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.
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. 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; 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.

Harriet Sommer, Dipl.-Math.
University Medical Center Freiburg
Freiburg, Germany
sommersm@imb.uni-freiburg.de

Jean-François Timsit, M.D., Ph.D.
Paris Diderot University
Paris, France

Martin Wolkewitz, Ph.D.
University Medical Center Freiburg
Freiburg, Germany

for the COMBACTE-NET Consortium

No potential conflict of interest relevant to this letter was reported.


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, and a recent systematic review concluded that they are not more effective than placebo for the prevention of primary infection in elderly hospitalized patients. 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.

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. 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
Correspondence

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.

Mark Wilcox, M.D.
Leeds Teaching Hospitals
Leeds, United Kingdom
mark.wilcox@nhs.net

Mary-Beth Dorr, Ph.D.
Alison Pedley, Ph.D.
Merck
Kenilworth, NJ

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


DOI: 10.1056/NEJMc1702531

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, but others show no significant benefit. 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. 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.

John G. Bartlett, M.D.
Johns Hopkins University School of Medicine
Baltimore, MD

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


DOI: 10.1056/NEJMc1702531

“Zombie” Outbreak Caused by Synthetic Cannabinoid

TO THE EDITOR: Adams et al. (Jan. 19 issue) 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. 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., C₉H₆NO⁺ and C₈H₅N₂O⁺) might make mass spectrometry a suitable qualitative screening test for AMB-FUBINACA and other new synthetic cannabinoids. 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.

Feng-Shuo Yang, M.D.
Chao-Ju Chen, M.D.
Kaohsiung Medical University Hospital
Kaohsiung, Taiwan

Yi-Ching Lin, M.D.
Kaohsiung Medical University
Kaohsiung, Taiwan

No potential conflict of interest relevant to this letter was reported.