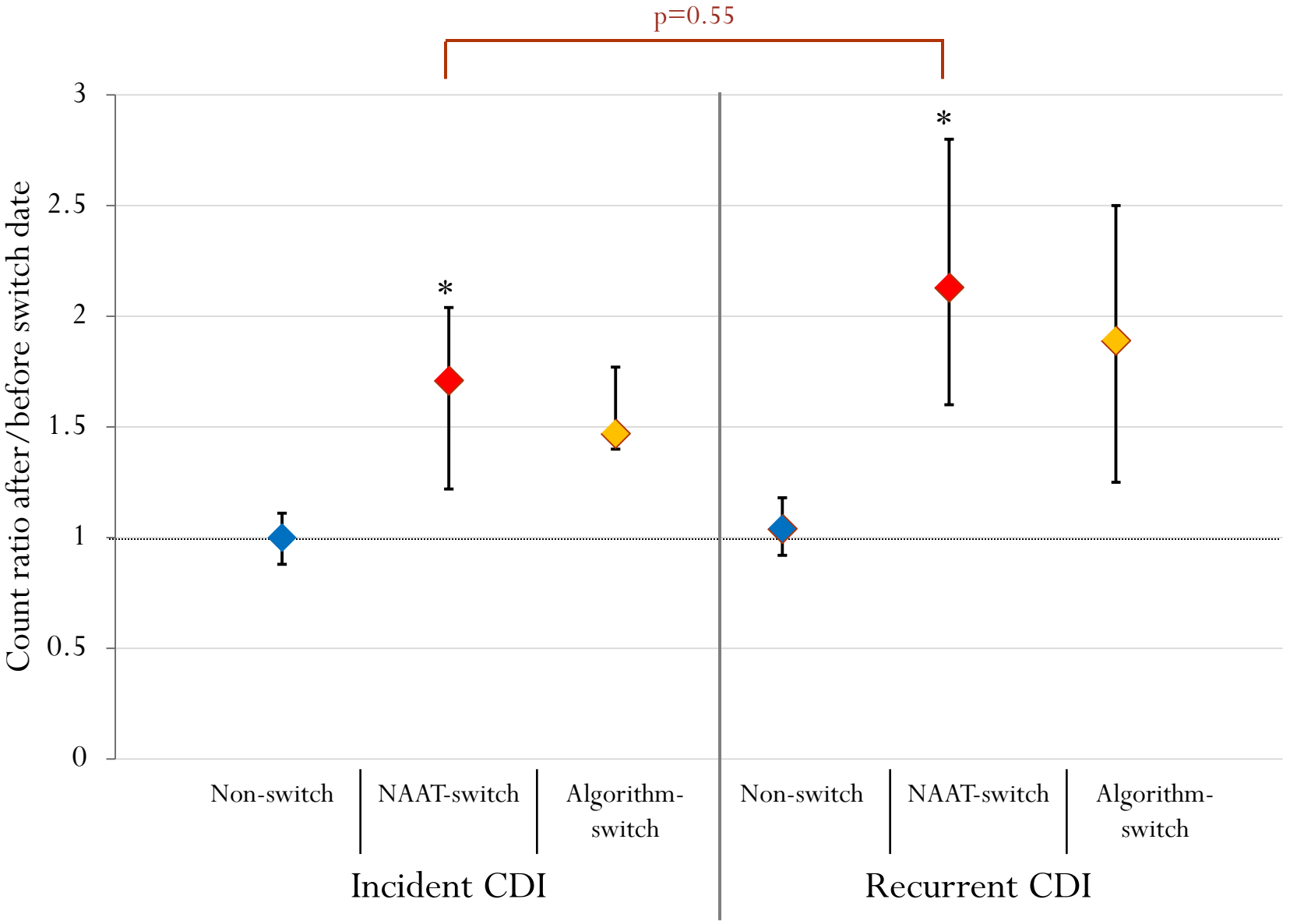
Reddy SC et al. Southern Regional Meeting 2015

Ratios of CDI counts after and before switch



*: $p<0.05$. Error bars represent range for non-switch and algorithm-switch labs. For NAAT-switch represent 95%CI

Ratios of CDI counts after and before switch



*: p<0.05. Error bars represent range for non-switch and algorithm-switch labs. For NAAT-switch represent 95%CI

Changing Diagnostics and Case counts

- After switching to NAAT, labs had increasing CDI counts
  - Incident CDI rate increased by 71%
    - 95%CI: 22-104%
  - Recurrent CDI rate increased by 113%
    - 95%CI: 60-180%
  - Increase in CDI rate was similar between recurrent and incident CDI ($p=0.55$)
- Labs switching to algorithm tests and to NAAT had similar increases in CDI rates
  - Median incident CDI increase of 47%
    - Range 40-77%
  - Median recurrent CDI increase of 89%
    - Range 25-150%
- No temporal increase in CDI in non-switch labs

What happens after the initial increase due to NAAT testing?

