Healthcare Quality Reporting Program

**HOSPITAL-ACQUIRED INFECTIONS AND PREVENTION ADVISORY SUBCOMMITTEE**

8:00-9:00am, 3/18/13 at Healthcentric Advisors

| Goals/Objectives |
|---|
| ▪ To discuss HAI work to date and make policy recommendations for pending and upcoming reports |

| Members | | |
|---|---|---|
| ☐ Nicole Alexander, MD | ☐ Maureen Marsella, RN, BS | ☐ Sheila Turner, RN, MA |
| ☐ Rosa Baier, MPH | ☐ Linda McDonald, RN | ☐ Lee Ann Quinn, RN, BS, CIC |
| ☐ Utpala Bandy, MD | ☐ Leonard Mermel, DO, ScM | ☐ Janet Robinson, RN, Med, CIC |
| ☐ Marlene Fishman, MPH, CIC | ☐ Pat Mastors | ☐ Nancy Vallande, MSM, MT, CIC |
| ☐ Yongwen Jiang | ☐ Robin Neale, MT (ASCP), SM,CIC | ☐ Cindy Vanner |
| ☐ Julie Jefferson, RN, MPH, CIC | ☐ Kathleen O'Connell, RN,BSN,CIC | ☐ Samara Viner-Brown, MS |

| Time | Topic/Notes |
|---|---|
| 8:00am | **Welcome & Administrative Updates**<br>*Leonard Mermel, DO, ScM*<br>*Samara Viner-Brown, MS*<br>- Today's objectives<br>- Previous meeting's action items:<br>• Share HEALTH's letter to nursing home administrators (Rosa)<br>• Ask Cindy when the CRE breakpoints will be incorporated into lab software (Nicole)<br>• Write the CDI vs. Lab ID letter to the editor (Len/Rosa) |
| 8:05am | **Discussion Topics**<br>*Rosa Baier, MPH*<br>- Healthcare Worker Employee Influenza Vaccination<br>• Interim data (handout)<br>• Data submission<br>- Hand Hygiene Preview Report (handout)<br>- Website development |
| 8:55am | **Open Forum & Action Items**<br>*Rosa Baier, MPH*<br>- Toolkits (attachments)<br>- Action items<br>- **Next meeting:** 4/15/13 at Healthcentric Advisors |

*Manuscript



# *Clostridium difficile* Surveillance: A Multi-Center Comparison of LabID Event and Use of Standard Definitions

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Rates of hospital discharges with *C. difficile* infections (CDI) increased in the United States from 38 to 85 per 10,000 discharges from 2000 to 2009 (1,2). Because of increased concern about the rising incidence of CDI, the Centers for Medicare & Medicaid Services (CMS) began requiring all acute-care hospitals to submit LabID event data to the National Healthcare Safety Network (NHSN) in 2013 and plans to publicly report these data on Hospital Compare beginning in 2014. CDI and LabID event rates are both based on positive laboratory test results, but LabID events do not incorporate clinical assessment and may, therefore, overestimate true incidence. CMS's requirement that hospitals submit LabID events, not CDI data, is partly due to the fact that LabID data can be uploaded directly to NHSN from some laboratory testing systems. This requires is less resource intensive than capturing CDI data, which requires clinical assessment and data entry.

To compare CDI and LabID incidence rates, the Rhode Island Department of Health requested that the 11 acute-care hospitals in the state voluntarily submit the number of hospital-acquired CDI based on surveillance by infection preventionists and the total patient-days between July 1 and September 30, 2012 (Quarter 3, 2012). Medicare mandated that hospitals submit *C. difficile* laboratory-identified event reporting (LabID events) and patient-days to NHSN for the same time period. After obtaining permission from all hospitals, Healthcentric Advisors (the Department's public reporting contractor and the state's Medicare Quality Improvement Organization) obtained the LabID event data from NHSN. We then calculated hospital-level rates per 10,000 patient-days.

Six of the 11 acute-care hospitals in Rhode Island submitted CDI data for Quarter 3, 2012. The six hospitals included academic teaching hospitals and community hospitals.



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All six hospitals used nucleic acid amplification testing methods for *C. difficile* detection and did not test formed stool for *C. difficile,* unless this was known to the patient's physician and the physician requested that such testing be done. Overall, we found that LabID event rates were 1.4 to 3.1 times higher than CDI rates (Figure).

Since a LabID event does not include clinical data, our results suggest that there may be bias towards including patients who had stool specimens sent that are formed stool, transient loose stools due to laxative use, stools sent for test of cure and those admitted with loose stools, but whose stool specimen is collected for *C. difficile* testing three to four days after hospital admission. Thus, it is not surprising that we documented that LabID event rates exceeded CDI rates at all six hospitals. On the other hand, it is possible that bias is introduced by those performing surveillance, leading to underreporting of CDI. For example, it may be that hospital E has a lower threshold to report CDI than the other hospitals.

We believe our findings are not unique and that public reporting of LabID events may overestimate the magnitude of the problem. This is concerning given CMS's plans to publicly report these data and the implicit encouragement that hospitals use such data for quality improvement purposes. Our findings suggest that more research is needed to better understand the differences between LabID events and CDI so that we can maintain integrity of infection control data reported to state and federal agencies, as well as to the public.

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Acknowledgements

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There was no financial support for this project.

Potential Conflicts of Interest

Dr. Mermel is a co-holder of a patent application entitled: Simultaneous Quantitative Multiple Primer Detection of Clostridium difficile. No other authors have any potential conflicts of interest.

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1. Lucado J, Gould C, Elixhauser A. Clostridium difficile infections (CDI) in hospital stays. Healthcare Cost and Utilization Project, Agency for Healthcare Research and Quality. Statistical brief #124. Available at: http://www.hcup-us.ahrq.gov/reports/statbriefs/sb124.pdf.
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Figure legend. Comparison of hospital-acquired *C. difficile* infections (CDI; gray) and LabID Events (pattern) per 10,000 patient-days at six acute care hospitals in Rhode Island, Q3 2012.

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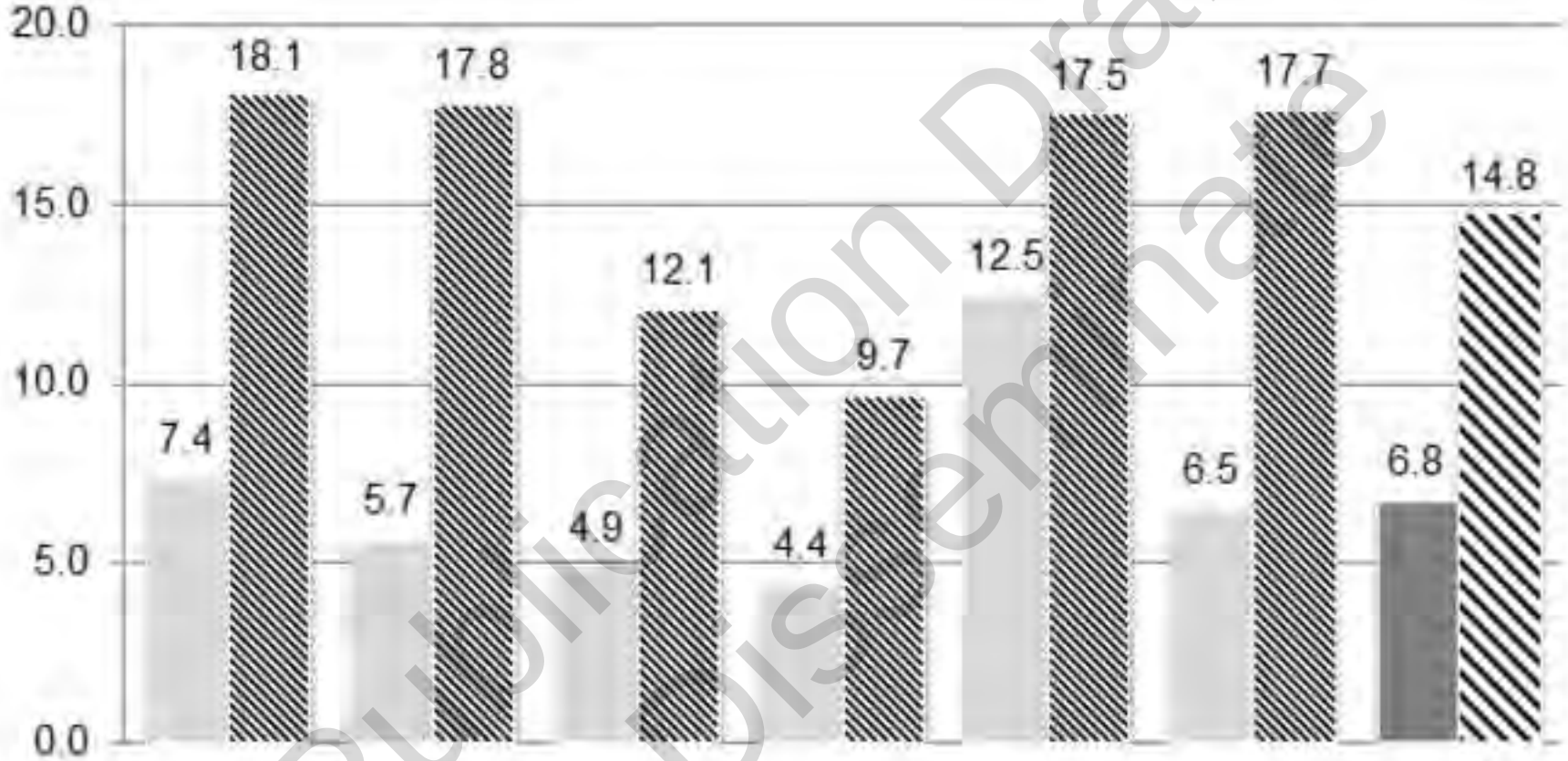
Figure




| Hospital | A | B | C | D | E | F | Overall |
|---|---|---|---|---|---|---|---|
| CDI | 11 | 4 | 24 | 2 | 22 | 7 | 70 |
| Lab ID Event | 27 | 12 | 56 | 5 | 31 | 19 | 150 |

