

# Impact of Misdiagnosis of *Clostridioides difficile* Infection (CDI) by Standard-of-care Specimen Collection and Testing on Estimates of Hospitalized CDI Incidence Among Adults in Louisville, Kentucky, 2019-2020

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## ABSTRACT

**Background:** A high population-based incidence of laboratory-confirmed cases of hospitalized *Clostridioides difficile* infection (CDI) is reported to public health surveillance in the United States based on standard-of-care (SOC) specimen testing. However, the impact of SOC misdiagnosis on the reported CDI incidence is uncertain.

**Methods:** Active surveillance from Oct 14, 2019, to Apr 11, 2020, identified inpatients aged ≥50 years with diarrhea (≥3 stools with Bristol score ≥5 in 24 hours) at all wards at 8 of the 9 adult hospitals in Louisville, Kentucky (population ≥50 years = 276 456). Study stool specimens from inpatients with diarrhea were screened by rapid GDH/toxin membrane enzyme immunoassay and the positive samples tested by PCR and cell cytotoxicity neutralization assay (CCNA). A study CDI case was a patient with a PCR positive/CCNA positive stool or PCR positive stool with pseudomembranous colitis (PMC). Incidence (non-recurrent CDI cases/100,000 persons aged >50 years per year) was adjusted for the hospitalization share of participating hospitals and, in a sensitivity analysis, for inpatients with diarrhea without a CDI test result. SOC stool specimen CDI testing occurred independent of the study.

**Results:** Among 1541 inpatients with diarrhea, study testing identified 109 non-recurrent CDI cases; 18 (16.5%) had PMC, 36 (33.0%) were admitted to intensive care, and 21 (19.3%) died during the 90-day follow-up. The study hospitalized CDI incidence was 154/100,000 per year (202/100,000 per year in the sensitivity analysis). The SOC hospitalized CDI incidence was 121/100,000 per year. Of the 109 study CDI cases, 44 (40%) were not SOC-diagnosed (SOC under-diagnosis). Of the 75 SOC CDI cases that had study testing, 12 (16%) were not study CDI cases (SOC over-diagnosis). SOC-undiagnosed and SOC-diagnosed CDI cases had similar demographics, medical histories, and clinical outcomes. Study testing identified 24% more CDI cases than SOC testing.

**Conclusions:** There was a high incidence of hospitalized CDI in persons aged >50 years (154-202/100,000 per year). Of the hospitalized CDI cases, one-third were admitted to ICU and one-fifth died. Public health surveillance estimates of the incidence of laboratory-confirmed hospitalized CDI cases, which are based on SOC testing, may be under-estimated by 24%.

## INTRODUCTION

Although there is a high population-based *C. difficile* infection (CDI) incidence in the United States, the extent of CDI overdiagnosis and underdiagnosis by standard-of-care (SOC) stool specimen collection and testing is not well described

## OBJECTIVES

Examine CDI underdiagnosis and overdiagnosis with SOC stool specimen collection and testing in a population-based study

