Reviewers report

Title: Clostridium difficile exposure as an insidious source of infection in healthcare settings: An epidemiological model

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Reviewer: Camilla Wiuff

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This theoretical study of the transmission dynamics of Clostridium difficile is a very important contribution to the literature in this area, as the role of asymptomatic carriage has not been sufficiently investigated and is still not understood well. In particular, there is a lack of conclusive molecular data confirming that strains of C. difficile spread from asymptomatic carriers to others in healthcare facilities. The mathematical model presented by Yakob and colleagues explores this question and is a welcome contribution to this field.

The authors have addressed all points in my previous comments, and the manuscript is much improved. In particular, the authors have discussed the limitations and biases of the model in more detail, and included a more comprehensive review of the literature of the current epidemiology of CDI.

However, the initial statement and underlying assumption for the model that 'asymptomatic carriage is fundamental to the epidemiology of CDI' (p3) is too strong as this has not been extensively studied nor confirmed with molecular data such as MLVA or whole genome sequencing data. The study by Loo et al (2011), that the authors refer to for this assumption, also found that asymptomatic carriers were more likely to be colonised with other strains than those causing infection in the majority of patients. However, in one very recent publication by Curry et al in Clinical Infectious Diseases (July, 2013, attached), using MLVA typing, it was found that carriers were the source of 29% (16/56) of (HAI) CDI cases while infected CDI patients were the source of 30% of (HAI) CDI cases (17/56), as having less than 2 tandem repeat differences, but more than half of these (in both groups) had not stayed within the same ward and only very small fractions of HAI cases could be proven to be through environmental contamination derived from asymptomatic carriage (2/56) or infected patients (2/56). Although, this single study, being the first of its kind and on a relative small patient population in one hospital, strengthens the evidence around asymptomatic carriage, I would recommend a more cautious interpretation of the existing evidence until larger investigations of molecular subtypes become available.

Level of interest: An article of importance in its field

Quality of written English: Acceptable
**Statistical review:** No, the manuscript does not need to be seen by a statistician.