Measuring the Impact of *Clostridium difficile* Infection With the NAP1 Strain on Severity and Mortality

To the Editor—I read with interest the manuscript by See et al [1], titled "NAP1 strain type predicts outcomes from *Clostridium difficile* infection [CDI]," and seek here to quantify the potential impact on outcomes. Several studies have suggested there is a causal link between infection with the North American pulsed-field gel electrophoresis type 1 (NAP1) strain of *C. difficile* and severe CDI [2–4], although this association remains somewhat controversial [5–10]. Many studies have evaluated the strength of this association but few have explored the overall impact, assuming that a causal relationship exists. Measures of impact such as attributable risk help evaluate the utility of interventions targeting a risk factor.

In the study by See et al, the prevalence of NAP1 infection was 28.4% among 2057 cases of CDI and was associated with severe disease (ileus, pseudomembranes, or toxic megacolon <5 days from diagnosis or white blood cell count >15 000 cells/mm$^3$ <1 day from diagnosis) in 17.6% of cases (odds ratio [OR], 1.74; 95% confidence interval [CI], 1.36–2.22; $P < .001$), severe outcomes (intensive care unit admission within 7 days after diagnosis, colectomy for CDI, or death due to CDI within 30 days of diagnosis) in 5.1% of cases (OR, 1.66; 95% CI, 1.09–2.54; $P = .02$), and mortality (all-cause within 14 days of diagnosis) in 2.7% of cases (OR, 2.12; 95% CI, 1.22–3.68; $P = .008$). The authors adjusted for age, race, epidemiologic class, comorbid disease, and/or medications. As noted in an accompanying editorial commentary, this work makes a strong case that the NAP1 strain contributes to disease severity and adverse outcomes [11].

Incidence, relative risks, and attributable risks were calculated to quantify the impact of NAP1 infection on development of adverse outcomes. To incorporate confounding, the adjusted ORs and CIs presented in the study were used to approximate relative risk and calculate attributable percentages. All analyses were done

<table>
<thead>
<tr>
<th>Measure$^a$</th>
<th>Severe CDI$^b$</th>
<th>Severe Outcome$^c$</th>
<th>Mortality$^d$</th>
</tr>
</thead>
<tbody>
<tr>
<td>Overall incidence</td>
<td>176 (160–194)</td>
<td>51 (42–62)</td>
<td>27 (21–35)</td>
</tr>
<tr>
<td>Incidence in NAP1</td>
<td>258 (224–295)</td>
<td>82 (62–107)</td>
<td>50 (34–71)</td>
</tr>
<tr>
<td>Incidence in non-NAP1</td>
<td>144 (127–163)</td>
<td>39 (30–50)</td>
<td>18 (13–27)</td>
</tr>
<tr>
<td>Relative risk</td>
<td>1.79 (1.49–2.16)</td>
<td>2.12 (1.46–3.07)</td>
<td>2.70 (1.61–4.53)</td>
</tr>
<tr>
<td>Attributable risk</td>
<td>114 (74–154)</td>
<td>43 (19–68)</td>
<td>31 (12–50)</td>
</tr>
<tr>
<td>Attributable risk %</td>
<td>44.2% (32.8–53.7)</td>
<td>52.8% (31.6–67.5)</td>
<td>63% (38.1–77.9)</td>
</tr>
<tr>
<td>Adjusted attributable risk %</td>
<td>42.5% (26.5–55)</td>
<td>40% (8.3–60.6)</td>
<td>52.8% (18–72.8)</td>
</tr>
<tr>
<td>Population attributable risk</td>
<td>32 (21–44)</td>
<td>12 (6–19)</td>
<td>9 (4–14)</td>
</tr>
<tr>
<td>Population attributable risk %</td>
<td>18.4% (12–24.8)</td>
<td>24.1% (11.2–37.1)</td>
<td>32.6% (14.6–50.7)</td>
</tr>
<tr>
<td>Adjusted population attributable risk %</td>
<td>17.7% (11–22.9)</td>
<td>18.1% (3.8–27.7)</td>
<td>27.4% (9.3–37.7)</td>
</tr>
</tbody>
</table>

Abbreviation: CDI, *Clostridium difficile* infection.

$^a$ Given per 1000 cases of CDI or as a percentage with 95% confidence intervals.

$^b$ Ileus, pseudomembranes, or toxic megacolon <5 days from diagnosis or white blood cell count >15 000 cells/mm$^3$ <1 day from diagnosis.

$^c$ Intensive care admission, colectomy, or death due to CDI within 30 days of diagnosis.

$^d$ All-cause mortality within 14 days of diagnosis.
in R version 3.0.2 (R Foundation for Statistical Computing, Vienna, Austria) and OpenEpi version 3.01 (A. G. Dean et al, www.OpenEpi.com).

The results of this analysis are presented in Table 1. The incidence of all outcomes was higher with NAP1 strains than with non-NAP1 strains. The attributable risk percentages ranged from 44.2% to 63% (40%–52.8%, adjusted), suggesting that a significant fraction of severe disease and adverse outcomes result from NAP1. A striking feature of these results is that although low in absolute terms, up to 32.6% (27.4%, adjusted) of mortality in this population could be prevented by targeting infection with NAP1. Furthermore, an additional 114 cases of severe disease (43 with severe outcome) per 1000 cases of CDI result from NAP1 infection.

The analysis of attributable risk from NAP1 infection in the study from See et al suggests that prevention of NAP1 infection through antimicrobial stewardship practices with previously demonstrated effectiveness against this strain, such as fluoroquinolone usage restriction [12, 13], may be of benefit. Altered infection control practices or modifications in the therapeutic regimen early in the course of disease could also have such an impact. These strategies would rely on availability of strain typing, which adds to cost and is not widely performed by clinical microbiology laboratories. The analysis presented here may actually underestimate the impact of targeting NAP1, as the nonspecific effects of such measures would likely reduce overall CDI incidence.

Any putative causal association between NAP1 infection and severe or adverse outcomes is likely mediated by host and environmental factors in addition to microbiological ones, complicating analysis of the strength and direction of the association. However, if these findings are confirmed in future investigations, the attributable risk of adverse outcomes would justify focusing resources on prevention of NAP1 infection.

Notes

Acknowledgments. The author thanks See et al for providing their data for analysis.

Disclaimer. The funders had no role in study design, data collection and analysis, decision to publish, or preparation of the manuscript.

Financial support. This work was supported by the Claude D. Pepper Older Americans Independence Center (grant number AG-024824) and the Michigan Institute for Clinical and Health Research (grant number 2UL1TR000433).

Potential conflicts of interest. Author certifies no potential conflicts of interest.

The author has submitted the ICMJE Form for Disclosure of Potential Conflicts of Interest. Conflicts that the editors consider relevant to the content of the manuscript have been disclosed.

Krishna Rao
Division of Infectious Diseases, Department of Internal Medicine, University of Michigan School of Medicine and Veterans Affairs Ann Arbor Healthcare System, Ann Arbor, Michigan

References


Correspondence: Krishna Rao, MD, Department of Internal Medicine, Division of Infectious Diseases, 3120 Taubman Center, 1500 E Medical Center Dr, SPC 5378, Ann Arbor, MI 48109-5378 (krirao@med.umich.edu).

Clinical Infectious Diseases 2014;59(8):1193–4
Published by Oxford University Press on behalf of the Infectious Diseases Society of America 2014. This work is written by (a) US Government employee(s) and is in the public domain in the US. DOI: 10.1093/cid/ciu500