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Determining the Attributable Costs of *Clostridium difficile* Infections When Exposure Time Is Lacking: Be Wary of "Conditioning on the Future"

To the Editor—We would like to comment on a recent paper by Mehrotra et al,[1] which presents an investigation of the attributable costs of *Clostridium difficile* infection (CDI) in pediatric patients. While there is an increasing body of literature on the costs of CDI, this study focused on the much less investigated area of pediatric inpatients.[2] While more reliable estimates in this field are needed, we would like to stress the importance of considering the methodological particularities of hospital-acquired infection and the scope and limitations of routine data for such analyses. We briefly outline the distinction of infections types by acquisition because this has important implications for the appropriate calculation of the attributable costs.

From the hospital perspective, the economic burden of *C. difficile* infections can be divided into 3 components: (1) hospital-acquired infections, (2) community-acquired infections that were the main reason for hospitalization, and (3) community-acquired infections that were not the main reason for hospitalization.

(1) Hospital-acquired *C. difficile* infections are those that occur 48 hours or more after admission, and therefore, *C. difficile* was not the main reason for hospitalization (ie, the main diagnosis group is not 008.45). For estimating the additional costs, these patients must be compared to appropriate controls. When selecting controls, the time-dependent nature of hospital-acquired infections should be taken into account (eg, via time-to-exposure matching).[3] In addition, clustering costs within main diagnosis groups should be accounted for (eg, via comparisons within the same main diagnosis only).[4] Because main diagnoses are the retrospectively coded principal reason for hospitalization, this ensures baseline comparability and prevents matching patients that incur different costs irrespective of the *C. difficile* infection. Finally, only comorbidities that cannot plausibly occur as a consequence of an infection should be used for risk adjustment.[4,5] This is usually an issue when using routine data, which often lack a time stamp for secondary diagnoses, so that it is possible to control for an outcome rather than a risk factor, thereby artificially reducing the effect. The authors acknowledge the time dependency of hospital-acquired infection but are faced with the unavailability of exposure time. The proposed matching (or adjusting) for total length of stay, however, may not be a second-best solution because it is subject to "conditioning on the future" by controlling for an outcome. This condition violates major epidemiological principles for analysis of such data.[6] Because *C. difficile* infections chiefly influence length of stay, which is a major driver of costs, the estimates likely substantially underestimate the true effect.[7] In addition, these authors failed to consider cost clustering within main diagnosis group, and they only adjusted for a limited set of main diagnosis and comorbidities. Thus, baseline costs between cases and controls are not necessarily comparable.
(2) For calculating the burden of *C. difficile* infections that were the main reason for hospitalization (ie, the main diagnosis group is 008.45), no control group, no time-to-exposure matching, no cost clustering and/or risk adjustment are necessary. The (additional) cost of *C. difficile* infections within this patient group is just the total cost of hospitalization because, per definition, the patient would not have been admitted to the hospital without the infection.
(3) The last group consists of patients, with a *C. difficile* infection that was detected <48 hours after admission but was not the main reason for hospitalization (ie, the main diagnosis group is not 008.45). These patients should be compared to controls within the same main diagnoses and baseline risk adjustment should be used as discussed above. Time-to-exposure matching is not necessary.

The lack of the timing of infection not only leads to time-dependent bias, it also makes it impossible to distinguish between these 3 infection types. This causes 2 issues in the study. First, the hospital-acquired cases in the sample were subject to the time-dependent bias and their effect was therefore overestimated. Controlling for length of stay was not sufficient to obtain appropriate estimates. In addition, being unable to distinguish between the 3 types of infections and analyzing all *C. difficile* cases together can lead to blurred estimates because the estimates partly present the (overestimated) incremental cost for hospital-acquired *C. difficile*.

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Another part of the estimates consisted of the difference between the costs of a patient being admitted to the hospital for *C. difficile* and the costs of a patient with a different disease but a similar comorbidity set.

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Got GAS? Ease the Bloat with Real-Time Whole-Genome Sequencing

To the Editor—Annually, more than 10,000 patients in the United States acquire an infection caused by invasive group A *Streptococcus* (GAS). The fatality rate of this illness is 11.7%, and many infections are transmitted person to person.[1,2] Outbreak investigations of postsurgical group A *Streptococcus* (GAS) infections can substantially disrupt surgical throughput if staff require furloughing, and they can be extremely labor intensive when surgeons practice at multiple facilities.[3] One benefit that has received little attention is the labor-saving potential that whole-genome sequencing (WGS) offers infection preventionists (IPs) when the turnaround time is sufficiently rapid to inform investigations and mitigation efforts.[4] Here, we highlight an outbreak involving 22 surgical staff, several of whom practice at multiple facilities that often care for the same patients within a regional care network.

On day 0, patient A underwent a procedure at community hospital X, performed by surgeon I who also practices at referral hospital Y (Table 1). On day 5, patient A developed an invasive GAS surgical wound infection while at hospital X. On day 7, patient B underwent a procedure performed by surgeon II at hospital X. On day 8, patient B developed a complication requiring escalation of care to hospital Y for follow-up surgery, again performed by surgeon II. On day 13, GAS was isolated from the surgical wound of patient B while at hospital Y. The 2 GAS isolates were sent for WGS, using methods described previously.[4,5] Simultaneously, IP staff initiated a retrospective review of all laboratory results beginning 6 months prior to the first surgery. Involved surgical staff at all facilities were contacted to have their throats and groins swabbed. Mitigation planning was begun in case staff furloughing would be required pending decolonization.

The core genome sequences of the 2 isolates differed by ~40,000 nucleotide changes, indicating that they were genetically unrelated.[5]

The WGS results were available within a week, before all staff had been swabbed and before any culture results of those that had been swabbed were available. On other occasions, results have been available in <50 hours.[4] For this event, WGS permitted earlier termination of the investigation and faster resumption to full surgical capacity, saving time, labor, and money (Table 1). The costs in Table 1 were calculated based on material and labor costs in this region[6] for screening all involved operating room staff (n = 22). If WGS had determined that the isolates were related, the cost would have been $80.00 more for the WGS approach compared to the conventional approach (not using WGS). When WGS revealed that the isolates were unrelated, the cost savings were substantial because surgical throughput was not slowed or disrupted, and IPs were able to devote their time and efforts