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Healthcare Quality Reports

# HOSPITAL HAND HYGIENE

Data Report, February 2013

Clean hands are the most important strategy to prevent germs from spreading in the hospital. As a result, how hospital healthcare workers clean their hands—their "hand hygiene"—is an important part of how the hospital controls infections. Hospitals' hand hygiene processes are reported on the Department of Health's (HEALTH's) Web site as part of the Department's hospital reporting work. You can learn more about these measures—including what each measure means, how it is calculated, and why this information is important—by reading the Technical Page. With questions about a hospital's performance, please contact the hospital directly by clicking on each hospital's name.

| Hospital *(Alphabetical)* | Hand Hygiene & Glove Use Education Provided* | Hand Hygiene Measured[H] | Hand Hygiene Reported[ɘ] |
|---|---|---|---|
| | (Yes/No) | | |
| Eleanor Slater Hospital | Yes | Yes | Yes |
| Kent Hospital | Yes | Yes | Yes |
| Landmark Medical Center | Yes | Yes | Yes |
| Memorial Hospital | Yes | Yes | Yes |
| Miriam Hospital | Yes | Yes | Yes |
| Newport Hospital | Yes | Yes | Yes |
| Our Lady of Fatima Hospital | Yes | Yes | Yes |
| Rhode Island Hospital | Yes | Yes | Yes |
| Roger Williams Medical Center | Yes | Yes | Yes |
| South County Hospital | Yes | Yes | Yes |
| Westerly Hospital | Yes | No | No |
| Women & Infants' Hospital | Yes | Yes | Yes |

* Hand hygiene and glove use educational program in place

H Hand hygiene compliance measured through direct observation, collected at least once every three months (quarterly)

ɘ Hand hygiene compliance measured through direct observation, collected at least once every three months (quarterly), with feedback provided to credentialed staff, the Chief Executive Officer, and Executive Leadership

CONFIDENTIAL PREVIEW REPORT

## Healthcare Worker (HCW) Influenza Vaccination Summary Report, as of January 31, 2013

| Employee Healthcare Workers | | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Facility type | Facililty Information | | | Reported # of Employee HCW | Vaccinated | | Not Vaccinated | | | | Unknown vaccination status | |
| | | | | | | | Medical contraindications | | Reasons other than medical contraind. | | | |
| | Total number of facilities in RI* | # facilities reported | % facilities reported | | # | % | # | % | # | % | # | % |
| **Adult Day Care** | n/a | 10 | n/a | 154 | 148 | 96% | 2 | 1% | 3 | 2% | 1 | 1% |
| **Assisted Living** | n/a | 5 | n/a | 212 | 117 | 55% | 5 | 2% | 77 | 36% | 13 | 6% |
| **Community health center** | 21 | 6 | 29% | 815 | 740 | 91% | 3 | 0% | 52 | 6% | 20 | 2% |
| **Home care provider** | n/a | 25 | n/a | 2,314 | 1,733 | 75% | 32 | 1% | 410 | 18% | 145 | 6% |
| **Home nursing care provider** | 60 | 14 | 23% | 1,599 | 1,114 | 70% | 17 | 1% | 183 | 11% | 285 | 18% |
| **Hospice care** | 9 | 2 | 22% | 291 | 264 | 91% | 1 | 0% | 14 | 5% | 2 | 1% |
| **Hospital** | 14 | 13 | 93% | 25,140 | 22,255 | 89% | 128 | 1% | 2,532 | 10% | 211 | 1% |
| **Kidney treatment center** | 13 | 7 | 54% | 149 | 135 | 91% | 3 | 2% | 11 | 7% | 0 | 0% |
| **Nursing facility** | 90 | 59 | 66% | 8,335 | 7,546 | 91% | 55 | 1% | 464 | 6% | 248 | 3% |
| **Nursing service agency** | 25 | 2 | 8% | 182 | 158 | 87% | 0 | 0% | 22 | 12% | 0 | 0% |
| **Physician ambulatory surgical center** | 11 | 5 | 45% | 64 | 60 | 94% | 1 | 2% | 3 | 5% | 0 | 0% |
| **Rehabilitation center** | n/a | 4 | n/a | 723 | 656 | 91% | 4 | 1% | 35 | 5% | 30 | 4% |
| **College health center** | n/a | 2 | n/a | 124 | 112 | 90% | 3 | 2% | 7 | 6% | 2 | 2% |
| **Surgi-center** | n/a | 4 | n/a | 134 | 126 | 94% | 1 | 1% | 7 | 5% | 0 | 0% |
| **Other** | n/a | 28 | n/a | 1,179 | 999 | 85% | 19 | 2% | 113 | 10% | 38 | 3% |
| **Total** | n/a | **186** | n/a | **41,415** | **36,163** | **87.3%** | **274** | **0.7%** | **3,933** | **9.5%** | **995** | **2.4%** |

* Preliminary

Healthcare Worker (HCW) Influenza Vaccination Summary Report, as of January 31, 2013

| Non-employee Healthcare Workers: Licensed Independent Practitioners (LIP: physicians, advanced practice nurses & physician assistants) | | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Facility type | Facililty Information | | | Reported # of Non-employee HCW: LIP | Vaccinated | | Not Vaccinated | | | | Unknown vaccination status | |
| | Total number of facilities in RI* | # facilities reported | % facilities reported | | | | Medical contraindications | | Reasons other than medical contraind. | | | |
| | | | | | # | % | # | % | # | % | # | % |
| **Adult Day Care** | n/a | 10 | n/a | 10 | 10 | 100% | 0 | 0% | 0 | 0% | 0 | 0% |
| **Assisted Living** | n/a | 5 | n/a | 6 | 5 | 83% | 0 | 0% | 1 | 17% | 0 | 0% |
| **Community health center** | 21 | 6 | 29% | 38 | 32 | 84% | 0 | 0% | 2 | 5% | 4 | 11% |
| **Home care provider** | n/a | 25 | n/a | 28 | 25 | 89% | 1 | 4% | 1 | 4% | 9 | 32% |
| **Home nursing care provider** | 60 | 14 | 23% | 6 | 6 | 100% | 0 | 0% | 0 | 0% | 0 | 0% |
| **Hospice care** | 9 | 2 | 22% | 7 | 7 | 100% | 0 | 0% | 0 | 0% | 0 | 0% |
| **Hospital** | 14 | 13 | 93% | 5,879 | 4,664 | 79% | 6 | 0% | 215 | 4% | 976 | 17% |
| **Kidney treatment center** | 13 | 7 | 54% | 32 | 32 | 100% | 15 | 47% | 0 | 0% | 0 | 0% |
| **Nursing facility** | 90 | 59 | 66% | 844 | 735 | 87% | 7 | 1% | 55 | 7% | 92 | 11% |
| **Nursing service agency** | 25 | 2 | 8% | 0 | 0 | --- | 0 | --- | 0 | --- | 0 | --- |
| **Physician ambulatory surgical center** | 11 | 5 | 45% | 24 | 22 | 92% | 0 | 0% | 2 | 8% | 0 | 0% |
| **Rehabilitation center** | n/a | 4 | n/a | 58 | 41 | 71% | 0 | 0% | 0 | 0% | 9 | 16% |
| **College health center** | n/a | 2 | n/a | 0 | 0 | --- | 0 | --- | 0 | --- | 0 | --- |
| **Surgi-center** | n/a | 4 | n/a | 66 | 63 | 95% | 0 | 0% | 3 | 5% | 0 | 0% |
| **Other** | n/a | 28 | n/a | 164 | 48 | 29% | 0 | 0% | 3 | 2% | 113 | 69% |
| **Total** | n/a | **186** | n/a | **7,162** | **5,690** | **79.4%** | **29** | **0.4%** | **282** | **3.9%** | **1,203** | **16.8%** |