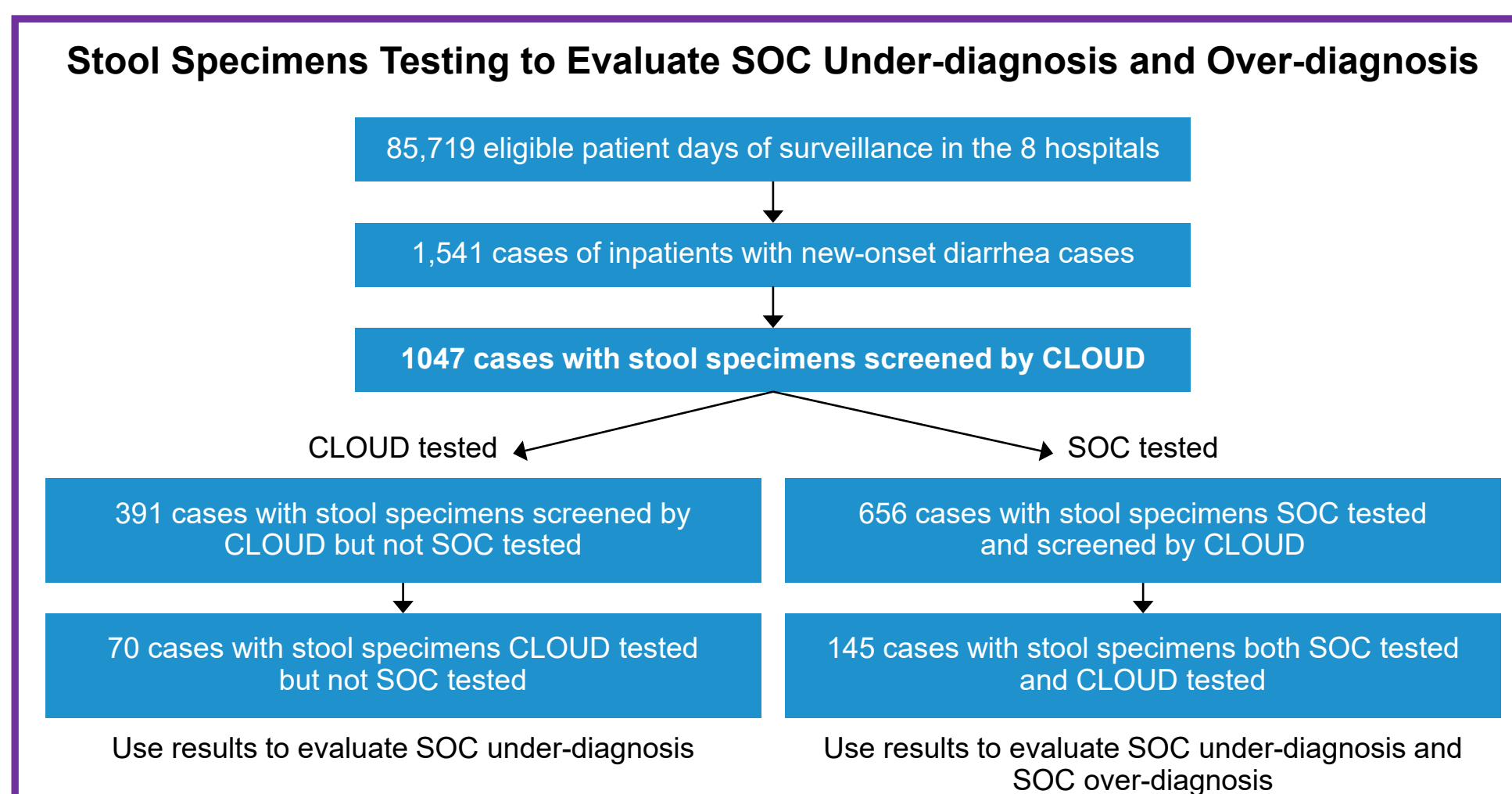
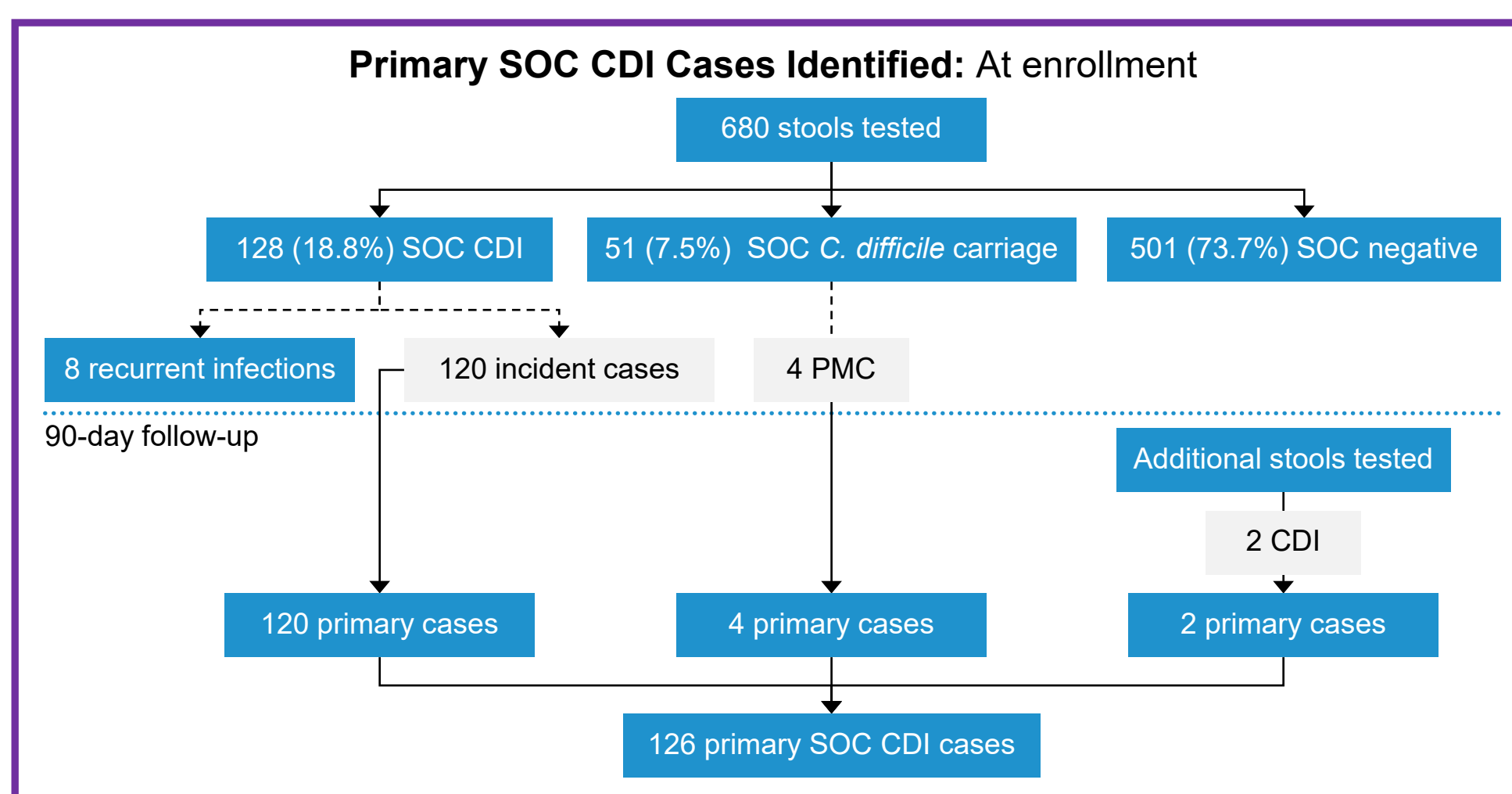
