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The Challenges of Tracking *Clostridium difficile* to its Source in Hospitalized Patients

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Clostridium difficile is responsible for between four and five-hundred thousand infections in the United States each year and is the leading cause of healthcare-associated infections [1, 2]. A major risk factor for *Clostridium difficile* infection (CDI) is a current or recent stay in a hospital where rates of both symptomatic CDI and asymptomatic colonization are higher than in the community [3–6]. Infection control recommendations for hospitals focus on preventing transmission from symptomatic CDI patients; active surveillance testing to detect asymptomatically colonized patients is not currently recommended [7]. However, asymptomatically colonized patients, as well as patients with active CDI, may transmit to other patients to cause CDI, yet their relative contributions to overall transmission remains uncertain [8–11]. For example, using restriction enzyme analysis typing, Clabots et al. found that 84% (16/19) of hospital acquisitions were linked to asymptomatic carriers while, in another study that used variable number tandem repeats genotyping, 29% (16/56) of acquisitions were linked to carriers [9, 10]. Transmission occurs via *C. difficile* spores that are resistant to commonly used hand sanitizers and environmental disinfectants [3]. Therefore, evidence that asymptomatic carriers are responsible for a large amount of transmission within hospitals would prompt new interventions designed to reduce transmission from such patients. In this issue, Kong et al. report findings from the largest study to date investigating the relative roles of carriers and cases as sources of transmission to patients with CDI [12].

In this study, the investigators sequenced the core genomes of 554 *C. difficile* isolates that were originally obtained from asymptomatically colonized and symptomatic CDI patients identified during a prospective cohort study conducted during 2006–2007 [13]. An epidemic of the NAP1 strain was occurring at the time, prompting the isolate collection in 15 wards across 6 hospitals. Kong et al. used the genetic data to identify pairs of sequences from different patients within each ward that were highly similar. For these matched pairs, data on patients' admission and discharge dates were analyzed to identify which pairs of patients had been admitted to the same ward around the same time and therefore represented plausible transmission events.

Overall, among 201 CDI cases, 105 (52%) could be genetically linked to a prior sample using a previously validated similarity cutoff of 0–2 nucleotide differences; 81 (77%) of

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these also had a plausible ward link to at least one previous patient carrying the same strain. Notably, 91% (74/81) of putative transmission events involved the NAP1 strain. Of those with a likely source, 34/81 (42%) of the linked cases were associated exclusively with a previous CDI case and 19/81 (23%) were associated exclusively with an asymptomatic carrier. Perhaps the most striking finding from Kong et al. is that *C. difficile* acquisition among cases with a genetic and ward link, 28/81 (35%) had an unclear source of transmission, being linked with both infected and colonized patients [12]. What makes this interesting is that the authors used genome sequencing, currently considered the most discriminatory typing method, and also incorporated patient movement data to further assess whether transmission could plausibly have occurred between patients with a genetic link. As the authors note, *C. difficile* has a slow rate of nucleotide substitution, and therefore identifying patients with a close genetic link does not necessarily imply that there was direct transmission between them [12]. This is especially true for an outbreak caused by the NAP1 strain that had evolved and spread widely not long before the collection of these isolates [14, 15]. This means that each patient in a possible transmission pair could have acquired the organism from an unidentified 3rd source, and who transmitted to whom (if anyone) is further obscured when ≥3 patients are genetically linked.

Symptomatic cases are more contagious than asymptomatically colonized patients due to increased shedding and longer hospitalizations, [8, 16–19], but it is still difficult to interpret why there were more exclusive linkages to previous CDI cases than carriers. Overall, only 44% of patients admitted to the study wards were enrolled in the original cohort study while just 5% of total admissions were ineligible due to a length of stay <2 days. Thus, and as the authors note, although there was incomplete ascertainment of both symptomatic case and asymptomatic colonized patients, there was likely relative under-enrollment of colonized compared to case-patients [12, 13]. This is because case-patients were sampled for clinical diagnostic purposes (as well as at regular study intervals) and therefore had additional opportunity to be tested without need for enrollment and consent to undergo sampling. While not discussed by Kong et al. [12], 68% (128/188) of the CDI cases reported in the original cohort study had onset of their symptoms after admission to the hospital and therefore could have transmitted while they were still asymptomatic [13, 20]. Consequently, some of the 'exclusive' linkages to transmission from a hospital-onset CDI case could be reclassified as being linked to both an asymptomatically colonized- and symptomatic case-patient (who happen to be the same person).

