of some other unknown cofactor that is not essential for GBS is required. A third possibility is that fear of the adverse consequences of ZIKV infection led to fewer conceptions or a greater number of pregnancy terminations in 2016. Routinely collected data are not yet complete enough to determine whether birth rates fell or abortion rates increased in 2016 (Section 6 in the Supplementary Appendix). However, since any changes in the number of live births would be small, this hypothesis cannot be the principal reason why few cases of microcephaly were reported in the northeast region in 2016.

Among these hypotheses, the first seems to be the most plausible — that is, both ZIKV and chikungunya viruses are important causes of GBS, but among the arboviruses circulating in Brazil, only ZIKV causes microcephaly and other neurologic disorders after infection during pregnancy. However, the three possibilities are not mutually exclusive, and none can be ruled out with the present data. Further investigations are needed — aided by more sensitive and specific diagnostic tools and the careful interpretation of surveillance data — to clarify the causal links between arbovirus infections, GBS, and microcephaly in Brazil.

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Bezlotoxumab and Recurrent *Clostridium difficile* Infection

TO THE EDITOR: Wilcox et al. (Jan. 26 issue)[1] found that the risk of recurrent *Clostridium difficile* infection was nearly 40% lower among patients treated with bezlotoxumab than among those who received standard care. In the accompanying editorial, Bartlett speculates about whether bezlotoxumab, although clearly efficacious, will be cost-effective.[2] We think this discussion would be incomplete without citing the efficacy and relatively low cost of probiotics in the prevention of *C. difficile* infection. In multiple systematic reviews that included meta-analyses of randomized, controlled trials in which the rates of both initial and recurrent infections were measured, probiotics were shown to have safety and impressive efficacy, with a relative risk reduction of more than 50% in the prevention of *C. difficile* infection in high-risk immunocompetent populations.[3,4] Probiotics have also been shown to be cost-effective.[5] Given their substantial efficacy and greatly reduced cost, we urge providers to review the literature and consider the use of probiotics for immunocompetent patients who are receiving antibiotics and are at high risk for *C. difficile* infection.

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TO THE EDITOR: In the analysis of the effects of a given agent on the recurrence of *C. difficile* infection, patients need to have been cured of their initial infection before acquiring a recurrent infection. Furthermore, patients might die during follow-up; thus, death is a classic competing event for cure and recurrent *C. difficile* infection.[1-3] Wilcox et al. censored data from patients without a clinical cure at the date of infusion of the medication. Conditioning on the future violates one principle of time-to-event analyses[4]; censoring competing events leads to bias (an overestimation of the risk of infection recurrence).

We emphasize that "get cured, stay alive, and remain free of recurrent infection over time" is a more relevant end point for patients with *C. difficile* infection. Using a multistate model, we have schematically displayed the competing risk bias and reconstructed our proposed end point (Fig. 1). Our analysis indicated the possibility that although both active-treatment groups had a lower risk of recurrent infection, the probability of being cured, alive, and free of recurrent infection is lower in the actoxumab–bezlotoxumab group than in the placebo group for the first 5 weeks. Such time-dependent effects are hidden in the original analysis but are highly relevant from the patients' perspective and should therefore be made transparent.

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THE AUTHORS REPLY: Maw et al. quote two systematic reviews and meta-analyses, both focused on the prevention of primary rather than recurrent *C. difficile* infection; recurrent *C. difficile* infection is the primary outcome that is reduced by bezlotoxumab. Others have concluded that there is little evidence to support the use of probiotics to prevent recurrent *C. difficile* infection,[1,2] and a recent systematic review concluded that they are not more effective than placebo for the prevention of primary infection in elderly hospitalized patients.[3] Meta-analyses of the efficacy of probiotics aggregate data on very different preparations and varying dosages. It is notable that by far the largest randomized, controlled trial of probiotics to prevent *C. difficile* infection showed no benefit.[4]

