National Burden of *Clostridium difficile* Infection in the United States

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26th ECCMID

April 10, 2016
Background: *Clostridium difficile* Infection in the United States

- Increasing incidence and severity of *Clostridium difficile infection* with the emergence of BI/NAP1/027
- From 1993 to 2009, hospital stays with CDI increased from 85,700 to 336,600\(^1\)
- In 2011, CDI was most commonly reported U.S. healthcare-associated infection (accounted for 12% of infections)\(^2\)
- CDI increasingly recognized in non-hospital settings and community
  - Ohio 2006: >50% of healthcare-associated CDI with onset likely in nursing homes\(^3\)
  - 2010: >30% of CDI were community-associated\(^4\)

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Surveillance for CDI in the United States

- Increasing CDI incidence and changing epidemiology highlight need for standardized definitions and surveillance methods
  - US Centers for Disease Control and Prevention (CDC) published interim recommendations for surveillance in 2007

- CDC surveillance systems for CDI:
  - National Healthcare Safety Network
  - Emerging Infections Program

National Healthcare Safety Network
National Healthcare Safety Network (NHSN)

- Internet-based surveillance system for tracking healthcare-associated infections (HAIs) in the United States
  - Started in 2005
  - Supersedes previous CDC surveillance system (including National Nosocomial Infections Surveillance system)

- NHSN data can be used to:
  - Identify infection prevention problems by facility, state, or specific quality improvement project
  - Comply with US state and federal reporting mandates
  - Drive national progress toward elimination of HAIs
Reporting of CDI to NHSN

- **NHSN Module specifically for reporting CDI by US healthcare facilities**
  - 2009: mandatory CDI reporting in certain US states
  - 2013: US Centers for Medicare and Medicaid Services required all participating hospitals to report CDI (~4000 facilities enrolled)

- **Laboratory identified (LabID) events of CDI**
  - Incident case: positive *C. difficile* toxin or molecular assay or a toxin-producing *C. difficile* organism detected by culture, obtained >8 weeks after prior positive test
  - Epidemiologic classification:
    - Hospital-onset (HO): collected >3 days after hospital admission
    - Community-onset (CO): collected ≤3 days after hospital admission
    - CO-healthcare-facility onset: CO event in patient discharged ≤4 weeks from the facility
Using NHSN to Track Hospital-Onset CDI at National or Local Level

- **Standardized infection ratio (SIR)** – metric used to track HAIs over time
  - Compare *observed* (actual) number of infections to the *predicted* (expected) number of infections

- **Determining predicted number of infections**
  - Develop model based on national aggregate data reported to NHSN during baseline period after adjusting for key risk factors
    - CDI baseline period: 2010-2011

- **Interpretation of SIR**
  - >1.0 = more infections observed than predicted
  - <1.0 = fewer infections were observed than predicted
# Characteristics of Facilities Contributing to CDI Baseline Period in NHSN, 2010-2011

<table>
<thead>
<tr>
<th>Facility Characteristics</th>
<th>N=846</th>
<th>%</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Facility type</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>General acute care</td>
<td>799</td>
<td>94.4</td>
</tr>
<tr>
<td><strong>Medical school affiliation</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Major teaching</td>
<td>103</td>
<td>12.2</td>
</tr>
<tr>
<td>Graduate teaching / non-teaching</td>
<td>743</td>
<td>87.8</td>
</tr>
<tr>
<td><strong>Facility bedsize</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>&gt;245 beds</td>
<td>273</td>
<td>32.4</td>
</tr>
<tr>
<td>101-245 beds</td>
<td>267</td>
<td>31.7</td>
</tr>
<tr>
<td>≤100 beds</td>
<td>302</td>
<td>35.9</td>
</tr>
<tr>
<td><strong>CDI test type</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>NAAT</td>
<td>388</td>
<td>45.9</td>
</tr>
<tr>
<td>EIA</td>
<td>399</td>
<td>47.2</td>
</tr>
<tr>
<td>All others</td>
<td>59</td>
<td>6.9</td>
</tr>
</tbody>
</table>