- Several studies suggest that improved diagnostics eventually lead to lower CDI rates
- Presumably due to improved isolation and infection control measures for patients with *C. difficile* in the stool
  - One study showed:
    - Decrease in HCA CDI
    - Reduction in patient isolation days
    - Fewer tests ordered
    - Reduction in duration of empirical metronidazole therapy

Burnham CA et al. Clin Microbiol Rev 2013.

Conclusions

- CDI causes almost half a million infections in the US per year
  - Still a significant cause of HAI, but also significant burden is seen in the community
  - Multiple recurrences are common
- NAAT methods are more sensitive but context is crucial
  - Policies for when to test
  - Colonization ≠ Infection, but may still be important
  - NAAT testing increase rates initially, but may not stay elevated
  - Diagnostics will continue to evolve
    - Impact on labs, clinical practice, infection control, and epidemiology

Questions?

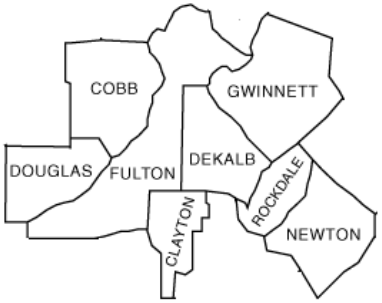
Thank you to:

- Zirka Smith
- Olivia Almendares
- Wendy Baughman
- Andrew Revis
- Catherine Espinosa
- Michelle Wiles
- Monica Farley

Extra slides

Georgia Emerging Infections Program (EIP) CDI Surveillance

- Active population and laboratory-based surveillance for positive *C. difficile* tests in 8 county metro Atlanta area
- All positive tests of residents in catchment area
  - 3.8 million persons under surveillance
  - 35 labs serving inpatients and outpatients
    - 45 Acute care facilities
    - 80 long term care facilities
    - >650 outpatient centers
- CDI surveillance started September 2009



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Should NAP/ribotype be shared?

- Few NAAT methods are able to discern NAP1/ribotype 027 strains, should labs result this information?
- Who will use it?
- Infection preventionists: NAP1 may help identify a potential cluster, but given reasonably high prevalence in populations, may not help guide interventions
- Clinicians: fidaxomicin vs vancomycin: fidaxomicin had lower recurrence rates than vancomycin, particularly in non-NAP1 strains

Carriage/Colonization vs Infection

- Colonization: persistence of bacteria in colon
- Carriage: transient passage of bacteria
- A single test does not differentiate
- In healthy community dwellers who had an initial positive *C. difficile* test, only 16-33% had a positive test on repeat testing

Public reporting of CDI rates

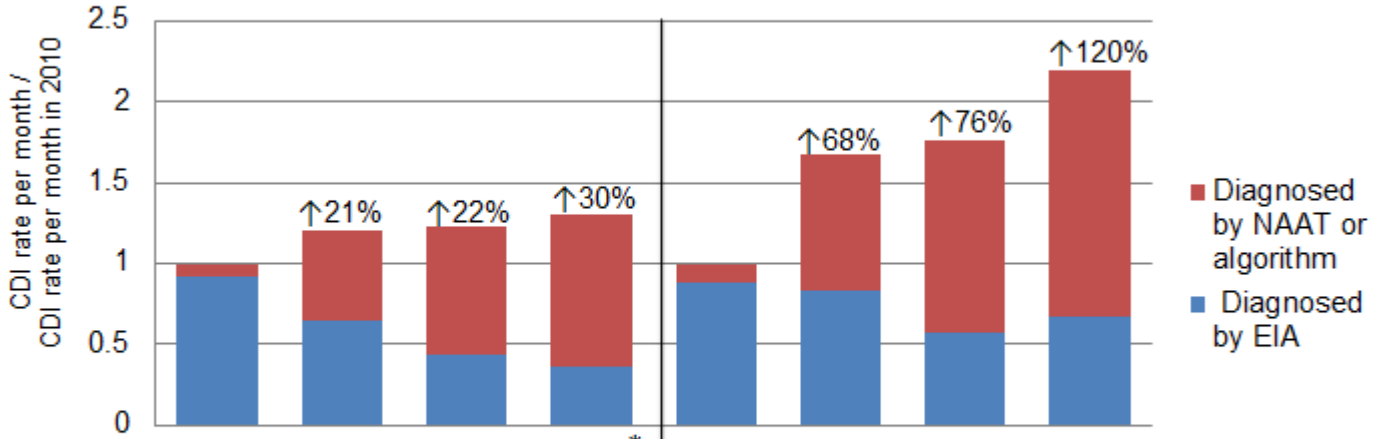
- Rates of healthcare facility onset CDI in hospitals are now being published through Medicare
- Standardized infection ratio (SIR) adjusts for[1]:
  - Community onset CDI prevalence rate
  - Facility bedsize
  - Medical school affiliation
  - Test type:
    - NAAT vs EIA vs other
    - Categorizes labs that use algorithm testing as NAAT labs

	No. of Infections Reported (A)	Number of Patient Days	Predicted No. Infections (B)	Standardized Infection Ratio (SIR) (A/B)	Evaluation
	155	165245	168.563	0.920	No Different than U.S. National Benchmark

Standardized infection ratio (SIR) national benchmark = 1.
Lower SIRs are better. A score of (0) – meaning no C.diff. infections – is best.