Maw et al. also referred to cost-effectiveness. In a post-hoc analysis of the data from our trials, treatment with bezlotoxumab was found to reduce 30-day *C. difficile* infection–associated hospital readmissions in the overall population and among patients who were at high risk for infection recurrence.[5] In the subgroup of participants who were hospitalized at the time of randomization (68% of the modified intention-to-treat population), 4.0% of bezlotoxumab recipients had a *C. difficile* infection–associated readmission, as compared with 9.6% of placebo recipients (difference, –5.7 percentage points; 95% confidence interval, –8.8 to –2.7).

In their analysis, Sommer et al. demonstrate that bezlotoxumab treatment results in a rate of recurrent *C. difficile* infection that is substantially lower than that associated with placebo. They propose an end point of "get cured, stay alive, and remain free of recurrent infection over time" to address bias that may have been introduced by failure to achieve initial clinical cure and by

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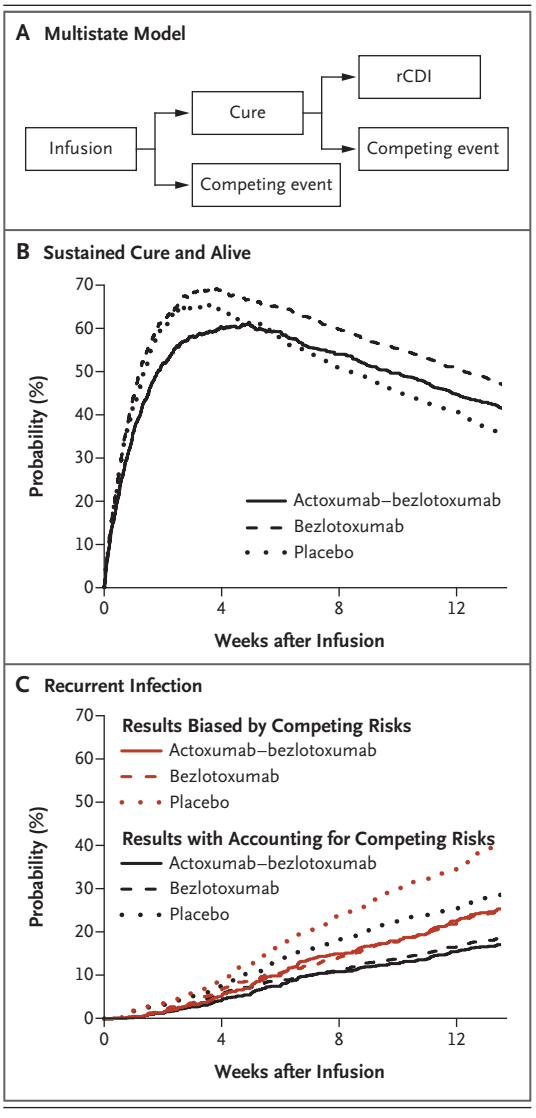

Figure 1. Patient-Relevant End Points and Analysis of Trials for the Prevention of Recurrent *Clostridium difficile* Infection.