## Risk Adjustment for CDI SIR

### Table 3. Model to predict healthcare facility-onset (HO) CDI LabID events, NHSN, 2010-2011.

<table>
<thead>
<tr>
<th>Effect</th>
<th>Parameter Estimate</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Intercept</td>
<td>-7.8983</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>CDI Test Type (NAAT vs. non-NAAT/EIA others)</td>
<td>0.3850</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>CDI Test Type (EIA vs. non-NAAT/EIA others)</td>
<td>0.1606</td>
<td>0.0013</td>
</tr>
<tr>
<td>CO Admission prevalence rate (continuous)*</td>
<td>0.3338</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Facility Bedsize (&gt;245 vs. ≤100)</td>
<td>0.2164</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Facility Bedsize (101-245 vs. ≤ 100)</td>
<td>0.0935</td>
<td>0.0022</td>
</tr>
<tr>
<td>Medical School Affiliation (Major teaching vs. Undergraduate/Non-Teaching)</td>
<td>0.1870</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Medical School Affiliation (Graduate vs. Undergraduate/Non-Teaching)</td>
<td>0.0918</td>
<td>0.0038</td>
</tr>
</tbody>
</table>

* Number of community-onset CDI LabID events \times 100

\[ \text{Number of admissions to the facility} \]


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<thead>
<tr>
<th></th>
<th></th>
<th></th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>CLABSI Nat'l Baseline: 2008</td>
<td>3,655</td>
<td>↓ 8%</td>
<td>↓ 50%</td>
<td>0.50</td>
</tr>
<tr>
<td>CAUTI Nat'l Baseline: 2009</td>
<td>3,791</td>
<td>↓ 5%</td>
<td>0%</td>
<td>1.00</td>
</tr>
<tr>
<td>SSI, Abdominal Hysterectomy Nat'l Baseline: 2008</td>
<td>3,225</td>
<td>↓ 5%</td>
<td>↓ 17%</td>
<td>0.83</td>
</tr>
<tr>
<td>SSI, Colon Surgery Nat'l Baseline: 2008</td>
<td>3,377</td>
<td>↑ 5%</td>
<td>2%</td>
<td>0.98</td>
</tr>
<tr>
<td>MRSA Bacteremia Nat'l Baseline: 2011</td>
<td>3,949</td>
<td>↓ 4%</td>
<td>↑ 13%</td>
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<tr>
<td>C. difficile Infections Nat'l Baseline: 2011</td>
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The number of hospitals that reported to NHSN and are included in the SIR calculation. This number may vary across HAI types; for example, some hospitals do not use central lines or urinary catheters, or do not perform colon or abdominal hysterectomy surgeries.

For additional data points, refer to the technical data tables.

The Nat'l baseline time period varies by HAI type. See first column of this table for specifics.


<table>
<thead>
<tr>
<th>HAI TYPE</th>
<th># OF U.S. HOSPITALS THAT REPORTED DATA TO CDC'S NHSN, 2014(^*)</th>
<th>2014 NAT'L SIR vs. 2013 Nat'I SIR</th>
<th>2014 NAT'L SIR vs. Nat'I Baseline†</th>
<th>2014 NAT'L SIR</th>
</tr>
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<tbody>
<tr>
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For additional data points, refer to the technical data tables. For data on these and other inpatient hospital infections, see the companion report to this report: National Healthcare Safety Network’s Multistate Point Prevalence Survey of Inpatient Hospital Infections - United States, 2014-2015. Additional data on healthcare-associated infections among patients who receive healthcare in the community or are discharged to a healthcare facility is provided in the following reports: National Healthcare Safety Network’s Hospital Outpatient Survey: Multistate Point Prevalence Surveys of Healthcare-Associated Infections, 2014-2015 and National Healthcare Safety Network’s Ambulatory Care Survey: Multistate Point Prevalence Surveys of Healthcare-Associated Infections, 2015-2016.

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Emerging Infections Network
Emerging Infections Program (EIP): CDI Surveillance

- Active population- and laboratory-based surveillance
- Started in 2009 in 7 states, currently in 35 counties in 10 states
  - CDC collaboration with state and local health departments and academic institutions
- All positive *C. difficile* lab reports (toxin or molecular assay) from inpatient and outpatient laboratories investigated
- Culture a convenience sample of stool specimens for molecular characterization
Participating EIP CDI Sites

2014 Total Population: ~11.7 million
- 28 metropolitan counties
- 7 non-metropolitan counties

- Oregon
- California
- Colorado
- Minnesota
- New Mexico
- New York
- Connecticut
- Maryland
- Georgia