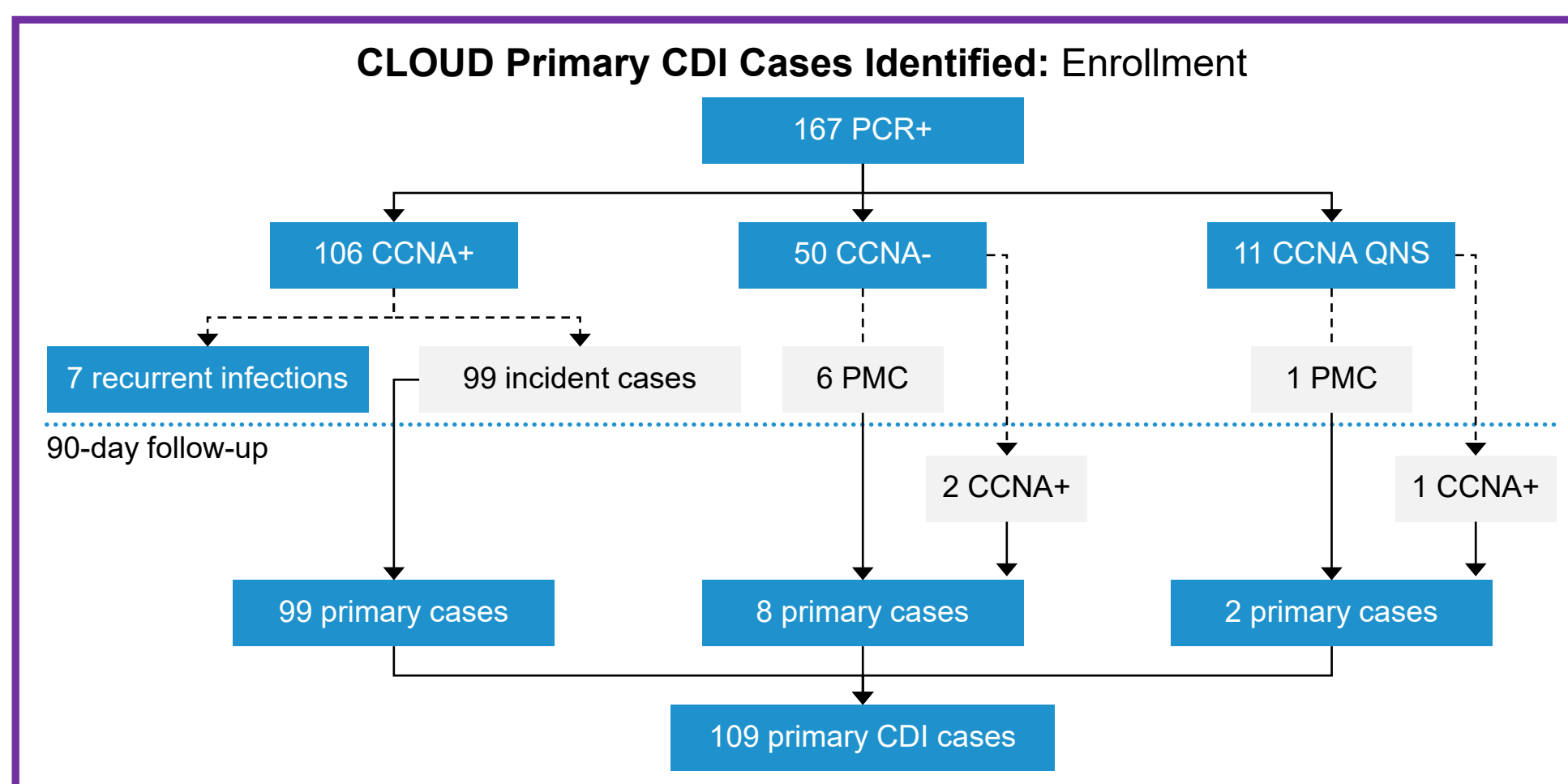
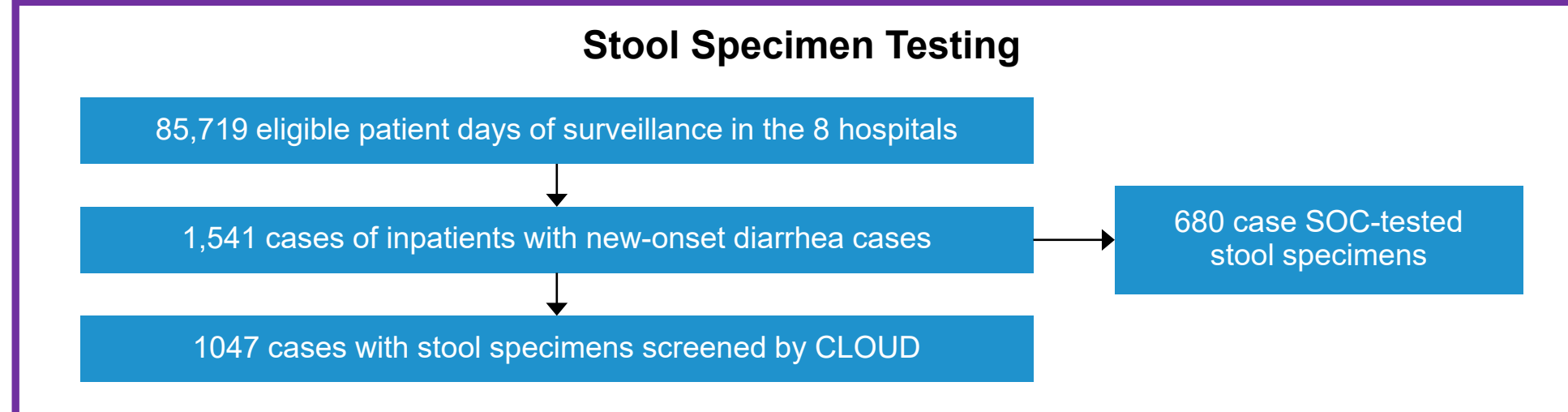
Estimate the population-based incidence of hospitalized CDI among Louisville adults ≥50 years (population aged ≥50 years: 276,456)