* Preliminary

**Healthcare Worker (HCW) Influenza Vaccination Summary Report,** as of January 31, 2013

| Non-employee Healthcare Workers: Students/Trainees and Volunteers (ASTV) | | | | | | | | | | | | Adult |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Facility type | Facililty Information | | | Reported # of Non-employee HCW: ASTV | Vaccinated | | Not Vaccinated | | | | Unknown vaccination status | |
| | Total number of facilities in RI* | # facilities reported | % facilities reported | | | | Medical contraindications | | Reasons other than medical contraind. | | | |
| | | | | | # | % | # | % | # | % | # | % |
| Adult Day Care | n/a | 10 | n/a | 107 | 95 | 89% | 1 | 1% | 7 | 7% | 5 | 5% |
| Assisted Living | n/a | 5 | n/a | 15 | 8 | 53% | 5 | 33% | 2 | 13% | 0 | 0% |
| Community health center | 21 | 6 | 29% | 129 | 86 | 67% | 0 | 0% | 0 | 0% | 33 | 26% |
| Home care provider | n/a | 25 | n/a | 95 | 84 | 88% | 0 | 0% | 11 | 12% | 0 | 0% |
| Home nursing care provider | 60 | 14 | 23% | 97 | 92 | 95% | 0 | 0% | 5 | 5% | 0 | 0% |
| Hospice care | 9 | 2 | 22% | 335 | 199 | 59% | 1 | 0% | 12 | 4% | 121 | 36% |
| Hospital | 14 | 13 | 93% | 4,792 | 2,390 | 50% | 8 | 0% | 170 | 4% | 2,240 | 47% |
| Kidney treatment center | 13 | 7 | 54% | 0 | 0 | --- | 0 | --- | 0 | --- | 0 | --- |
| Nursing facility | 90 | 59 | 66% | 288 | 257 | 89% | 51 | 18% | 8 | 3% | 24 | 8% |
| Nursing service agency | 25 | 2 | 8% | 14 | 14 | 100% | 0 | 0% | 0 | 0% | 0 | 0% |
| Physician ambulatory surgical center | 11 | 5 | 45% | 4 | 4 | 100% | 0 | 0% | 0 | 0% | 0 | 0% |
| Rehabilitation center | n/a | 4 | n/a | 4 | 2 | 50% | 0 | 0% | 0 | 0% | 0 | 0% |
| College health center | n/a | 2 | n/a | 18 | 13 | 72% | 0 | 0% | 0 | 0% | 0 | 0% |
| Surgi-center | n/a | 4 | n/a | 0 | 0 | --- | 0 | --- | 0 | --- | 0 | --- |
| Other | n/a | 28 | n/a | 202 | 12 | 6% | 1 | 0% | 1 | 0% | 185 | 92% |
| **Total** | **n/a** | **186** | **n/a** | **6,100** | **3,256** | **53.4%** | **67** | **1.1%** | **216** | **3.5%** | **2,608** | **42.8%** |

* Preliminary

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# Performance of *Clostridium difficile* Toxin Enzyme Immunoassay and Nucleic Acid Amplification Tests Stratified by Patient Disease Severity

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**Many clinical laboratories in the United States are transitioning from toxin enzyme immunoassays (EIA) to nucleic acid amplification tests (NAATs) as the primary diagnostic test for *Clostridium difficile* infection (CDI). While it is known that the analytical sensitivity of the toxin EIA is poor, there are limited clinical data on the performance of these assays for patients with mild or severe CDI. Two hundred ninety-six hospital inpatients with diarrhea and clinical suspicion for CDI were tested prospectively by toxin EIA, by *C. difficile* NAAT, and with a reference standard toxigenic culture. Following completion of laboratory testing, retrospective chart reviews were performed to stratify patients into mild and severe disease groups based on clinical criteria using a standard point-based system. One hundred forty-three patients with CDI confirmed by toxigenic culture were evaluated in this study. Among the patients with mild CDI, 49% tested positive by toxin EIA and 98% tested positive by NAAT. Among patients with severe CDI, 58% tested positive by toxin EIA and 98% tested positive by NAAT. Increased CDI disease severity was not associated with an increased sensitivity of EIA ($P = 0.31$). These data demonstrate that toxin EIA performs poorly both for patients with severe CDI and for those with mild CDI and support the routine use of NAAT for the diagnosis of CDI. The presence of stool toxin measured by EIA does not correlate with disease severity.**

*Clostridium difficile* infection (CDI) is a significant cause of morbidity and mortality in the health care setting. The incidence and severity of CDI are increasing in the United States (1), as is the number of patients who experience recurrent disease (2). Diagnosis of CDI requires evaluation of both clinical and laboratory findings. Patients may be considered to have CDI if they have both diarrhea (defined as passage of 3 or more unformed stools within a 24-h period) and a positive laboratory stool test for the presence of toxigenic *C. difficile* (2).

Laboratory tests available for the detection of *C. difficile* in stool specimens include culture, toxin antigen detection, and detection of toxin genes by nucleic acid amplification tests (NAATs). While culture for toxin-producing *C. difficile* is considered the gold standard, this test is ill suited to the clinical laboratory, as it is technically demanding and requires, at minimum, 3 days to perform. In contrast, enzyme immunoassays (EIA) for toxins A and/or B in stool have been widely used by clinical laboratories in the United States as a rapid method by which to detect *C. difficile.* However, the sensitivity of these EIAs is poor compared to culture, ranging from 33 to 65% (2, 3). In 2010, the Society for Healthcare Epidemiology (SHEA) and the Infectious Diseases Society of American (IDSA) indicated that toxin EIAs were no longer sufficient as standalone diagnostic tests for *C. difficile* (2). Because of their increased sensitivity and specificity compared to toxin EIAs (4–7), many laboratories are transitioning to NAATs as an alternative for the detection of *C. difficile.*

One main disadvantage of NAATs is that they do not detect the presence of biologically active toxin in stool specimens. The toxins expressed by *C. difficile* are this organism's main virulence factor, and some feel that the presence of toxin in stool is a positive correlate of disease (8). The significance of detecting *C. difficile* in the absence of the toxins, such as in the patient who tests positive by NAAT but negative by toxin EIA, is unclear. Furthermore, few well-controlled studies have established the clinical efficacy of NAATs (2), and none have evaluated the EIA and NAATs in parallel for the diagnosis of severe CDI. In this study, we investigated the sensitivity of a toxin A and B EIA and a *C. difficile* NAAT compared to toxigenic culture, stratified by CDI severity. Specifically, we sought to determine if patients who tested negative for *C. difficile* toxins by EIA but positive by NAAT were more likely to have mild CDI than patients who tested positive by both methods.

## MATERIALS AND METHODS

**Study population.** The UCLA Health System (Los Angeles, CA) consists of a 300-bed acute care teaching hospital and a 600-bed tertiary care teaching hospital affiliated with the University of California, Los Angeles. From November 2011 through July 2012, adult inpatients were included in this study if they had a liquid stool specimen submitted to the clinical microbiology laboratory for *C. difficile* testing. All patients with a positive NAAT in the study were matched with an equal number of patients with negative NAAT results daily. All protocols were approved by the UCLA Institutional Review board.

Following completion of laboratory testing, retrospective chart reviews were performed in order to stratify patients into mild and severe disease groups based on the criteria of Zar and colleagues (9). Patients were assigned points based on age (>60 years, 1 point), temperature (>38.3°C, 1 point), albumin level (<2.5 mg/dl, 1 point), peripheral white blood cell (WBC) count (>15,000/mm$^3$, 1 point), treatment in the intensive care unite (ICU) (2 points), or endoscopic evidence of pseudomembranous colitis (2 points). Patients with ≥2 points were considered to have severe disease. Additional data on all patients were collected: hospital

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**TABLE 1** Interpretation of laboratory test results for the diagnosis of CDI in patients with diarrhea and suspect *C. difficile* disease for this study[a]

| Case definition | Laboratory test result | | | | Interpretation | No. of patients (no. with severe disease) |
|---|---|---|---|---|---|---|
| | NAAT | EIA | Toxigenic culture | Cepheid Xpert | | |
| CDI | − | − | + | − | NAAT and EIA FN | 3 (1) |
| CDI | + | − | + | NP | EIA FN | 51 (19) |
| CDI | − | + | + | NP | NAAT FN | 0 (0) |
| CDI | + | + | + | NP | TP | 70 (32) |
| CDI | + | − | − | + | EIA FN | 13 (5) |
| CDI | + | + | − | + | Culture FN | 6 (3) |
| No CDI | + | + | − | − | NAAT and EIA FP | 0 (NA) |
| No CDI | + | − | − | − | NAAT FP | 6 (NA) |
| No CDI | − | + | − | NP | EIA FP | 9 (NA) |
| No CDI | − | − | − | NP | TN | 138 (NA) |

[a] EIA, toxin A and B enzyme immunoassay; FN, false negative; TP, true positive; FP, false positive; TN, true negatives; NP, not performed; NA, not applicable.

length of stay, 28-day all-cause mortality, laboratory evidence of recurrent *C. difficile* disease (e.g., positive NAAT on a liquid stool specimen submitted ≤1 month following appropriate treatment and abatement of symptoms), gastrointestinal disease comorbidity, immunosuppression, treatment with a stool softener, duration of symptoms, and number of stools on the day a specimen was collected for *C. difficile* testing. Community-associated CDI (CA-CDI) was defined as a positive *C. difficile* test within 3 days of hospital admission; all other cases were considered hospital-associated (HA)-CDI.

***C. difficile* testing.** Liquid stool specimens submitted to the microbiology laboratory were tested using the illumigene *C. difficile* (Meridian Bioscience, Cincinnati, OH) assay, a NAAT that detects the presence of *C. difficile* through amplification of the 5′ end of the toxin A gene. In parallel, a *C. difficile* toxin A/B immunoassay (Premier Toxin A+B; Meridian Bioscience) was performed on all samples. Samples were frozen at −20°C and shipped to a reference laboratory in batches for toxigenic culture by standard protocols. Results that were discrepant by toxigenic culture and NAAT were resolved by the Cepheid Xpert *C. difficile* assay, which detects the *tcdB* gene of *C. difficile*. Cases were defined as either patients with a positive toxigenic culture or patients who were toxigenic culture negative but tested positive by both the *C. difficile* illumigene and Cepheid Xpert tests (Table 1). Specimens that tested negative by EIA were further evaluated for potential postzone effect (e.g., antigen excess) by dilution of stool 1:10 and 1:100 in the Meridian Toxin A+B diluent and retesting in duplicate by the EIA, at these dilutions.

