Risk Factors for *Clostridium difficile* Acquisition in Infants: Importance of Study Design

To the Editor—There is a paucity of evidence on the etiology of community-associated *Clostridium difficile* infection
(CDI). The study of Rousseau et al supports the theory that infants may act as a reservoir for toxigenic strains [1], in agreement with, but not acknowledged by the authors, a previous case-control study demonstrating that kissing contact with infants was significantly associated with community CDI [2]. However, the small sample size (85 infants in the point-prevalence cohort; 10 followed longitudinally) raises 2 major concerns. First, it may lead to chance effects (random error); second, it prevented any multivariate analysis, potentially leading to systematic error from confounding bias in the crude associations reported.

Rousseau et al reported that all 10 infants followed longitudinally from birth were colonized by toxigenic or nontoxigenic *C. difficile* strains by 12 months of age; they only enrolled infants in a point-prevalence cohort who attended 1 of 2 day-care facilities [1]. Preliminary data from a much larger point-prevalence cohort (276 UK infants), of whom 67 were followed longitudinally, provide a significantly lower *C. difficile* acquisition estimate of only 55% (median recruitment age, 2 months; median follow-up, 7 months) [3]. Notably, we found that attendance at a nursery/creche independently increased risk of acquisition, as did formula milk feeding, household pets, and older age. Only breastfeeding (not formula feeding) was reported by Rousseau et al; interestingly, 7 of 10 infants followed longitudinally acquired *C. difficile* before nonparental care commenced [1]. Thus, limited cohort size and confounding bias possibly influenced both the rates of and risk factors for *C. difficile* colonization recorded by Rousseau et al [1, 3].

Rousseau et al also suggest 2 peaks in *C. difficile* acquisition, one shortly following birth and one at 4 months [1]. However, the exact timing of acquisition was not known for 2 of 10 infants who did not submit their first sample until 3 months of age. Estimating whether 8 (or even 10) observations of acquisition time follow a unimodal or bimodal distribution is simply impossible. This exploratory analysis only serves to highlight the further work required in this area, particularly with regard to weaning, as most (8/10) infants were colonized by *C. difficile* strictly before food diversification, even though late acquisition (months 4–6) was considered to correspond to the weaning period [1]. Such associations may be more legitimate for toxigenic strains, but as only 4 infants acquired these strains, the sample is too small for results to be robust.

A recent large UK study demonstrated much lower rates of *C. difficile* transmission from symptomatic hospital inpatients than previously expected [4]. Clearly, further adequately powered studies are required to establish the origin of *C. difficile* acquisition both in community- and healthcare-associated CDIs, particularly as neither *C. difficile* ribotype 027 nor 078 strains were recovered by Rousseau or ourselves among 226 or 203 isolates, respectively. Establishing the significance of potential community sources of CDI will require combining detailed epidemiologic data with improved molecular technologies, such as whole genome sequencing, especially as such approaches show that some CDI cases assumed to be related based on epidemiology are actually not linked [5].

### Notes

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