immunity after DENV infection does not cross-protect from SARS-CoV-2 infection and COVID-19 in Amazonian Brazil. The same vulnerable individuals appear to be at increased risk of both DENV infection and clinically manifest COVID-19, with dire public health consequences. We conclude that COVID-19 illuminated local inequalities, as does dengue. Overlapping epidemics that disproportionally affect the most vulnerable may further increase the gap between the haves and the have nots if special policies are not effectively launched. We are now addressing the effect of exposure to both viruses between November 2020 and April 2021, corresponding to the annual dengue season and the second COVID-19 wave in our study site, this time dominated by the variant of concern gamma (previously known as P.1).

Note

Potential conflicts of interest. M. U. F. reports funds for field work, materials, page charges for the original research mentioned in this letter from FAPESP, during the conduct of the study. V. C. N. reports a scholarship that supported the original research mentioned in this letter from FAPESP, during the conduct of the study. M. C. C. reports no potential conflicts. All authors have 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.

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Why 2 Studies That Used the Same Probiotic May Have Come Up With Different Outcomes

To the Editor—Two recent studies tested the same 3-strain Lactobacillaceae probiotic mixture for the prevention of *Clostridium difficile* infection (CDI), yet reported conflicting results [1, 2]. In studies that test probiotics for CDI prevention, different efficacies are often reported, but typically it is due to not accounting for the strain-specific efficacy of probiotics [3]. In this case, 2 quasiexperimental studies (QES) tested the same type of probiotic using an electronic decision support tool that triggered a flag for probiotic use for eligible inpatients receiving antibiotics and then compared CDI rates during the intervention to a control time period prior to the intervention. A review of 28 QES found that limitations included low implementation of the probiotic and not accounting for changes in infection control measures or antibiotic use during the 2 time periods [4]. With these limitations in mind, we examined these 2 studies to attempt to determine why the same probiotic was effective in the Maziade et al study [1] but not in the Heil et al study [2].

Both QES designs used the same probiotic, the same dose (10^{11}/day), and the same duration (during antibiotics use plus 5 days afterward), and the electronic orders were triggered within 12–24 hours of the first antibiotic dose. Both studies compared hospital-onset CDI level data and patient-level data and also adjusted risk estimates for CDI risk factors.

Differences in the 2 studies (Table 1) show different trends in CDI rates during the control period, increasing in one study [1] and decreasing in the other [2]. During the intervention period, CDI rates significantly decreased in one study [1] but increased in the other study [2]. Similar results were seen in the patient-level data, and adjustment for CDI risk factors resulted in nonsignificant differences the in Heil et al study [2] but significant efficacy remained in the Maziade et al study [1].

Other factors that may influence CDI rates during the 2 study time periods were also compared, but the rates of antibiotic use, types of antibiotic used, age of inpatients, changes in infection control practices, and similar factors did not explain why the CDI increased in one study and decreased in the other. Part of the intervention period for the most recent study [2] did occur during the coronavirus disease 2019 pandemic, when increased antibiotic use was being observed [5]. However, in 3 of the 4 hospitals in the Heil et al study, the rates of CDI increased in January 2020, a few months before the pandemic.

The most significant difference between these 2 studies was the degree of successful implementation of the probiotic intervention (Table 1). The electronic tool was triggered for 100% of eligible inpatients in the Maziade et al study [1] but was triggered for only 35% in the Heil et al study [2]. Additionally, while 75% of eligible patients actually received the probiotic in one study [1], only 17% received the probiotic in the other [2]. For a probiotic intervention to have a significant impact on hospital-wide CDI rates, this shows the importance of the degree of penetration that an intervention needs to achieve. This might explain the markedly different results.

Table 1. Comparison of Study Design Factors and Results of 2 Quasiexperimental Studies That Implemented a 3-Strain Probiotic for the Prevention of *Clostridiodies difficile* Infections

Factor/Outcome	Heil et al	Maziade et al
CDI rate during		
Control period	Decreased	Increased
Probiotic intervention period	Increased	Decreased
Hospital-wide CDI rate (per patient-days)		
Control period	1/10 000[a]	8.6/10 000
Probiotic intervention period	2.5/10 000[a]	5.2/10 000[b]
Patient-level CDI rate		
Control period	132/17 536 (0.75%)[c]	84/5666 (1.5%)[d]
Probiotic intervention period	153/15 023 (1.1%)[c,b]	73/8266 (0.9%)[d,b]
Adjusted CDI risk estimate (95% confidence interval)	1.46 (0.87–2.45)	0.42 (0.28–0.63)[b]
Intervention implementation		
Electronic order triggered[c]	5203/15 023 (35%)	6079/6079 (100%)
Received probiotic[c]	2489/15 023 (17%)	4543/6079 (75%)

The 3-strain probiotic was (*Lactobacillus acidophilus* CL1285, *Lacticaseibacillus* [*Lactobacillus*] *casei* LBC80R, and *Lacticaseibacillus* [*Lactobacillus*] *rhamnosus* CLR2.

Abbreviation: CDI, *Clostridium difficile* infection.

[a]Estimated from Figure data in Heil et al., no raw hospital-level data reported.

[b]$P < .05$ compared with control period.

[c]Among eligible inpatients.

[d] Among number of patient visits.

Note

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Reply to McFarland et al

To the Editor—We appreciate the comments from McFarland and colleagues [1] regarding the differences in findings between our respective studies regarding the use of probiotics for the primary prevention of *Clostridioides difficile* infection (CDI) [2, 3]. The primary reason cited for the difference in results was the difference in penetration of the probiotic intervention. For safety concerns, by design, the electronic alert in our study fired for a narrower group among patients potentially eligible based on age and antibiotic receipt, owing to other exclusion criteria (eg, patients not taking medications by mouth or located on oncology units). The electronic alert in our study fired as intended among this smaller group of eligible patients and resulted in an order for probiotics in 46% of them.

The lowest adherence in our study was 34%, at the academic medical center, where more patients may have met safety exclusion criteria for probiotic use than accounted for by the electronic alert. Two of our hospitals had very high adherence to the intervention (88% and 69%), more like the 70% adherence in the study [2]. CDI rates at both of these hospitals did not decrease between the preintervention and postintervention periods, as shown in Supplementary Table 3 [3] of our study (0.13% vs 0.16% [$P = .85$] and 0.87% vs 1.01% [$P = .61$], respectively). Finally, our propensity score–matched analysis, comparing all patients who received probiotics with those who did not, also did not find a benefit of probiotic use.