ESGID eLibrary by author
Participating EIP CDI Sites

2014 Total Population: ~11.7 million
- 28 metropolitan counties
- 7 non-metropolitan counties

Population: ~65,500
- Oregon
- California

Population: ~3.9 million
- New York
- Connecticut
- Maryland
- Tennessee
- Minnesota
- Colorado
- New Mexico
- Georgia
EIP CDI Surveillance Case Definition

- Incident CDI: positive *C. difficile* toxin or molecular assay on a stool specimen from a person without a positive test in the prior 8 weeks
  - Detailed medical record review and abstraction performed on incidence CDI cases
Epidemiologic Classification of CDI Cases

- HA or CA*
- Healthcare-associated
- Community-associated

Similar to NHSN for defining HO and CO CDI

* classification will depend on healthcare exposure in the prior 12 weeks
** includes hospital-onset and nursing home-onset

Epidemiologic Classification of CDI Cases

- HA or CA*
- Healthcare-associated
- Community-associated

Admission
3 days
HCFO**
12 weeks
CO-HCFA
CA-CGI

> 12 weeks

Time
Different from NHSN

* classification will depend on healthcare exposure in the prior 12 weeks
** includes hospital-onset and nursing home-onset

Epidemiologic Classification of CDI Cases

* classification will depend on healthcare exposure in the prior 12 weeks
** includes hospital-onset and nursing home-onset

CDI Incidence Rates and Epidemiologic Distribution, EIP Surveillance 2014

- Median crude CDI incidence rate of EIP sites in 2014: 160 per 100,000 population (96 to 195 per 100,000 population)

  How to compare CDI rates across regions and generate reliable national CDI estimates?
CDI Incidence Rates and Epidemiologic Distribution, EIP Surveillance 2014

- Median crude CDI incidence rate of EIP sites in 2014:
  160 per 100,000 population (96 to 195 per 100,000 population)

How to compare CDI rates across regions and generate reliable national CDI estimates?

- Community-associated: 41%
- Hospital onset: 23%
- Nursing home onset: 17%
- CO-HCFA: 19%
CDI Incidence Rates and Epidemiologic Distribution, EIP Surveillance 2014

- Median crude CDI incidence rate of EIP sites in 2014: 160 per 100,000 population (96 to 195 per 100,000 population)

How to compare CDI rates across regions and generate reliable national CDI estimates?

National CDI estimates:
- Should include hospitalized and non-hospitalized (nursing home patients and outpatients)
- Should account for factors that influence CDI rates

Which factors?
Effect of Nucleic Acid Amplification Test (NAAT) on Population-Based CDI Incidence Rates

Table 1. Ratios of Monthly Postswitch *Clostridium difficile* Infection (CDI) Case Counts to Preswitch CDI Case Counts

<table>
<thead>
<tr>
<th>State</th>
<th>Switch Laboratories</th>
<th>Nonswitch Laboratories</th>
<th>Median Test P Value</th>
<th>Attributable % Increase due to NAAT</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>No. of Month-Pairs</td>
<td>Median Ratio (95% CI)</td>
<td>No. of Month-Pairs</td>
<td>Median Ratio (95% CI)</td>
</tr>
<tr>
<td>California</td>
<td>14</td>
<td>1.52 (.69-2.50)</td>
<td>56</td>
<td>1.0 (1.00-1.50)</td>
</tr>
<tr>
<td>Colorado</td>
<td>24</td>
<td>1.43 (1.21-2.33)</td>
<td>161</td>
<td>1.0 (.85-1.06)</td>
</tr>
<tr>
<td>Georgia</td>
<td>50</td>
<td>1.67 (1.50-2.08)</td>
<td>149</td>
<td>1.0 (.89-1.04)</td>
</tr>
</tbody>
</table>

Data are for laboratories that changed from toxin enzyme immunoassay (EIA) to nucleic acid amplification testing (switch laboratories) versus laboratories only using toxin EIA (nonswitch laboratories). Each month-pair represents 2 matching pre- and postswitch months (e.g., October 2010 vs October 2009) used to calculate the postswitch to preswitch ratios. Therefore, the number of postswitch months was equal to the number of preswitch months for each state.

