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CORRESPONDENCE

Authors' reply to:

English *C. difficile* - can we stop hospital infection control (THELANCETID-D-17-00215)

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Here, mathematical modelling shows that hospital infection control (HIC) interventions can preferentially reduce hospital-adapted strains over community-adapted strains within and outside hospitals, questioning our conclusion that restrictions in fluoroquinolone use were responsible for most of the decline in *C. difficile* infection (CDI).[1] "All models are wrong, but some are useful" [George Box]. The key is not whether a model can reproduce findings from an empirical study, but whether its underpinning assumptions are sufficiently plausible. Unfortunately, several features are implausible in this model, which seems more appropriate to MRSA.

Firstly fluoroquinolone-resistant strains are assumed to be hospital-adapted, i.e. transmit more efficiently in hospital, and, crucially, fluoroquinolone-susceptible strains are assumed community-adapted. The former is possible, since *C. difficile* transmission may be promoted, at least partly, by resistance itself. But why the latter should hold is unclear, particularly as most fluoroquinolone use in our study was in the community. Additionally, if resistance itself confers hospital-adaptation, reducing fluoroquinolone use would be expected to reduce hospital-adaptation; this is not considered in the model.

The second assumption is competition between fluoroquinolone-resistant and fluoroquinolone-susceptible *C. difficile*, i.e. infection by one precludes the other. This is required for the incidence of susceptible strains to remain unchanged despite HIC interventions. However, as acknowledged, this is a simplification; rates of CDI with multiple genotypes are ~7%.[2] Third, the model's parameters produce implausibly high *C. difficile*

prevalence (>20%/10% in hospital/community), contradicting empirical observations (typically ≤10% and ~4%, respectively).[3] Both exaggerate competition in the model.

Fourth, the model assumes that bacteria are transmitted in hospitals exclusively via healthcare workers (HCW). Whilst patient-to-patient transmission is modelled in the community, it is not within hospitals, and no contribution from the environment or other reservoirs is allowed. This clearly substantially amplifies the effect of any HCW intervention.

Fifth, the model considers only asymptomatic colonisation, which is never treated, so the mean 200-day carriage duration of resistant-bacteria, regardless of location, may be reasonable. However, for unclear reasons, susceptible-bacteria are assumed to be lost 3.3-fold faster in hospital than resistant-bacteria, but at the same rate in the community. Infections are not directly modelled, despite CDI symptoms being a key determinant of transmission (in contrast with MRSA).[4] Instead, the model assumes 1 in 10 colonisations result in symptomatic infections; these would be treated, and the vast majority of fluoroquinolone-susceptible and fluoroquinolone-resistant isolates are equally susceptible to first-line CDI therapy (metronidazole/vancomycin), giving no advantage to either.

The authors raise an intriguing question that merits careful consideration across a range of healthcare-associated infections. We would welcome the opportunity to work with them to explore the performance of their model under realistic assumptions for *C. difficile*; particularly to explore why stewardship interventions may achieve CDI control despite prior multi-factorial HIC measures not doing so,[5] and why reductions in CDI have not occurred in North America, despite similar HIC interventions, but without fluoroquinolone restriction.

References

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