Panel A shows a multistate model suitable for the present scenario, with an initial infusion state, a cure state, a state of recurrent *Clostridium difficile* infection (rCDI), and competing event states (including, e.g., treatment failure and death). The direction of arrows indicates the potential transitions between the states determined by transition hazards. For a simulated data set, the following rates per patient-day, which are assumed to be time-constant for illustration purposes, were reconstructed with values taken from the article by Wilcox et al.: a cure rate of 0.082 for actoxumab–bezlotoxumab, 0.089 for bezlotoxumab, and 0.089 for placebo; a competing event rate before cure of 0.029 for actoxumab–bezlotoxumab, 0.022 for bezlotoxumab, and 0.021 for placebo; a rate of recurrent infection of 0.003 for actoxumab–bezlotoxumab, 0.003 for bezlotoxumab, and 0.005 for placebo; and a competing event rate after cure of 0.003 for actoxumab–bezlotoxumab, 0.003 for bezlotoxumab, and 0.003 for placebo. To show the competing risk bias, we censored data from patients who did not have clinical cure at day 1. Panel B shows the probability of having a sustained cure (i.e., cure and no recurrent infection, a secondary end point used by Wilcox et al. at week 12) and being alive as the proposed time-dependent patient-relevant quantity. The curves for actoxumab–bezlotoxumab and placebo cross because placebo is associated with a higher cure rate but also with a higher rate of recurrent infection. Panel C shows the probability of recurrent infection based on the modified intention-to-treat population (primary end point used by Wilcox et al.), which is easily and adequately estimated on the basis of this model. The probability after 12 weeks coincides approximately with the raw proportions: 119 of 773 (15%) for actoxumab–bezlotoxumab, 129 of 781 (17%) for bezlotoxumab, and 206 of 773 (27%) for placebo. When data from patients are censored at day 1, the risks are overestimated.

deaths that occurred during follow-up. We also considered the effect of these factors on the primary end point (see the Sensitivity Analyses section of the Supplementary Appendix, available with the full text of our article at NEJM.org). Because the rates of competing events were similar for bezlotoxumab and placebo recipients, it is not surprising that the bezlotoxumab effect size was consistent between the multistate model analysis (Fig. 1B and 1C of their letter) and the analysis in our article. Despite the limitations of the multistate model (which assumes a constant failure rate during follow-up after initial clinical cure), the results align with our predefined primary end point. Moreover, the rates of recurrent infection from the Kaplan–Meier analysis are similar, given the censoring, to those among participants with initial clinical cure — another clinically important end point.

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Since publication of their article, the authors report no further potential conflict of interest.

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THE EDITORIALIST REPLIES: Probiotics were not included in my editorial because evidence supporting their use to prevent *C. difficile* infection seemed inadequate. Admittedly, there are some controlled trials that support the use of probiotics,[1] but others show no significant benefit.[2] A review of guidelines for the management of *C. difficile* infection from five international societies shows that either they have not endorsed the use of probiotics for this purpose or they have failed to address probiotics in their recommendations.[3] To my knowledge, none of these agents have been approved by the Food and Drug Administration (FDA) for this indication. Thus, there appears to be a lack of convincing and consistent support from trials, *C. difficile* infection guidelines from five learned societies, or FDA reviews. Note that this does not mean that they do not work — only that this recommendation needs better and more consistent evidence for support. Also worrisome is the fact that "probiotics" is a broad term that includes many different products that may differ substantially in their results, making product specificity a likely need.

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Since publication of his article, the author reports no further potential conflict of interest.

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"Zombie" Outbreak Caused by Synthetic Cannabinoid

TO THE EDITOR: Adams et al. (Jan. 19 issue)[1] describe an outbreak of synthetic cannabinoid AMB-FUBINACA intoxication that was identified with the use of a new approach that involved predicting and synthesizing analytical standards of possible cannabinoid analogues before their emergence in markets.[1,2] This method is effective for detecting new synthetic drugs that have never been reported. However, since there are numerous potential derivatives for every illicit drug, characterizing them fully in clinical laboratories is impractical.

All the synthetic cannabinoids that the authors mention contain structural motifs of their raw materials, indole or indazole. Because there are no indole or indazole rings in common psychoactive substances such as amphetamines, cocaine, and tetrahydrocannabinol, the presence of fragment ions of indole and indazole derivatives (e.g., $C_9H_6NO^+$ and $C_8H_5N_2O^+$) might make mass spectrometry a suitable qualitative screening test for AMB-FUBINACA and other new synthetic cannabinoids.[3-5] After qualitative screening of specific motif fragment ions in clinical laboratories, the results could be confirmed in reference laboratories by the approach presented by Adams et al.

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