## METHODS

- Active surveillance conducted each day (Monday–Friday) for new-onset diarrhea (≥3 stool specimens with Bristol score ≥5 in 24 hours) on all wards of participating hospitals
  - Inclusion criteria: age ≥50 years and Louisville resident
  - Sought enrollment of eligible inpatients with new-onset diarrhea
  - Stool specimen collected from enrolled patients
- SOC specimens collected and SOC tested (independent of CLOUD) at SOC laboratories
- 8 of 9 adult hospitals conducted surveillance from October 14, 2019 - April 11, 2020 (when surveillance was paused due to COVID-19)
- Stool specimens tested at University of Louisville laboratory by Quik Chek (GDH/toxin)
  - GDH+ and GDH+/toxin+ specimens sent to Pearl River for PCR/CCNA testing
  - Patients with GDH+ or GDH+/toxin+ specimens followed for 90 days

### Estimating population-based hospitalized CDI incidence

- Population-based hospitalized CDI incidence** in persons ≥50 years of age in Louisville = number of hospitalized CDI cases per 100,000 persons ≥50 years of age per year in Louisville
- Steps for estimating population-based hospitalized CDI incidence:
  - Estimate hospitalization share of CLOUD-participating hospitals
  - Annualize the number of hospitalized CDI cases ascertained in surveillance during the pre-COVID period
  - Calculate the “base case” incidence of hospitalized CDI cases during the pre-COVID period, adjusting for hospitalization share and stool testing percentage
  - Calculate the “sensitivity analysis” incidence, adjusting for stool specimens not tested by PCR and CCNA



## RESULTS

### SOC CDI Under-diagnosis

- Failure to collect a stool specimen:**
  - There were 70 cases with stool specimens CLOUD tested but not SOC tested
  - 28 were CLOUD primary CDI cases**
  - The failure of SOC stool specimen collection practices to collect a stool specimen from an inpatient with diarrhea resulted in missing 28 CLOUD primary CDI cases
- Inaccurate laboratory testing:**
  - Of the 145 cases with stool specimens that were both SOC tested and CLOUD tested, 7 had recurrent CDI; therefore, there were 138 inpatients with diarrhea that had stool specimens that were both SOC tested and CLOUD tested

|                          | CLOUD primary CDI case | Not CLOUD primary CDI case | Total      |
|--------------------------|------------------------|----------------------------|------------|
| SOC primary CDI case     | 63                     | 12                         | 75         |
| SOC carriage             | 13                     | 17                         | 30         |
| Not SOC primary CDI case | 3                      | 30                         | 33         |
| <b>Total</b>             | <b>79</b>              | <b>59</b>                  | <b>138</b> |

SOC testing practices failed to diagnose 16 CLOUD primary CDI cases

### Summary: SOC CDI Under-diagnosis:

- SOC specimen collection and testing missed 44 CLOUD primary CDI cases
- 28 CLOUD primary CDI cases were missed by failure to collect a specimen
- 16 CLOUD primary CDI cases were missed by SOC testing practices
- CLOUD Louisville identified 109 primary CDI cases
- SOC specimen collection and testing missed 40.4% (44/109) CLOUD primary CDI cases
- 40.4% of CLOUD primary CDI cases were under-diagnosed by SOC