**Statistical design and analysis.** The study was powered using a 2-tailed β of 0.05 and α of 0.10, with the assumption of 90% sensitivity for the illumigene test to detect *C. difficile* and 60% sensitivity for the toxin A+B enzyme immunoassay. Based on these assumptions, a minimum of 40 patients with severe disease and 40 with mild disease were required in the study to detect a difference in the ability of the EIA and NAAT to diagnose patients with severe disease. At the time of study completion, 66 patients with severe disease and 89 with mild disease were included. Patient outcomes with respect to EIA results were compared using Fisher's exact test. Unpaired Student's *t* test and the Wilcoxon rank-sum test were used for comparison of continuous variables. A $P$ value of $<0.05$ was considered statistically significant. All statistical analyses were performed using MedCalc Software version 12.3.0.0.

## RESULTS

**Patient characteristics.** Two-hundred ninety-six patients with liquid stool sent for *C. difficile* testing were enrolled in the study. One hundred forty-three patients met the study criteria for laboratory-confirmed CDI (Table 1), whereas 153 patients tested negative for *C. difficile* (Table 1). Among the patients with CDI, 76 tested positive by both EIA and illumigene, 64 negative by EIA but positive by illumigene, and 3 negative by both EIA and illumigene (Table 1). Eighty-three cases (58%) were defined as mild disease and 60 (42%) as severe (Tables 1 and 2). Patients with mild disease were more likely to have CA-CDI (odds ratio [OR] = 1.51, $P$ = 0.05) and shorter hospitalizations (average of 17 days versus 29 days for severe disease, $P$ = 0.002) and had 2.7 times lower odds for all-cause mortality at 28 days ($P$ = 0.0001; Table 2). No patients in this study had colectomy, and only one patient had endoscopic evidence of pseudomembranous colitis, though only 4 patients had endoscopy performed within 72 h of *C. difficile* testing. Ten patients died within 28 days of CDI diagnosis, all of whom were classified with severe disease.

**Factors associated with false-negative toxin EIA results.** Toxin EIA results were not correlated with CDI severity ($P$ = 0.31; Table 3). Similarly, no difference was found between the EIA sensitivity levels in patients with severe (58% positive by EIA) and mild (49% positive by EIA) disease ($P$ = 0.31, data not shown).

**TABLE 2** Characteristics of patients with mild and severe CDI

| Characteristic | Disease severity | | OR | $P^a$ |
|---|---|---|---|---|
| | Mild ($n$ = 83) | Severe ($n$ = 60) | | |
| No. (%) that were male | 39 (46.9) | 32 (51.6) | | |
| No. (%) of patients with CA-CDI | 38 (45.7) | 18 (30) | 1.51 | 0.05 |
| No. (%) of patients with documented recurrent disease | 14 (16.8) | 10 (16.6) | 0.98 | 1.0 |
| Avg no. of stools per day ± SD | 3 ± 3.4 | 3 ± 2.6 | | 0.43 |
| Avg duration of symptoms ± SD (days) | 8 ± 3.1 | 6 ± 3.8 | | 0.16 |
| No. (%) of patients treated with immunosuppressive agent | 25 (30.1) | 10 (16.6) | 0.67 | 0.09 |
| No. (%) of patients treated with stool softener | 34 (40.9) | 22 (36.6) | 0.99 | 1.0 |
| No. (%) of patients with a GI[b] comorbidity | 26 (31.3) | 17 (28.3) | 1.01 | 0.9 |
| Mean hospital stay ± SD (days) | 17 ± 20 | 29 ± 29 | | 0.002 |
| No. of patients with all-cause 1-mo mortality | 0 | 10 | 2.66 | 0.0001 |

[a] $P$ values were calculated using Fisher's exact test, except for average age, duration of symptoms, number of stools per day, and mean hospital days, which were calculated by the unpaired *t* test.
[b] GI, gastrointestinal.

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**TABLE 3** Characteristics of patients with CDI who tested positive or negative for *C. difficile* toxin A/B EIA

| Characteristic | EIA result | | OR | $P^a$ |
|---|---|---|---|---|
| | Negative | Positive | | |
| Total no. of patients (male:female) | 67 (31:36) | 76 (40:36) | | |
| Avg age ± SD | 62.3 ± 20.6 | 65.8 ± 20.1 | | 0.16 |
| No. (%) >60 years of age | 42 (63) | 46 (61) | 0.96 | 0.86 |
| No. (%) under ICU treatment | 11 (17) | 18 (24) | 1.22 | 0.30 |
| No. (%) with temp of >38.3°C | 8 (11.9) | 8 (10.5) | 0.93 | 0.79 |
| No. (%) with albumin level of <2.5 mg/dl[b] | 9 (28) | 14 (35) | 1.14 | 0.62 |
| No. (%) with WBC count of >15,000 cells/mm$^3$ | 8 (11.9) | 8 (10.5) | 0.93 | 0.79 |
| No. (%) showing presence of pseudomembranous colitis | 0 (0) | 1 (1.3) | 1.89 | 1.00 |
| No. (%) with severe disease | 25 (37) | 35 (46) | 1.18 | 0.31 |
| No. (%) with CA-CDI | 31 (46) | 27 (36) | 1.18 | 0.31 |
| No. (%) with documented recurrent disease | 10 (16) | 14 (18) | 1.11 | 0.66 |
| No. of stools per day ± SD | 3 ± 3.6 | 3 ± 2.6 | | 0.43 |
| Duration of symptoms ± SD (days) | 6 ± 6 | 8 ± 10.9 | | 0.18 |
| No. (%) of patients under treatment with immunosuppressive agent | 24 (36) | 24 (32) | 0.91 | 0.71 |
| No. (%) of patients with GI[c] comorbidity | 22 | 21 | 0.62 | 0.31 |
| Mean hospital stay ± SD (days) | 18 (±18) | 25 (±28) | | 0.04 |
| No. (%) of patients with 1-mo all-cause mortality | 5 (7.4) | 5 (6.6) | 1.01 | 1.00 |

[a] *P* values were calculated using Fisher's exact test, except for average age, duration of symptoms, number of stools per day, and mean hospital days, which were calculated by the unpaired *t* test.
[b] Only 72 patients were tested for albumin within 48 h of stool collection for *C. difficile* testing, encompassing 32 EIA-negative (48%) and 40 EIA-positive (53%) patients.
[c] GI, gastrointestinal.

Analysis of covariation for other patient characteristics measured in this study did not alter this result (not shown). The only factor identified by univariate analysis to be associated with EIA result was length of hospital stay (Table 3). Patients with positive EIAs had an average hospital stay of 25 ± 28 days, and patients with negative EIA results had an average hospital stay of 18 ± 18 days ($P = 0.04$; Table 3). Among the 10 patients who died within 28 days of CDI diagnosis, 5 tested positive by both EIA and NAAT and 5 tested negative by EIA and positive by NAAT (Table 3).

**Performance of the illumigene *C. difficile* and toxin enzyme immunoassay for the detection of *C. difficile*.** Sensitivity, specificity, and negative and positive predictive values for illumigene and toxin EIA are presented in Table 4. The sensitivity of the NAAT was 97.1% compared to toxigenic culture and 97.9% once culture/NAAT discrepant results were resolved by Cepheid Xpert testing. Three false-negative results were obtained by illumigene (Table 1); all three were culture positive but tested negative by both EIA and Cepheid Xpert. These patients included a 73-year-old man with mild disease and a history of antimicrobial exposure, a 31-year-old man with mild disease and no history of antimicrobial exposure, and a 54-year-old man with severe disease (defined in this patient by ICU treatment and WBC count of 15,600 cells/mm$^3$) and a history of antimicrobial exposure. Six false-positive results were obtained by illumigene, which tested negative by EIA, toxigenic culture, and Cepheid Xpert testing (Table 1).

In this study, EIA sensitivity was 47.1% compared to toxigenic culture and 53.1% compared to resolved NAAT results (data not shown). Resolved specificity was 94.1%; nine false-positive EIA results were documented in this study (Table 1). Specimens that were EIA negative but culture positive were diluted at 1:10 and 1:100 and retested in the attempt to identify a possible postzone effect; all diluted specimens remained EIA negative.

## DISCUSSION

While no optimal strategy for clinical laboratory diagnosis of CDI has been defined, it is well recognized that the analytical sensitivity of the toxin EIA is unacceptably low (2). As toxin expression is thought to be one factor related to CDI severity (10), we sought to determine if false-negative toxin EIA results occurred in all patients with CDI or only in those patients with mild disease and presumably a low fecal concentration of *C. difficile* toxins (11). In contrast to this supposition, our data demonstrate that toxin EIA was negative in 42% of patients with severe CDI. NAAT, on the other hand, was negative in only one patient (2%) with severe disease, reinforcing the superior clinical performance of NAAT over EIA for laboratory diagnosis of CDI.

In this study, 60 patients were defined to have severe disease according to the criteria of Zar and colleagues (9). Factors associated with severe disease included HA-CDI and immunosuppression, and patients with severe disease were more likely to have longer hospitalizations and a higher rate of all-cause mortality at 28 days (Table 2). Alternative definitions for severe CDI have been proposed, including death within 30 days of *C. difficile* diagnosis, colectomy, or treatment in the ICU (12). No patients in our study

**TABLE 4** Performance of illumigene *C. difficile* assay and toxin EIA compared to toxigenic culture for the detection of *C. difficile*

| Characteristic[a] | illumigene results: | | | | EIA results compared to: | | | |
|---|---|---|---|---|---|---|---|---|
| | Compared to toxigenic culture | | Resolved by Cepheid testing | | Toxigenic culture | | Resolved illumigene results | |
| | % | 95% CI | % | 95% CI | % | 95% CI | % | 95% CI |
| Sensitivity | 97.1 | 91.9–99.0 | 97.9 | 93.5–99.5 | 47.1 | 37.8–56.6 | 53.1 | 42.5–54.2 |
| Specificity | 79.8 | 71.7–86.1 | 96.1 | 80.2–92.2 | 87.4 | 91.3–98.4 | 94.1 | 88.8–97.1 |
| PPV | 80.8 | 72.6–87.1 | 95.9 | 90.9–98.3 | 76.6 | 64.0–85.8 | 89.4 | 80.4–94.7 |
| NPV | 96.9 | 90.7–99.2 | 98.0 | 93.8–99.4 | 65.4 | 57.4–72.6 | 68.2 | 61.4–74.3 |

[a] CI, confidence interval; PPV, positive predictive value; NPV, negative predictive value.

