Reviewer’s 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 C. difficile is aimed at investigating the potential impact of existing control measures, including antibiotic stewardship and environmental cleaning. There is currently a lack of understanding of the quantitative impact of these control measures and of the molecular epidemiology of transmission of C. difficile strains, and the study is therefore highly relevant. The mathematical model developed in this study is based on classic principles of population dynamics of infectious diseases including a micro-organism and host populations of susceptible, colonised and infected individuals.

The model explores if asymptomatic carriers play a central role in the spread of epidemic strains of C. difficile. However, the initial assumptions made around introduction of C. difficile into healthcare settings via asymptomatic carriers (and by shedding from those individuals) are not well supported by epidemiological observational and molecular studies. The Riggs et al study (2007), from which this key assumption is based on, was carried out in an outbreak situation in a long-term care facility where patients had extended periods of stay, which may represent an entirely different transmission dynamics than currently seen in acute hospitals in the UK (and Europe) where outbreaks and the prevalence epidemic strains are decreasing and average length of stays (LOS) are 6-7 days or less. Other debatable assumptions include; whether shedding from asymptomatic carriers is having any impact on the epidemiology in acute settings under these circumstances (where non-outbreak situations and short LOS are common); and whether asymptomatic carriers frequently go on to develop disease. Other patient risk factors (including underlying co-morbidities, age, immune status), which could affect the transmission dynamics considerably depending on the composition of the patient population, have not been included in the model.

The chosen incidence rate for the simulations seems high (2.8 cases per 1,000 hospital bed days) as the European study suggested 4.1 cases per 10,000 hospital bed days.

The description of the current background epidemiology seems slightly out of date (at least from a UK/European perspective) as incidence and number of outbreaks are decreasing, and the molecular epidemiology of C. difficile is getting increasingly diverse (i.e. less clonal). The increasing number of reports on CDI in people who received no antibiotics, pregnant women and children may be
caused by more testing in these group (and therefore biased).

The authors conclude (based on the outcome of simulations run in this model) that antibiotic stewardship is likely to be an ineffective control measure, but do not discuss in sufficient detail the discrepancy between this theoretical finding and actual outcomes reported in observational studies (Valiquette 2007, Aldeyab 2011, 2012, Jump 2012 and others) and from national programmes which all suggested major impact of antibiotic stewardship (Nathwani et al, 2011).

The paper requires a more thorough literature review of observational and recent molecular epidemiology studies to establish valid assumptions for the mathematical model (or include a range of possible reasonable assumptions to be tested), an expanded analysis of the simulated results and a more extensive discussion of the theoretical findings in relation to relevant observational findings.

**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.

**Declaration of competing interests:**

I have no competing interests.