The replication machinery of Clostridium difficile:a potential target for novel antimicrobials

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STELLINGEN BEHOREND BIJ HET PROEFSCHRIFT

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1. The bacterial replisome can be used to develop both broad- and narrow-spectrum antimicrobials (this thesis, chapter 2).

2. Horizontal gene transfer between bacteria and its consequences are actively investigated, but intragenic translocation of genes and its (phenotypic) effect within bacteria such as *C. difficile* deserves equal attention (this thesis, chapter 3).

3. The mechanism of loading and activation of the replicative helicase of *C. difficile in vitro* is critically different from the Gram-positive model organism *B. subtilis* (this thesis, chapter 4 and 5).

4. Both direct and indirect effects of gene dosage shifts are likely to contribute to the transcriptional response of *C. difficile* to replication inhibition (this thesis, chapter 6).

5. Variation in stability of the helicase-primase interaction between bacterial species and species-specific cross-stimulation by helicase and primase suggests that molecules that inhibit this interaction may exert species-specific effects (this thesis, chapter 7).

6. Documenting provenance and whole genome sequencing should be common practice for laboratories using bacterial reference strains for their molecular work (Roberts AP and Smits WK. Anaerobe 2018).

7. Narrow-spectrum antimicrobials, such as fidaxomicin, are useful to prevent or treat opportunistic infections such as CDI, that are associated with dysbiosis of the microbiome (Louie *et al.* Clin Infect Dis. 2012, Ajami *et al.* Antimicrob. Agents Chemother. 2018).

8. The importance of gene order is reflected in the strong conservation of the *oriC*-proximal co-localization of important growth factors involved in replication, transcription and translation (Slager J and Veening JW. Trends Microbiol. 2016).

9. Guidelines and statistical practice should abandon the sharp division between superiority and non-inferiority in clinical trials and be more closely aligned to the clinical and public health questions that motivate the trial (adapted from Dunn *et al.* Trials 2018, Gerding *et al.* Lancet Infect Dis. 2019).

10. Effective automation in clinical microbiology does not mean making the system do what is done without automation. It may require a revolutionary different approach. (Adapted from Burckhardt I. Bioengineering 2018).

11. Obtaining a PhD – like travel – in the younger sort, is a part of education; in the elder, a part of experience (Adapted from Francis Bacon. Essayes of Counsels, Civill and Morall, 1625).

Erika van Eijk, Leiden 16 mei 2019