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required colectomy, but 29 patients required ICU treatment (11 of whom were EIA negative [Table 3]) and 10 patients died within 28 days of *C. difficile* diagnosis, including 5 EIA-negative patients (Table 3). Thus, even by more stringent criteria to define severe CDI, toxin EIA was not a reliable diagnostic test in our study.

Few other studies have evaluated toxin EIA performance in the context of patient disease severity, although de Jong and colleagues investigated peripheral white blood cell count in patients who tested negative or positive by toxin EIA. In their study, patients with toxin EIA-negative results were less likely to have leukocytosis of >15,000/ml than those patients who tested positive by both EIA and NAAT (13). However, only 10 patients were EIA negative/NAAT positive in this study. In contrast, among 64 patients with EIA/NAAT discordant results in our current study, no correlation between leukocytosis and EIA result was found (Table 3). In a large prospective study, Wilcox and colleagues recently demonstrated that the presence of toxin in stool specimens remains important to the definition of CDI. In their study, 6,524 hospital inpatients with diarrhea and suspected CDI were evaluated prospectively by both toxigenic culture and cell cytotoxicity neutralization assay (CCNA), which detects the presence of biologically active toxin through evaluation of cytopathic effect on Vero cells. CCNA results were found to correlate with 30-day mortality, length of hospitalization, and leukocytosis, whereas toxigenic culture did not correlate with these clinical characteristics (8; M. H. Wilcox, presented at ID Week 2012, San Diego, CA, 2012). These authors suggest that patients who test positive for *C. difficile* but negative for toxin be defined as "potential *C. difficile* excretors" for the purposes of infection control alone, but not necessarily be treated for CDI. However, in the Wilcox study, patients were not treated based on the CCNA results but rather on local *C. difficile* testing practices, and as such the outcomes associated with not treating patients with diarrhea and positive NAAT or glutamate dehydrogenase antigen (GDH) test but negative CCNA are unknown. Furthermore, how laboratories may test for the presence of toxin remains a dilemma, as in this same population, the sensitivity of the toxin EIAs was found to be only 68.2 to 82.3% compared to CCNA (14). Regardless, because CCNA may take up to 1 week to perform and requires laboratory proficiency in culturing cell monolayers and reading cytotoxicity, the United Kingdom's National Protection Agency endorses use of toxin EIAs to confirm the presence of toxin in patients who test positive for *C. difficile* by either NAAT or GDH screen. Outcome data from this approach, which is now in effect (http://www.dh.gov.uk/prod_consum_dh/groups/dh_digitalassets/@dh/@en/documents/digitalasset/dh_133016.pdf), will be revealing.

A clear etiology for EIA false-negative results has not yet been defined. Interstrain variability in toxin expression (15) may be one reason for false-negative toxin results (16). Alternatively, toxin may be diluted to below the limit of detection for the EIAs in some patients, due to increased volume and frequency of stools. However, in our analysis, no correlation was found between the number of stools per day and the EIA result (Table 3). Furthermore, repeat testing in two or more additional stool specimens by EIA does not result in an appreciable improvement in this test's sensitivity (17–19), suggesting that intermittent toxin shedding is not the basis for false-negative results. We evaluated specimens for postzone effect as a third possible cause of false-negative EIA results, but dilution and retesting of EIA-negative/NAAT-positive specimens did not yield any increase in EIA sensitivity. Finally, toxin stability may play a role in EIA results, although we did not evaluate specimen transport time to the laboratory in our study. The only factor associated with increased sensitivity of positive EIA results was greater length of hospitalization, although this correlation achieved a *P* value of relatively low significance (Table 3). Wilcox and colleagues noted that the presence of toxin also correlated with length of hospitalization when measured by CCNA (8). It is possible that these patients were infected with strains of *C. difficile* that express higher levels of toxin (10, 16) and thus required more lengthy hospitalizations, although we did not strain type the isolates in this study or evaluate their *in vitro* levels of toxin expression. Six false-positive results were obtained by the illumigene assay, an incidence similar to that noted by other studies (3, 6). The mechanism of these false positives is unclear, although some have suggested that loop-mediated isothermal amplification is more sensitive than toxigenic culture, and these may thus represent true-positive results, albeit at very low levels of organism presence (20, 21). However, others have reported that the sensitivity of the Xpert *C. difficile* assay, which was used as an arbiter test in our study, is greater than that of the illumigene assay (22).

While the clinical data to support routine use of NAAT for CDI diagnosis remain sparse, single institutional studies of patient outcomes before and after laboratory conversion from EIA to NAAT have demonstrated the benefits of NAAT. Benefits include fewer patients with CDI complications such as colectomy, admission to the ICU, and death (23) and earlier recognition of patients with CDI (24). NAATs may help with early diagnosis of CDI and may lead to treatment of patients before they progress to severe CDI, although this has not yet been specifically demonstrated. Additional benefits for the use of NAAT at an institutional level include elimination of unnecessary antimicrobial therapy for patients with presumptive, but toxin EIA-negative, CDI (25). It remains clear, however, that the use of laboratory stool tests in the diagnosis of CDI is complicated by those patients who are asymptomatically colonized with *C. difficile.* Use of colonoscopy, histopathology findings, and a sensitive toxin detection test, such as CCNA, may aid with diagnosis, but all laboratory tests must be interpreted in the context of patient symptoms and risk factors for CDI. As diarrhea is a common symptom in the hospitalized, elderly, or long-term care facility patient, it remains difficult to distinguish the patient with CDI from the patient for whom a positive *C. difficile* test is related to underlying colonization.

This study presents some limitations, primarily the fact that it was performed in a single center. Regardless, the findings strongly support the use of NAAT as the primary diagnostic laboratory test for CDI. While NAATs are roughly 10 times more costly than EIAs on a per test basis, prompt recognition of patients with CDI is imperative not only for patient management but also for infection prevention and control and antimicrobial stewardship.

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Brief report

# Improved detection of toxigenic *Clostridium difficile* using the Cepheid Xpert *C difficile* assay and impact on *C difficile* infection rates in a tertiary hospital: A double-edged sword

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*Key Words:*
*Clostridium difficile*
Diagnosis
Infection

Recent recommendations suggest implementation of a 2-step diagnostic algorithm for the laboratory detection of toxigenic *Clostridium difficile*. We found that the rate of toxigenic *C difficile* detection in our laboratory doubled after the introduction of an algorithm that incorporated polymerase chain reaction testing. This led to an abrupt 70% increase in the overall rate of *C difficile* infection in our institution.

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Infection with toxigenic *Clostridium difficile* is the most common cause of health care–associated diarrhea. The global spread of epidemic strains of *C difficile*, notably the NAP1/027/BI strain, is of concern and has contributed to the increased incidence of *C difficile* infection (CDI) in several geographic regions.[1,2] Rapid, sensitive, and specific laboratory diagnosis of toxigenic *C difficile* is essential, both for optimal patient treatment and for timely implementation of infection control measures. Recent recommendations suggest a 2-step algorithmic approach for diagnosing CDI, using detection of the *C difficile* common antigen glutamate dehydrogenase (GDH) as an initial screening method, followed by a more specific method to detect toxigenic *C difficile*, such as toxigenic culture.[3] However, despite their specificity, culture-based methods are complex and laborious, often taking 48-72 hours to complete. Recently, several molecular assays have been approved for the detection of *C difficile* toxin genes from stool specimens. The Cepheid Xpert *C difficile* assay (Cepheid, Sunnyvale, CA) detects the *C difficile* toxin B gene (*tcdB*) directly from stool and has been shown to have high sensitivity compared with other testing methods.[4,5] In this study, we sought to compare the laboratory rate of toxigenic *C difficile* detection before and after the introduction of the Xpert *C difficile* assay, and to determine the impact of this change in testing strategy on overall CDI rates in our hospital.

## METHODS

Between June 2009 and June 2010, stool specimens submitted to our laboratory for CDI diagnosis were tested using the C DIFF Quik Chek Complete test (Techlab, Blacksburg, VA), an enzyme immunoassay (EIA) that simultaneously detects GDH and toxins A or B in fecal specimens. Specimens that tested positive for both GDH and *C difficile* toxin were reported as positive for toxigenic *C difficile*. Samples that tested GDH-positive but toxin-negative were reported as being "indeterminate" for the presence of toxigenic *C difficile*, and these results were interpreted according to the clinical presentation.

From July 2010 onward, all stool specimens that tested indeterminate for toxigenic *C difficile* by the C DIFF Quik Chek test underwent polymerase chain reaction (PCR) analysis for the *tcdB* gene using the Xpert *C difficile* assay according to the manufacturer's instructions. Specimens that tested positive for the *tcdB* gene were reported as positive for the presence of toxigenic *C difficile*; conversely, if the *tcdB* gene was not detected, specimens were reported as negative for toxigenic *C difficile*. Throughout the study period, only unformed stool specimens were processed, and duplicate samples from the same patient within a 28-day period were excluded. In addition, specimens from patients under age 2 years were not included.