[1] Dudeck et al. http://www.cdc.gov/nhsn/pdfs/mrsa-cdi/RiskAdjustment-MRSA-CDI.pdf.

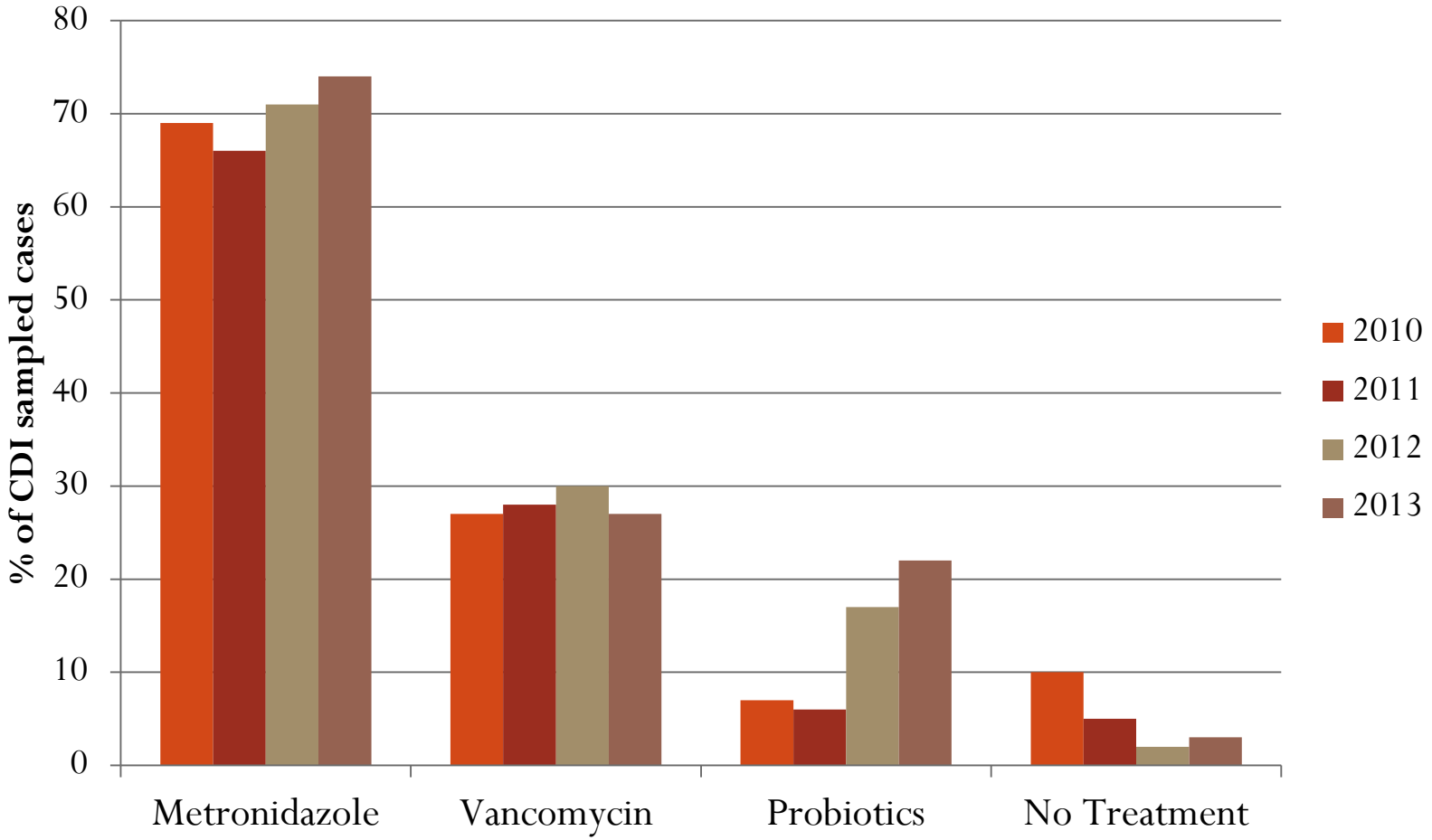
Increased CDI Rates Compared to 2010 By Year, Test Method and Initial vs Recurrent



	2010	2011	2012	2013*	2010	2011	2012	2013
	Initial Cases per Year				1st Recurrent Cases per Year			
Rate per month	226	273	277	293	36	60	63	79
% EIA	92	53	36	28	88	50	33	30

*2013 initial rate calculated from 1/13-9/13

Treatment of Sampled* Incident CDI 2010-2013



*Healthcare facility onset cases are sampled 1:10