### SOC CDI Over-diagnosis

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### Summary: SOC CDI Over-diagnosis:

- Of the 75 SOC primary CDI cases, 16.0% (12/75) were incorrectly diagnosed
- 16.0% of SOC primary CDI cases were over-diagnosed**

### Summary of Results: SOC CDI Under-diagnosis and Over-diagnosis

- Although a high proportion (18.8%) of stool specimens selected by clinicians for SOC testing were laboratory-identified CDI cases
  - Because SOC collection was not comprehensive, SOC collection practices missed CDI cases
- SOC testing practices also missed CDI cases
- The SOC diagnosed CDI cases appear similar to SOC missed CDI cases

### Taken Together:

- SOC collection and testing under-diagnosed 40.4% of the CLOUD primary CDI cases
- SOC over-diagnosed 16.0% (compared with CLOUD primary CDI cases)

### Epidemiologic Category of 109 Primary CDI Cases (All Hospitalized)

- Healthcare-associated = 78.9% (86/109)
  - 31 were hospital-onset cases
  - 55 were community-onset healthcare-associated cases
- Community-associated = 21.1% (23/109)

### Number (%) of the 109 Primary CDI Cases with the Following Characteristics

|                                       |                                |                           |                                       |  |
|---------------------------------------|--------------------------------|---------------------------|---------------------------------------|--|
| Median (range) age = 72 (50-98) years | Female: 63 (57.8)              | <b>Symptoms</b>           | <b>Comorbidities</b>                  | <b>Outcomes</b>                          |
| • 35 (32.1) aged 50–64 years          | Admitted from home: 104 (95.4) | Fever: 13 (12.3)          | Cancer: 31 (28.4)                     | Pseudomembranous colitis: 18 (16.5)      |
| • 30 (27.5) aged 65–74 years          | Admitted from LTCF: 4 (3.7)    | Abdominal pain: 50 (47.6) | Congestive heart failure: 45 (41.3)   | Admitted to ICU: 36 (33.0)               |
| • 27 (24.8) aged 75–84 years          |                                | Dehydration: 7 (7.6)      | Pneumonia: 28 (25.7)                  | Died in 90 days after visit 1: 21 (19.3) |
| • 17 (15.6) aged ≥85 years            |                                |                           | Inflammatory bowel disease: 11 (10.1) |  |
|                                       |                                |                           | Diabetes: 45 (41.3)                   |  |
|                                       |                                |                           | Hemiplegia/quadruplegia: 3 (2.8)      |  |
|                                       |                                |                           | Parenteral/enteral feeding: 7 (6.5)   |  |

### Deaths Among Primary CDI Cases

- 21 of 109 primary CDI cases died: case fatality ratio 19.3%
- Median (range) age in years at death = 78 (56–95) years
- Median (range) days from diarrhea onset to death = 49 (4–106) days
- 3 deaths attributed to CDI
- 18 deaths attributed to other causes

### Case Fatality Ratio by Age Groups

- 55–64 years: 8.0% (2 of 25 CDI cases aged 55–64 years died)
- 65–74 years: 26.7% (8 of 30 CDI cases aged 65–74 years died)
- 75–84 years: 18.5% (5 of 27 CDI cases aged 75–84 years died)
- ≥85 years: 35.3% (6 of 17 CDI cases aged ≥85 years died)

### Number (%) of Comorbidities Among 21 Primary CDI Cases that Died

- Immunocompromised: 2 (9.5)
- COPD: 10 (47.6)
- Congestive heart failure: 13 (61.9)
- Stroke: 5 (23.8)
- Cardiovascular disease: 17 (81.0)
- Cancer: 7 (33.3)
- Diabetes: 11 (52.4)
- Chronic kidney disease: 9 (42.9)
- Inflammatory bowel disease: 4 (19.0)
- Dementia: 9 (42.9)
- Pneumonia: 11 (52.4)
- Urinary tract infection: 8 (38.1)