Abbreviations: CI, confidence interval; NAAT, nucleic acid amplification testing.
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Abbreviations: CI, confidence interval; NAAT, nucleic acid amplification testing.
Effect of Nucleic Acid Amplification Test (NAAT) on Population-Based CDI Incidence Rates

Switching from EIA to NAAT increased CDI incidence rates by 43%-67%

Proportion of stool tests that were positive almost doubled (10.4% to 19.4%) with NAAT compared to toxin EIA

<table>
<thead>
<tr>
<th>State</th>
<th>Switch Labor Pairs</th>
<th>No. of Month Pairs</th>
<th>Month (CI)</th>
<th>Attributable % Increase due to NAAT</th>
</tr>
</thead>
<tbody>
<tr>
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<td>14</td>
<td>1.52 (.69-2.50)</td>
<td>56</td>
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<td>Colorado</td>
<td>24</td>
<td>1.43 (1.21-1.62)</td>
<td>161</td>
<td>1.0 (85-1.06)</td>
</tr>
<tr>
<td>Georgia</td>
<td>50</td>
<td>1.61 (1.38-1.88)</td>
<td>243</td>
<td>1.0 (1.03-1.06)</td>
</tr>
</tbody>
</table>

Data are for laboratories (laboratories) versus laboratory and postswitch months (each laboratory). The number of postswitch months was equal to the number of preswitch months for each state.

Abbreviations: CI, confidence interval; NAAT, nucleic acid amplification testing.
Used 2010 EIP CDI data to determine factors that might influence measurements of CDI incidence

- Diagnostic test (NAAT)
- Demographic factors
  - Socioeconomic factors
  - Healthcare utilization

Data based on 7 EIP sites: California, Colorado, Connecticut
Factors Associated with High Community-Associated CDI Incidence, EIP Surveillance 2010

Candidate variables for community-associated CDI:
- Age, sex, race, NAAT usage, percentage of urban population, percentage of population aged 18-64 years without health insurance, average number of outpatient visits per hospital in surveillance area

Multivariate model for community-associated CDI

<table>
<thead>
<tr>
<th>Predictor</th>
<th>Category</th>
<th>Incidence Rate Ratio(^b)</th>
<th>95% CI</th>
<th>(P)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age</td>
<td>1-17 (reference)</td>
<td>1.00</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>18-44</td>
<td>1.72</td>
<td>1.38-2.14</td>
<td>&lt;.0001</td>
</tr>
<tr>
<td></td>
<td>45-64</td>
<td>3.42</td>
<td>2.77-4.24</td>
<td>&lt;.0001</td>
</tr>
<tr>
<td></td>
<td>&gt;65</td>
<td>7.17</td>
<td>5.76-8.94</td>
<td>&lt;.0001</td>
</tr>
<tr>
<td>Sex</td>
<td>Male (reference)</td>
<td>1.00</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Female</td>
<td>1.41</td>
<td>1.23-1.61</td>
<td>&lt;.0001</td>
</tr>
<tr>
<td>Race</td>
<td>Non-white (reference)</td>
<td>1.00</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>White</td>
<td>1.45</td>
<td>1.21-1.75</td>
<td>&lt;.0001</td>
</tr>
<tr>
<td>Test</td>
<td>NAAT use by 10% increase</td>
<td>1.11</td>
<td>1.06-1.16</td>
<td>&lt;.0001</td>
</tr>
</tbody>
</table>

NAAT = Nucleic acid amplification tests (e.g., PCR)

Factors Associated with High Healthcare-Associated CDI Incidence, EIP Surveillance 2010

- **Candidate variables for healthcare-associated CDI:**
  - Age, sex, race, NAAT usage, percentage of population in nursing homes, and average inpatient-days per hospital in surveillance area

- **Multivariable model for healthcare-associated CDI**

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<tr>
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<td>2.67</td>
<td>2.01–3.54</td>
<td>&lt;.0001</td>
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<td>45–64</td>
<td></td>
<td>11.23</td>
<td>8.54–14.76</td>
<td>&lt;.0001</td>
</tr>
<tr>
<td>≥65</td>
<td></td>
<td>68.79</td>
<td>52.56–90.03</td>
<td>&lt;.0001</td>
</tr>
<tr>
<td><strong>Inpatient-days</strong></td>
<td>Increase in 10 000 inpatient-days per hospital</td>
<td>1.10</td>
<td>1.01–1.20</td>
<td>.02</td>
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<td><strong>Test</strong></td>
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</table>