Regardless of the exact cause, sample collection methods favoring enrollment of case-patients may have contributed to a low colonization-to-infection ratio in the cohort selected by Kong et al. [12]. These investigators sequenced isolates from 353 asymptomatic carriers and 201 CDI cases, reflecting an overall colonization-to-infection ratio of 1.8:1. This drops to a ratio of 1.3:1 when patients colonized with non-toxigenic strains are excluded as potential sources of transmission to CDI cases. This stands in contrast to Curry et al., who only sampled a portion of their asymptomatic population using specimens collected for detecting vancomycin-resistant enterococcus colonization, and found a toxigenic *C. difficile* colonization-to-infection ratio of at least 2.1:1 [10]. In a study of active surveillance for *C. difficile* and isolation of colonized patients, Longtin et al. screened only patients admitted through their emergency room for toxigenic *C. difficile* and found an admission colonization

rate of 4.8% and, when compared to all hospitalized CDI cases identified, obtained a colonization (on admission)-to-infection ratio of 6.5:1 [21]. One can see the potential impact of differential ascertainment of case vs. colonized-patients by Kong et al.'s sensitivity analysis restricted to two hospitals that had more complete CDI case ascertainment; with an overall colonization-to-infection ratio of 0.8:1 (patients colonized with non-toxigenic strains were not reported by hospital). Here, 65% (30/46) of linked cases were tied exclusively to a previous symptomatic case while only 11% (4/35) were attributed exclusively to a prior case in the 4 study hospitals where CDI case ascertainment was less complete (colonization-to-infection ratio of 3.2:1).

As noted by the authors, an additional cause of both the low colonization-to-infection ratio and the relatively small contribution of colonized patients to overall transmission may be the high frequency of the NAP1/027/ST1 strain in the cohort [12, 13]. Several studies have identified NAP1 as being more virulent than other *C. difficile* strains [22, 23]. If acquisition of NAP1 leads to symptomatic disease more often than with acquisition of other toxigenic strains, then similar studies conducted in settings where NAP1 is less predominant could find that case patients contribute less (and colonized patients more) to overall hospital transmission than found by Kong et al. [12]. Therefore, these results may not generalize to other settings that have a lower frequency of the NAP1 strain and/or a different ratio of colonized-to-infected patients.

The results of Kong et al. indicate that it is still unclear whether symptomatic case- or asymptomatic colonized-patients are most responsible for hospital transmission of *C. difficile*. However, current infection control practices that focus on cases are still justified, given both the increased shedding of symptomatic case-patients and their ease of identification. The results of Kong et al. do not provide strong evidence that use of sporicidal disinfectants in all patient rooms instead of just rooms of CDI patients to remove *C. difficile* spores would be considerably more effective; however, neither do their findings conflict with the adoption of such practices where deemed appropriate by local infection control practitioners. It also remains unclear whether targeting interventions at asymptomatically colonized-patients would be broadly effective (e.g., active surveillance and targeted use of enhanced cleaning, antimicrobial stewardship, diagnostic stewardship, contact precautions, isolation, or other control measures).

The use of genetic and patient movement data to identify a subset of patients enriched for true transmission events is a promising approach and one that should be used more widely to study healthcare infections. Several modifications could make the results of future studies even more useful, categorized as involving either additional data collection or additional data analyses. First, measures to improve study participation rates could improve the validity of results and better trace cases to their source. Second, sampling healthcare workers' hands and the environment could permit better estimates of the fraction of transmissions that could be prevented by improvements in hand hygiene and enhanced environmental cleaning. Third, use of survival analysis techniques could help in estimating the contribution of hospital-onset CDI cases to transmission while they were still asymptomatic by treating symptom status as a time-varying variable. Fourth, including acquisition events that did not progress to being a (known) symptomatic case would better capture the total contribution of

different sources to onward transmission and allow for better estimation of the indirect effects of reducing transmission on the number of new symptomatic cases. Fifth, it could be determined whether the large category of CDI cases linked to both case- and colonized-patients could be partitioned using attributable fraction methods. Sixth, conducting simulations to determine the suitability of particular data collection approaches and analyses seems like a promising avenue for improving this type of study and could be more widely used [14, 24]. Seventh, characteristics of CDI case-patients associated with a higher probability of transmitting were recently identified and similar studies could be repeated for both carriers and cases [25].

We commend Kong et al. for their study due to its size, quality, and the combination of genomic information with patient movement data to identify possible transmission sources. Additional similar epidemiologic studies will be valuable for informing infection control decisions by providing insights not available from traditional risk factor studies. Finally, determining best practices for relevant data collection and analyses could facilitate wider use of studies like that presented by Kong et al.

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