To estimate the rate of health care facility–onset, health care facility–associated (HO-HCFA) CDI, we excluded results from those patients who had stool samples sent within 72 hours of hospital admission.[3] The $\chi^2$ test was used for comparison between study periods.

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**Table 1**
Impact of the 2-step diagnostic algorithm on laboratory detection of toxigenic *C difficile*

| | First testing period (July 2009 to June 2010) | Second testing period (July 2010 to December 2011) |
|---|---|---|
| Total number of specimens tested | 3,100 | 4,006 |
| Number of GDH-positive specimens by EIA* | 473 | 605 |
| Number of GDH-positive/toxin-positive specimens by EIA | 145 | 181 |
| Number of GDH-positive/toxin-negative specimens by EIA | 328 | 424 |
| Number of GDH-positive/toxin-negative specimens positive for the presence of *tcdB* by PCR† | NA | 218 |
| Overall laboratory rate of toxigenic *C difficile* detection, % | 4.7 | 9.9 |

*NA*, not applicable.
*EIA: *C difficile* Quik Chek complete test.
†PCR: Cepheid Xpert *C difficile* assay.

## RESULTS

Between August 2009 and September 2011, a total of 7,106 specimens were sent to the laboratory for diagnosis of CDI. Of these, 3,100 specimens were tested using the C DIFF Quik Chek EIA alone, and 4,006 specimens were tested using our 2-step approach, incorporating the Xpert *C difficile* assay for *tcdB* detection. Of note, the overall laboratory rate of toxigenic *C difficile* detection increased from 4.7% to 9.9% ($P < .001$) after the change in testing strategy (Table 1).

Befoe the change in laboratory testing, the estimated rate of HO-HCFA CDI was 2.3 cases per 10,000 patient-days; this increased to 3.9 cases per 10,000 patient-days after the introduction of *tcdB* PCR testing ($P < .001$). Throughout the study period, there were no known outbreaks of CDI within our institution.

## DISCUSSION

The rate of toxigenic *C difficile* detection in our laboratory doubled after the introduction of a 2-step diagnostic algorithm that incorporated PCR testing. This subsequently led to a significant increase in the overall rate of HO-HCFA CDI in our institution. These findings have notable implications for several reasons.

First, the change in testing strategy resulted in more than 200 additional patients being diagnosed with CDI. In clinical settings where patients may have several possible etiologies for hospital-onset diarrhea (eg, receipt of laxative medication, intestinal mucositis, enteral feeding), it is important that a sufficiently sensitive method be used to diagnose CDI to ensure timely initiation of treatment. This is particularly relevant in view of the global spread of the NAP1/027/BI strain, which is associated with severe clinical outcomes.[6]

Second, the improved diagnosis of CDI is more likely to ensure the appropriate implementation of infection control measures.[3] This is especially important when considering the distinct patient groups most affected by CDI, notably elderly persons and individuals with significant comorbidities.[7] In such clinical settings, which are likely to contain other vulnerable patients, suitable interventions to reduce the spread of *C difficile* are particularly important.

Finally, the incorporation of *tcdB* testing into our diagnostic algorithm led to a sharp 70% increase in the overall CDI rate in our institution. Although public reporting of nosocomial CDI is not mandatory in New Zealand, as it is in several other countries, our institutional rates of CDI likely would be far higher than in those hospitals using EIA testing alone for detecting toxigenic *C difficile*. Notably, a recent survey of laboratories in Australasia demonstrated a wide variety of laboratory testing strategies for detecting toxigenic *C difficile*, with only 6% of laboratories using PCR-based diagnostic methods.[8] The incomparability of institutional CDI rates depending on differing laboratory diagnostic algorithms has been described in other settings, but at present there are no definite recommendations regarding the routine use of PCR testing for toxigenic *C difficile*.[3,9,10]

Our study had several limitations, most notably the fact that we did not collect information on the presenting symptoms and clinical course of each patient. Although only unformed stool specimens were processed during the study period, it is possible that our specificity for diagnosing true *C difficile*–associated diarrhea was reduced. In addition, we did not collect information on how many of the additional 218 patients who had toxigenic *C difficile* detected actually began treatment for CDI. We also did not specifically collect information about concurrent antimicrobial prescribing practices in our institution; however, a study carried out in 2006-2009 in our organization demonstrated comparatively low and stable rates of antimicrobial consumption.[11] During our study period (2009-2010), there were no changes in our hospital's antimicrobial formulary or in antimicrobial prescribing guidelines; thus, we have no reason to believe that this potential confounding factor contributed to the increased rates of CDI between the 2 study periods.

In summary, although the improvements in CDI diagnostic techniques may have benefits for both clinical outcomes and infection prevention measures, the increased sensitivity of PCR testing may in fact be a double-edged sword if institutions incur inappropriate financial penalties for having higher CDI rates than other institutions in which less-sensitive laboratory testing methods are used.

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MAJOR ARTICLE

# Agreement in Classifying Bloodstream Infections Among Multiple Reviewers Conducting Surveillance

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***Background.*** Mandatory reporting of healthcare-associated infections (HAIs) is increasing. Evidence for agreement among different reviewers applying HAI surveillance criteria is limited. We aim to characterize agreement among infection preventionists (IPs) conducting surveillance for central line–associated bloodstream infection (CLABSI) with each other and as compared with simplified laboratory-based definitions.

***Methods.*** Abstracted electronic health records were assembled from inpatients with positive blood cultures at a tertiary-care Veterans Affairs (VA) hospital over a 5-year period. Identical patient records were made available to VA IPs from different facilities to report on CLABSI using their usual surveillance methods. Positive blood cultures were also evaluated using laboratory-based definitions. Standard indices of interrater agreement, expressed as a κ statistic, were computed between IPs, and between IPs and simplified laboratory-based methods.

***Results.*** Overall, 114 patient records were reviewed by 18 IPs, the majority of whom specified they followed National Healthcare Safety Network criteria. The overall agreement among IPs by κ statistic was 0.42 (standard error [SE], 0.06). IPs had better agreement with a simple laboratory-based definition with an average κ of 0.55 (SE, 0.05). The proportion of patient records that 18 IPs reported with CLABSI ranged from 14% to 39% (overall mean, 28% with a coefficient of variation of 25%). When simple laboratory-based methods were applied to different sets of patient records, classification was more consistent with CLABSI assigned in a proportion ranging from 36% to 42% (overall mean, 39%).

***Conclusions.*** Reliability of IP-conducted surveillance to identify HAI may not be ideal for public reporting goals of interhospital comparisons.

Although public reporting of healthcare-associated infections (HAIs) is increasing [1, 2], the determination of HAI is not straightforward and comparisons across institutions can be misleading [3]. Surveillance conducted by infection preventionists (IPs) is time consuming, and the traditional reference standards they use are Centers for Disease Control and Prevention (CDC) National Healthcare Safety Network (NHSN) standardized case definitions [4, 5]. Application of these partially subjective criteria requires considerable clinical judgment, extensive education, and training and can be complicated by variation in skill, knowledge, and experience [6–9]. Several studies have compared prospective IP evaluations with retrospective review to classify bloodstream infections (BSIs), with interrater correlation coefficients, or κ statistics, ranging from 0.31 to 0.66 [10–13]. For tracking trends within an institution, variation is unlikely a problem in facilities with low IP turnover, established training programs, and stable supervision. However, using a subjective system across institutions raises comparability concerns, and simpler laboratory-based definitions that can be automated have been proposed [3, 11, 14–18].

Studies assessing interrater reliability of IP-applied surveillance in practice would assist policy makers in

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determining optimal methods for public reporting. To our knowledge, our study is the first to characterize agreement among multiple IPs reviewing identical patient records presented in a standardized "actual-practice" format. IPs were asked to use their traditional surveillance methods, with agreement among IPs in assigning the determination of central line–associated BSI (CLABSI) at the individual patient record and as a proportion of a set of patient records. We hypothesized that IP disagreement would occur and potentially was more likely if IPs reviewed ambiguous or complicated patient records or had different thresholds in reporting a CLABSI.

## METHODS

### Patient Sample and IP Participants

Patients admitted to a 110-bed tertiary-care Veterans Affairs (VA) Health Care System hospital between January 2001 and December 2005 with blood cultured >2 days from admission growing a microorganism(s) met criteria for inclusion. Patients defined as sensitive (*International Classification of Diseases, Ninth Revision* codes for human immunodeficiency virus, substance abuse, or mental health treatment) were excluded [19]. From a pool of 441 eligible patients, 114 admissions were randomly selected.

Study participants were recruited via email to IPs at 138 acute inpatient VA facilities. The first respondent from each facility with at least 6 months of experience was eligible to participate during enrollment (September–December 2009). Eighteen participants enrolled and were free to withdraw at any time, their responses were kept confidential, and compensation was based on the number of patient records reviewed.

The study was approved by the institutional review boards of the University of Utah and the Salt Lake City VA Health Care System.

### Web Application to Display and Report on Patient Records

Data extracted from the data warehouse included microbiology, unit location and room transfers, antimicrobial therapy, white blood cell counts, vital signs, and selected clinical narratives over a hospitalization. All documents of a particular category (admission and discharge summaries, infectious disease consultations) and selected documents around the time of positive blood cultures (physician/nursing notes and radiograph reports) were used. Patient records lacking physician notes were excluded. A deidentification software tool removed all identifiers except dates [20, 21]. Information on central venous catheters was not standardized and reviewers needed to infer catheter use from clinical narratives and radiographic reports. Patient records were displayed and accessible to IPs in a familiar electronic health record "search and select" format through a password-protected Web-based interface on a secure VA site. Webinar training and an online manual informed participants how to access data and report surveillance decisions.

