Reply to Walk et al

To the Editor—We appreciate Walk et al’s comments [1] regarding our recent publication and welcome the opportunity to clarify the meaning of some terminology regarding the epidemiologic models used in our article [2].

For any factor with >2 levels, several different questions can be asked in one epidemiologic model. The most common is whether there is any evidence of a different impact of one level of a factor compared to the reference/baseline category on the outcome (as in Tables 2 and 3 [2]; eg, the impact on 14-day mortality of polymerase chain reaction [PCR] ribotype 027 Clostridium difficile infection [CDI] vs enzyme immunoassay [EIA]–negative diarrhea [the reference category]). However, different questions can also be asked from the same model, such as “is there any evidence that the effect of clades 1, 2, and 5 versus EIA-negatives are the same as or different from each other?” This is typically termed a heterogeneity test, as we described [2]. The simplest form is to test whether clade 1 and 2 have the same or different effects on mortality versus EIA-negatives, which is identically equal to a pairwise test of whether clades 1 and 2 have the same effect on mortality as each other.

Thus, in contrast to Walk et al’s assertion that “head-to-head comparisons (clade 1 vs clade 2 etc) . . . were not conducted,” these tests were performed and were presented by statistical tests throughout our article, albeit within the context of a larger epidemiologic model, rather than by using crude unadjusted head-to-head comparisons. These pairwise tests are illustrated in Figure 3 [2], where we followed standard notation indicating P values corresponding to pairwise comparisons using brackets. In contrast to Walk et al’s assertion, these do not reflect comparisons versus EIA-negatives (which are instead implicit within the 95% confidence interval). The overall test of heterogeneity of mortality impact across the 5 clades is marked by “het” on our Figure 3.

We can therefore reassure Walk and colleagues that we definitively have demonstrated that significant between-clade
differences exist after adjustment for host factors, including biomarkers such as sodium; this is stated explicitly for the 2 most common clades at the end of the Results section via a direct pairwise statistical test: “However, even after adjusting for these biomarker differences [including sodium] across C. difficile clades . . . significantly higher mortality persist[ed] in clade 2 (PCR ribotype 027) versus clade 1 \((P = .01)\) CDIs.” We emphasize that all adjusted analyses explicitly included age as an explanatory variable; thus, the effects of clade reported were independent from age-related comorbidity.

We would also like to clarify that we found no evidence for an interaction between age and clade in terms of mortality, and note that the crude associations with clade by age in Figure 1C [2] do not adjust for other risk factors. It is well recognized that relying on underpowered “within-subgroup” tests of association to judge interaction, as, for example in Miller et al [3], is fraught with danger and so is not recommended [4]. Rather, the most rigorous approach is a test of interaction [5]; using this we found no evidence that the excess PCR ribotype 027–associated mortality was restricted only to older ages, in contrast to Miller et al’s findings [3]. This emphasizes the critical role that controlling spread of this epidemic strain can have on outcomes.

**Note**

Potential conflicts of interest. The institution of D. W. C. and T. E. A. P. has received per-case funding from Optimer Pharmaceuticals to support fidaxomicin trial patient expenses. D. W. C. and T. E. A. P. have also received honoraria from Optimer Pharmaceuticals for participation in additional meetings related to investigative planning for fidaxomicin. M. H. W. has received honoraria for consultancy work, financial support to attend meetings, and research funding from bioMérieux, Optimer, Novacta, Pfizer, Summit, The Medicines Company, and Viropharma. A. S. W. and D. W. E. report 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.

A. S. Walker,1 D. W. Eyre,1 D. W. Crook,1 T. E. A. Peto,1 and M. H. Wilcox2,3
1Oxford National Institute of Health Research Biomedical Research Centre; 2Leeds Teaching Hospitals National Health Service Trust; and 3University of Leeds, Leeds Institute of Biomedical and Clinical Sciences, United Kingdom

**References**


Correspondence: A. S. Walker, PhD, MSc, MA, Oxford NHR Biomedical Research Centre, John Radcliffe Hospital, Headley Way, Oxford OX3 9DU, UK (sarah.walker@ndm.ox.ac.uk).

Clinical Infectious Diseases 2013;57(4):626–7
© The Author 2013. Published by Oxford University Press on behalf of the Infectious Diseases Society of America. All rights reserved. For Permissions, please e-mail: journals.permissions@oup.com.
DOI: 10.1093/cid/cit312