### Population-based Hospitalized CDI Incidence

- Estimate the hospitalization share of CLOUD-participating hospitals**
    - According to the 2017 Kentucky Health and Human Services (KHHS) hospital census, 84.4% (2596/3077) adult hospital beds in Louisville were in a CLOUD-participating hospital
    - According to 2020 University of Louisville of KHHS hospitalization data, 99.0% of hospitalizations of Louisville adults occur in Louisville hospitals
    - The proportion of Louisville adult hospitalizations that occur at CLOUD-participating hospitals is therefore estimated to be = 83.5% (84.4% x 99.0%)
  - Annualize number of hospitalized CDI cases ascertained in surveillance during pre-COVID period**
    - Surveillance was conducted in CLOUD Louisville for 45.2% of 1-year
    - 85,719 patient-days / projected 189,695 patient-days in year
    - There were 109 hospitalized primary CDI cases ascertained in surveillance during pre-COVID period
    - If annualized = **241 hospitalized CDI cases in one year**
  - Calculate “base case” incidence of hospitalized CDI cases during pre-COVID period, adjusting for hospitalization share and stool testing percentage**
    - Hospitalized CDI cases incidence adjusted by hospitalization share and stool testing percentage
    - = annualized # hospitalized CDI cases in ≥50 years / 276,456 Louisville residents ≥50 years per year x 1/(83.5%) x 1/(67.9%)
    - = **154 hospitalized CDI cases per 100,000 population ≥50 years per year**
  - Calculate “sensitivity analysis” incidence, adjusting for stool specimens not tested by PCR and CCNA**
    - 14 GDH+ specimens (3 toxin+ and 11 toxin-) not PCR tested (13 QNS to ship, 1 PCR QNS)
    - Since 97.2% (69/71) of GDH+/toxin+ specimens and 64.6% (93/144) of GDH+/toxin- specimens were PCR+, would expect 10 PCR+ specimens among the 14 GDH+ specimens not PCR tested
    - With the assumption that 50% of PCR+ specimens are CCNA+, would have been **5 additional CDI cases**
    - 11 GDH+ specimens that were PCR+ not CCNA tested due to QNS:
      - With assumption that 50% of PCR+ specimens are CCNA+, of 11 PCR+/CCNA QNS specimens, there would have been 6 additional cases.
      - During the 90-day follow-up period, 2 became primary CDI cases (1 PMC and 1 CCNA+), so there are **4 additional CDI cases**
    - 816 GDH- specimens not PCR or CCNA tested:
      - Since 6.2% (7/113) GDH- specimens in the post-COVID period were PCR+, would expect 51 PCR+ specimens among the 816 GDH- specimens not PCR tested
      - With the assumption that 50% of PCR+ specimens are CCNA+, would have been **25 additional CDI cases**
    - We conducted a sensitivity analysis of having 34 (5+4+25) additional CDI cases added to the detected 109 primary CDI cases = **143 primary CDI cases**
- Base case (based on 109 primary CDI cases) = **154 hospitalized CDI cases per 100,000 population ≥50 years per year**
  - Further age stratifications
    - = 226 hospitalized CDI cases per 100,000 population ≥65 years per year
    - = 334 hospitalized CDI cases per 100,000 population ≥75 years per year
  - Sensitivity analysis (based on 143 primary CDI cases) = **202 hospitalized CDI cases per 100,000 population ≥50 years per year**
  - Further age stratifications
    - = 296 hospitalized CDI cases per 100,000 population ≥65 years per year
    - = 438 hospitalized CDI cases per 100,000 population ≥75 years per year

## CONCLUSION

CLOUD Louisville identified a high population-based incidence of hospitalized CDI

- CDI was associated with important clinical consequences, including PMC, admission to ICU, and death

SOC specimen collection and testing failed to identify an important proportion of CDI cases

- SOC-missed CDI cases appear similar as SOC-identified CDI cases, indicating that there are clinical consequences of SOC-missed CDI cases

CLOUD Louisville builds on the EIP surveillance, demonstrating the important population-based CDI disease burden in the United States

- SOC CDI under-diagnosis is common, therefore CDI burden identified by EIP surveillance is even higher
- SOC CDI over-diagnosis is less common than SOC under-diagnosis