### Surveillance by IP Review and Laboratory-Based Definitions

An efficient allocation strategy was used to simulate a "real-practice" workload for IPs while maximizing the spectrum of reviewers and patient records. The study dataset of 114 patient records was randomly divided into 4 smaller workable sets. Eighteen IPs were randomly divided into 4 groups, with each IP group randomly assigned to a set of patient records. IPs were instructed to perform surveillance for CLABSI as they normally would and were given a deadline. To explore the level of certainty related to dichotomous yes/no decision making typical for surveillance [4], IPs were asked to provide their level of confidence for CLABSI on a 7-point Likert scale ("definite no" to "definite yes"), describe their decisions, and comment on adequacy of the data and, upon completion of the full review, surveillance criteria used. IPs were considered in agreement if all identified no CLABSI or if all IPs identified ≥1 CLABSI per patient record.

An algorithm to identify CLABSI comprised solely of simplified laboratory-based definitions approximating NHSN criteria as previously published was developed for reference comparison [3, 11]. Because not all data were in an easily retrievable electronic format, a document to standardize manual application of the algorithm was developed. A series of rules applied to blood cultures classified distinct BSI episodes. Blood positive for organisms spanning a 5-day period were defined as a discrete episode, or 30-day period when the same organism was recovered. An episode was classified as a true BSI or contaminant based on organism type and number of positive cultures. A true BSI was identified as secondary if the same organism was cultured from other specified sources 5 days before through 10 days after BSI onset. Primary BSI was classified as CLABSI if a central venous catheter was in place within 48 hours prior to onset. Two investigators independently applied the algorithm to each patient record and adjudicated oppositional cases to consensus.

## Statistical Analysis

Power calculations using statistical simulation supported a strategy where patient records were randomly divided into a number of workable sets, with each set randomly assigned to one of multiple IP groups. The motivation for this strategy was the limited time available to IP participants; it also provided a more precise estimate of the interrater κ statistic than the alternative strategy of having all IPs review the same patient records from a smaller dataset. The projected standard error (SE) for κ with 114 records divided into 4 sets of patient

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records, where each set was given to 1 of 4 IP groups, was 0.058, compared to a projected SE of 0.079 if a single set of 30 patient records was reviewed by all 18 IPs.

IP agreement was assessed using Fleiss's generalization of Cohen κ statistic to multiple raters [22, 23]. Systematic variation between raters in the proportion of positive classifications was evaluated by the coefficient of variation of proportion of positive ratings across IPs, with correction for random sampling error. The coefficient of variation scales the standard deviation of the respective rater's proportions of positive ratings to the average proportion, and indicates the extent to which differences among IPs could lead to systematic biases in comparisons of their infection rates. Because the study design subdivided patient records into multiple sets, each reviewed by a separate group of IPs, separate estimates of κ and the coefficient of variation were computed for each group of IPs and then pooled to produce overall estimates.

## RESULTS

### Characteristics of IP Study Participants and the Patient Sample

IPs reported a median of 4.3 years of surveillance experience (range, 1.75–25 years). Seventy-two percent were certified in infection prevention and control. Although only 22% of IPs formally reported to NHSN, 83% specified that they adhered to NHSN surveillance criteria. IP hospitals were representative of VA acute inpatient facilities nationwide in size and geographic location. The median bed size for the 18 IP hospitals was 125 (range, 21–347) while that of VA nationwide was 114 (range, 9–397). IP hospitals were from 14 of 21 geographical regions. The number of IPs and their makeup by years of experience and facility size were similar across IP groups.

Patient characteristics and microbiology were similar across sets of patient records (Table 1). The overall distribution of organisms for review comprised common skin commensals in 38%, gram-positive recognized pathogens in 31%, gram-negatives in 19%, yeast in 8%, or polymicrobial with recognized pathogens in 4%. More than one set of blood cultures was positive in 50% of episodes for review. Thirty-six percent of patients with positive episodes were located on a critical care unit.

### CLABSI Assignment by Algorithm and IP Review

Classifications assigned by researchers applying the laboratory-based algorithm are provided in Table 2. There were 2 disagreements in 114 patient records, which were resolved upon further review (overlooked nonblood culture; difficulty determining central line presence). In addition, when researchers applied the algorithm, 87% of episodes (46 of 53) from common skin commensals were assigned as "contaminants" whereas 43% of episodes (37 of 85) associated with recognized pathogens were assigned as CLABSI.

The proportion of patient records classified as CLABSI by algorithm was similar across sets of patient records and

**Table 1. Characteristics of the Patient Sample (N = 114 Patient Records)**

| Description of Individual Records[a] | Median | Range |
|---|---|---|
| Patient age, y | 66 | 32–89 |
| Length of stay, d | 24 | 3–107 |
| Clinical notes, no. | 43 | 10–124 |
| Microbiology cultures, no. | 11.5 | 1–61 |
| Blood culture sets, no. | 5 | 1–28 |
| **Overall microbiologic data** | **n** | |
| All blood culture sets (positive sets) | 750 (210) | |
| Episodes of positive blood cultures for review[b] | 138[c] | |
| Episodes by organism | | |
| Common skin commensals[d] | 53 | |
| *Staphylococcus aureus* | 26 | |
| *Enterococcus* spp | 13 | |
| *Klebsiella* spp | 10 | |
| *Candida* spp | 11 | |
| *Enterobacter* spp | 8 | |
| β-hemolytic streptococcus | 3 | |
| *Escherichia coli/Serratia/Pseudomonas* | 2 each | |
| *Acinetobacter/Proteus/Mycobacterium fortuitum* | 1 each | |
| Mixed | 4 | |

[a] Ninety-nine percent of patients were male.

[b] Positive cultures were grouped into episodes for review over a 5-day period, or, if the same organism was recovered from an initial infection, a 30-day period.

[c] 20 records had >1 episode for review.

[d] Common skin commensals as defined by the National Healthcare Safety Network.

**Table 2. Classification of Culture-Positive Episodes (n = 138)[a] Applying a Simple Laboratory-Based Definition**

| Classification Category | Episodes, n |
|---|---|
| Contaminant | 46 |
| Secondary BSI | 30 |
| Primary BSI without central venous catheter | 14 |
| CLABSI | 48 (from 44 records) |
| Due to common skin commensal vs recognized pathogen[b] | 11 vs 37 |
| Occurred in ICU vs non-ICU location | 20 vs 28 |

Abbreviations: BSI, bloodstream infection; CLABSI, central line–associated bloodstream infection; ICU, intensive care unit.

[a] Consensus determinations of 2 research reviewers applying a laboratory-based definition.

[b] As defined by the National Healthcare Safety Network.



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**Table 3. The Proportion of Records With Agreement Among Infection Preventionists and a Laboratory-Based Definition in Assigning Central Line–Associated Bloodstream Infection**

| | | | Proportion of Records Assigned With CLABSI | | | |
|---|---|---|---|---|---|---|
| | | | | IP | | |
| Group | IPs, n | Patient Records, n | Laboratory-Based Definitions | Mean | Range | Coefficient of Variation (%) |
| 1 | 4 | 29 | 0.42 | 0.30 | 0.21–0.38 | 24 |
| 2 | 4 | 29 | 0.39 | 0.26 | 0.17–0.350 | 32 |
| 3 | 5 | 28 | 0.36 | 0.21 | 0.14–0.290 | 26 |
| 4 | 5 | 28 | 0.39 | 0.33 | 0.25–0.390 | 9 |
| Overall[a] | 18 | 114 | 0.39 | 0.28 | 0.14–0.390 | 25 |

Abbreviations: CLABSI, central line–associated bloodstream infection; IPs, infection preventionists.

[a] Separate estimates of coefficient of variation computed for each group of IPs and pooled across groups to produce overall estimates.

ranged from 36% to 42% (mean, 39%) (Table 3). In contrast, the proportion of patient records reported by IPs as having CLABSI varied significantly across IPs, even within the same patient record sets. Overall, IPs reported a minimum of 14% to a maximum of 39% of patient records with CLABSI, for an overall mean of 28% and a coefficient of variation of 0.25.

Agreement on surveillance decisions for individual records within IP groups were calculated as separate κ statistics and pooled across groups to produce the overall κ of 0.42 (SE, 0.06) (Table 4). There was a trend for IPs to have better agreement with classifications made by algorithm than with each other (Table 4), with an overall average κ across 18 IPs of 0.55 (SE, 0.05). In addition to data provided in tables, IPs uniformly agreed with each other when reviewing identical patient records in 55% of records. Discordant classifications were noted in 5% of patient records where an IP identified a CLABSI but the algorithm did not, and in 16% of patient records where the algorithm identified a CLABSI and the IP did not.

**Table 4. Agreement Among Infection Preventionists and With a Laboratory-Based Definition Assigning Central Line–Associated Bloodstream Infection for Individual Patient Records**

| | | | Interrater Agreement for Individual Patient Records | |
|---|---|---|---|---|
| Group | IPs, n | Patient Records, No. | IP vs IP, κ (SE) | IP vs Laboratory-Based, κ (SE) |
| 1 | 4 | 29 | 0.50 (0.11) | 0.66 (0.09) |
| 2 | 4 | 29 | 0.46 (0.13) | 0.62 (0.10) |
| 3 | 5 | 28 | 0.30 (0.13) | 0.29 (0.13) |
| 4 | 5 | 28 | 0.43 (0.09) | 0.65 (0.09) |
| Overall[a] | 18 | 114 | 0.42 (0.06) | 0.55 (0.05) |

Abbreviations: IPs, infection preventionists; SE, standard error.

