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Caution is warranted for using cephamycin antibiotics against recurrent *Clostridioides difficile* infection

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To the editor - In their article, Srikhanta et al. suggest that cephamycin antibiotics can be used to treat recurrent *Clostridioides difficile* infection (CDI) through the inhibition of sporulation. We are concerned that based on existent data, the use of cephamycins for CDI may not be appropriate.

C. difficile is an important nosocomial pathogen, which is selected by antibiotics that inhibit the gut microbiota. It causes a range of clinical presentations (CDIs) that are associated with high rates of recurrence. CDI recurrence is linked to colonic survival and persistence of *C. difficile* spores despite antibiotic treatment. The identification of therapeutics that inhibit sporulation is therefore of clinical importance.

Srikhanta et al. propose that cephamycins can be implemented as an adjunct to vancomycin to treat fulminant and recurrent CDI. However, this suggestion conflicts with previous clinical studies implicating cephamycin use as an independent risk factor for the development of CDI.[1-5] Cephamycin administration may also lead to severe disruption of the gastrointestinal microbiota [6] as a consequence of the marked inhibitory effect that cephamycins can have on gut bacteria. Indeed, the cephamycin cefoxitin is used in media in clinical and research settings to selectively culture *C. difficile* from patient samples. Microbiota perturbation caused by cephamycins may therefore leave patients susceptible to infection by other bacterial pathogens. In agreement with this is a previous study showing that the administration of cefoxitin in human subjects was associated with increases in drug-resistant

bacteria and in faecal β-lactamase content in comparison to other antibiotics,[7] and another study that found overgrowth of enterococci in subjects given cefoxitin.[8]

Previous mouse studies have also shown that cefoxitin can promote growth and toxin production by *C. difficile* in the murine gastrointestinal tract,[9] and that administration of cefotetan results in persistent and high-level gut colonisation by vancomycin-resistant *Enterococcus faecium* (VRE).[10] The use of cephamycins in CDI patients could therefore exacerbate the symptoms of disease, and leave patients susceptible to gastrointestinal colonisation by nosocomial pathogens such as VRE and carbapenem-resistant enterobacteria, which are major infection control threats, difficult to treat and associated with poor patient outcomes.

I contend that the use of cephamycins to treat CDI patients could lead to adverse patient outcomes. Thus, I caution that the suggestion that "this study could directly and immediately affect treatment of *C. difficile* infection" is premature based on clinical experience with cephamycins. It is therefore imperative that if the observed effects are indeed reproducible in animal models, cephamycins should then be tested through formal early phase human trials, before proceeding to appropriately controlled clinical trials designed to assess efficacy, and importantly, adverse effects of cephamycins in combination with vancomycin for the treatment of recurrent and fulminant CDI. These studies should also actively monitor the impacts that this broad-spectrum antimicrobial combination therapy have on the human gastrointestinal microbiota, in order to determine the extent to which it would leave already vulnerable patients susceptible to potentially serious nosocomial infections.

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Competing Interests

MHW has received research funding and/or consultancy funding from several companies developing CDI treatment/prevention therapeutics, including Astellas, Da Volterra, Merck, Pfizer, Sanofi-Pasteur, Seres, Summit, Synthetic Biologics, Valneva and Vaxxilon.