NAAT = Nucleic acid amplification tests (e.g., PCR)

U.S. National CDI Burden, 2011

- Estimated 453,000 incident *C. difficile* infections, incidence rate: 147.2 infections per 100,000 population*
  - Females vs males: rate ratio 1.26 (95% CI: 1.25-1.27)
  - Whites vs nonwhites: rate ratio 1.72 (95% CI: 1.56-2.00)
  - Persons aged ≥65 years vs. persons aged < 65 years: rate ratio 8.65 (95% CI: 8.16-9.31)

- 159,000 community-associated CDI (51.9 per 100,000 population),
  293,300 healthcare-associated CDI (147.2 per 100,000 population)

- Estimated 83,000 first recurrences and 29,300 deaths within 30 days of initial diagnosis

*Adjusted for age, sex, and race of US population and % of cases diagnosed by nucleic acid amplification test (NAAT) for community-associated cases; adjusted for age of US population, volume of inpatient days, and % of cases diagnosed by NAAT for healthcare-associated cases

Lessa FC et al. NEJM 2015;372:825-834.
Estimated U.S. Burden of CDI by Epidemiological Classification, 2011

- CO-HCA community-onset healthcare-associated
- NHO nursing home onset
- HO hospital onset

Lessa FC et al. NEJM 2015;372:825-834.
Comparison With Other National Estimates

- Previous U.S. national estimates in 2006-2007: 240,000 to 333,000 infections\(^1,2\)
  - Passive surveillance data from healthcare facilities in a single state
  - Administrative data
  - Data from managed care populations in a specific region

- Comparison limited by different definitions, analytical methodology, and diagnostic tests

- Few population-based estimates from other countries
  - Community-associated estimates in UK and Sweden: 20-40 per 100,000 population\(^3,4\)

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Impact of NAAT Usage on 2011 National CDI Estimates

52% of CDI Cases Diagnosed by NAAT

Lessa FC et al. NEJM 2015;372:825-834.
U.S. Burden of Nursing Home-Onset CDI, 2012

- Used EIP data for projection of NHO burden estimate
- Adjusted for age (only significant variable in model*) and NAAT usage rate of 74% (across EIP sites)
- Estimated 112,800 NHO CDI (95% CI, 93,400–131,800) in the United States in 2012
- Assuming NAAT usage rate in 2011 was also 74%: NHO in 2011 would have been 116,000 (instead of 104,400), which is 3% lower than 2012 NHO CDI estimate

*Evaluated same candidate variables previously demonstrated to be significantly associated with CDI incidence

Hunter J et al. OFID 2016 Jan 18;3(1):ofv196
Challenges with Adjusting for NAAT Usage Rates

- **EIP**
  - NAAT usage not significant in models for generating national HA-CDI (since 2010) and CA-CDI (since 2012) burden estimates
    - Increasing uptake of NAAT use → minimal variation in average NAAT usage rates when county-level data are aggregated for site-level analysis
    - HA CDI rates driven more by patient age and facility characteristics?

- **Recent data suggest NAAT use might be overcalling CDI diagnosis**
  - 2011 national burden estimate might be over estimation of true burden of disease

- **NHSN**
  - Healthcare facilities switching between NAAT and EIA use
  - Preliminary data suggest increasing CDI incidence with EIA use
Next Steps for CDC

How to evaluate changes in national CDI burden and progress of CDI prevention efforts?

- **EIP surveillance**
  - Assess trends in CDI incidence from 2011-2014
    - More data points would allow better evaluation of effect of NAAT usage

- **NHSN**
  - Establish new baseline period for CDI for calculating SIR
    - Reassess key variables (including diagnostic test type) used for risk adjustment
Summary

- U.S. national burden of CDI is substantial
  - Approximately half a million infections in the United States in 2011
  - Risk of infection increases with age
  - Large proportion of cases with onset outside of the hospital setting

- National progress in prevention of hospital-onset CDI since 2011, although more work needs to be done

- Two complementary surveillance systems that allow tracking of national disease burden and progress in prevention
  - Further efforts needed to better evaluate effect of diagnostic test type on CDI incidence
For more information, contact CDC
1-800-CDC-INFO (232-4636)

The findings and conclusions in this report are those of the authors and do not necessarily represent the official position of the Centers for Disease Control and Prevention.