[a] Separate estimates of κ computed for each group of IPs and pooled across groups to produce overall estimates.

There were 4 patient records where the algorithm identified CLABSI but all IPs did not. IP discrepancies for these cases included: (1) enterococcus considered secondary (though blood and secondary isolates had different susceptibilities); (2) candida considered secondary to respiratory source (laboratory-based definition classified yeast in sputum a contaminant); (3) candida from blood considered a contaminant; and (4) a second BSI episode not addressed.

Patient records for IP review contained actual data, and some had inconsistencies or difficult-to-locate or missing information as found in real practice. The majority of IPs reported data quality problems in 14 of 114 patient records, with 12 due to difficulties in determining the duration, though not presence, of central venous catheterization.

### IP Uncertainty

We found differences among IPs on their self-reported certainty that a CLABSI was or was not present. The "least sure" IP was definitely certain in only 20% of patient records reviewed, as compared to the "most sure" who was definitely certain in 97% of records (median, 58%). However, even when certainty was not definite, responses still leaned toward a yes or no. "Completely unsure" was selected only 23 times in 512 reviews (4.5%) by 8 IPs (Figure 1). Definite yes or definite no certainty was most common in patient records where all IPs reviewing uniformly agreed (Figure 1). For 233 reviews associated with disagreement, the distribution of certainty was bimodal (Figure 1) with definite/probable yes or definite/probable no most commonly selected. Thus, although there was a nearly linear relationship for the average certainty score from definite no through definite yes, the full distribution of IP certainty levels revealed IP disagreement rather than uncertainty. In other words, there were 2 distinct camps in which some IPs were certain CLABSI was present, while others were certain it was not.

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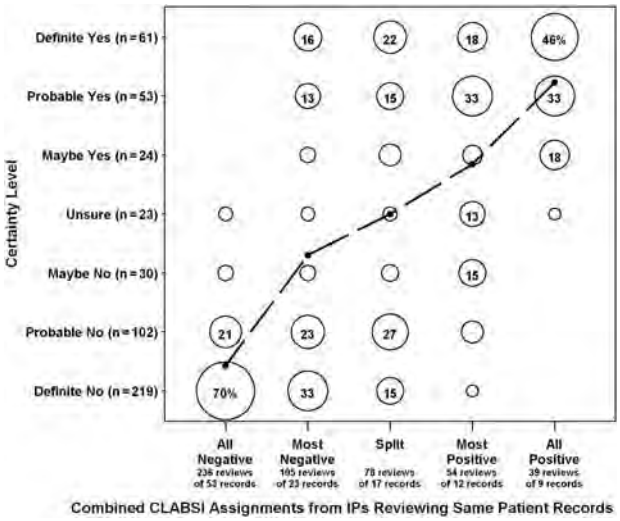


**Figure 1.** The distribution of infection preventionist (IP) certainty for central line–associated bloodstream infection (CLABSI) within categories of combined CLABSI assignments when 18 IPs evaluated the same 114 patient records in 512 reviews. The categories where IPs all agreed CLABSI was not present is "All Negative" and where all agreed CLABSI was present is "All Positive;" other categories had some IP disagreement. Numbers within bubbles represent percentages of IPs with that level of certainty for CLABSI within that combined CLABSI assignment category (columns sum to 100%). The mean IP certainty level for each combined CLABSI assignment category is the average of individual IP reported certainty levels ("Definite No" as 1 through "Definite Yes" as 7) represented by the dashed line.

## DISCUSSION

Surveillance is defined as the ongoing systematic collection, interpretation, and dissemination of data reflecting the status of a population [24, 25]. Various stakeholders use HAI surveillance for different reasons, and different approaches may be needed to address divergent goals [26]. When evaluating the impact of improvement processes within facilities, it is most important to accurately identify each infection. On the other hand, the objectives of public reporting to benchmark and accurately rank facilities call for criteria providing the most consistent outcomes, even at the expense of clinical accuracy [18]. Conventional IP surveillance applying NHSN definitions to identify HAIs has been the practice standard [4]. NHSN criteria, though standardized, require subjective judgment and are not explicit, such as in determining a primary BSI when "a recognized pathogen cultured from one or more blood cultures and the organism cultured from blood is not related to an infection at another site" [4]. Although a uniform and reliable system is essential for comparison across facilities, several recent reports documented variation in IP surveillance determinations. One state health department found that >50% misclassified NHSN-reported CLABSIs, the bulk of discordant assignments representing underreporting [7]. Another study found that more than half of CLABSIs were missed in Australian hospitals [27].

We present the results of a large, systematic study assessing reliability of IP surveillance using multiple reviewers examining identical patient records presented in a simplified real-life electronic health record format and then compared to a solely laboratory-based method. Neither explicit surveillance criteria nor standardized abstraction forms were provided in order to assess reproducibility of IP surveillance as normally practiced. We found substantial variation in IP surveillance for CLABSI, considered the most straightforward HAI, at both an ecologic (proportion of patient records reported with CLABSI) and an individual patient record level (interrater agreement). A novel approach, soliciting IP-perceived certainty for CLABSI, was used to explain differences in IP decisions: in the majority of patient records where IPs disagreed, IPs were certain. When we compared surveillance classifications using a laboratory-based definition to that assigned by IPs, although the simplified algorithm called more infections, individual IPs agreed more often with the laboratory-based definition than with each other. There are several potential explanations for differences in IP surveillance decisions. Discrepancies may have been due to oversights or differences in locating data, but an important contributor is the CLABSI surveillance criteria. These criteria require some subjective judgment and differences may arise with different mental models in approaching surveillance. Comments from IPs revealed variation in how criteria were applied and data were interpreted, and in the level of evidence needed to assign CLABSI to a patient record.

Clinicians implementing preventive measures expect reductions in infections and covet specific definitions that identify confirmed clinical infections [28, 29]. Despite an expectation that trained IPs conducting detailed reviews identify only unambiguous infections, there remains risk for variation. Lin et al [3] used a retrospective cohort of 20 intensive care units across multiple medical centers to examine the correlation between prospective IP-derived CLABSI rates and a retrospectively applied computer algorithm reference standard. Median IP rates (3.3 per 1000 line days; interquartile range, 2.0–4.5) and algorithm rates (9.0 per 1000 line days; interquartile range, 6.3–11.3) had weak correlation ($P = .34$) [3]. Regression modeling revealed significant heterogeneity between IP and algorithm rates among institutions, suggesting local variation in surveillance practices. Interestingly, the facility with the lowest IP rate had the highest rate by algorithm, highlighting how variation in surveillance can complicate interfacility comparisons [3]. Likewise, higher interrater agreement with original surveillance decisions by blinded IPs conducting evaluations for ventilator-associated pneumonia

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was found with a streamlined version using objective quantitative measures (κ = 0.79; confidence interval, .62–.97) than with conventional NHSN criteria (κ = 0.45; confidence interval, .26–.64) [30]. The pressure to "get to zero" raises concerns that partially subjective surveillance definitions applied inconsistently could be exploited or prone to subconscious cognitive bias to lower infection rates [31]. Variability may arise from the same cognitive biases described in clinical decision making, including the tendency to opt for decisions that lead to good outcomes (outcome bias), the benign condition during situations of ambiguity (frequency gambling), and affective sources of error (visceral bias) [32]. These biases can be removed through application of simplified laboratory-based definitions, albeit automated or manually.

Our study and those of others have shown that surveillance done across hospitals using laboratory-based definitions perform more uniformly and is a preferred signal to traditional surveillance when the goal is interinstitutional comparison [3, 18, 30]. Although simulation models suggest that laboratory-based definitions likely overcall CLABSI compared to clinical criteria, laboratory-based definitions provide more accurate rankings of institutions [18]. Evaluation for the future should address implications of reliability in surveillance methods when the outcome of interest is a rare occurrence, as is becoming the case for CLABSI [33, 34]. Consideration of a "blended" surveillance method, where IPs could report disagreements with algorithmic decisions, would provide the standardization of laboratory-based criteria yet improve the positive predictive value through expert confirmation. Such a system was used and supported by IPs across healthcare systems from 2008 to 2010 in the state of Utah (local experience).

Our study had several limitations. IP review was retrospective and we could not replicate some practices, including consultation with clinicians or unlimited access to patient information. Although reviewers were told there was no "right answer" and to work normally, they still may have altered their decision making. The population under study was comprised of mainly men within the VA Health Care System, and thus patient comorbidities and microbiologic and surveillance practices may not be generalizable to other healthcare organizations. The patient records used were from a time when national CLABSI rates were higher, and while this allowed us to maximize efficiency with essentially an enriched sample, the positive predictive value of the laboratory-based definitions may have been inflated. However, given a setting of lower CLABSI prevalence, the objective criteria we used could be modified to minimize the potential for false positives.

In summary, our study adds to previous literature evaluating HAI surveillance systems by allowing multiple IPs to review and report on the same records. We showed, as did others using single reviewers, that laboratory-based definitions had less heterogeneity for HAI detection between hospitals than did routine IP surveillance [3, 30]. Furthermore, we found that IP discordant surveillance classifications were due to disagreement, rather than from uncertainty or ambiguous cases. Our results support the use of laboratory-based definitions as better suited for public reporting of infection rates when the primary goal is to rank facilities [3, 18, 26]. There is a need for infection preventionists, healthcare epidemiologists, and policy makers to come to consensus on the value and limitations of more streamlined objective quantitative measures of identifying HAIs as compared with traditional manual methods for the purposes of reproducible public reporting and performance measurements.

## Notes

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