Colonisation of the gut microbiome by Escherichia coli during international travel

Appendix One

Addendum

A.1 Impact

Antimicrobial resistance is recognised as one of the largest current threats to global health. Many Low- and Middle-income countries contain a high degree of AMR bacteria amongst their populations which, alongside the increase in globalisation throughout the years, has contributed to an exceptional rate of transmission between countries. This is especially problematic with ESBL-E which is recognised as one of the predominant highly virulent and AMR pathogens that plague the world. Meanwhile, there is an upwards trend in the amount of focus that the gut microbiome receives from the scientific community as research discovers the many links it has with human health. A known role of the gut microbiome is in creating a colonisation resistance to invading species, but the sheer complexity behind the number of interactions between microorganisms and the host has meant that it is still a field of research with an unquantifiable potential. This research in this thesis aims to better link these two fields and explain how involved the gut microbiome is with the acquisition of AMR bacteria during travel to Low- and Middle-income countries.

The ability to predict the risk of acquiring AMR internationally could aid how guidance is provided to travellers before travel, especially high-risk individuals, in order to minimise the transmission of AMR bacteria. In this thesis, we first studied the impact that the pre-travel gut microbiome content has on the predisposition to acquiring ESBL-E. Our findings show that the microbiome structure and composition are measurements that are either too insignificant with the acquisition of ESBL-E, or too imprecise in making a solid prediction. As this thesis highlights that the bacterial population alone does not distinguish into a protective 'type' of microbiome, there is a

need for additional omics analyses of the bacterial transcription or metabolic profiles. These results are the foundation to this field, but with further analyses, the guidance offered to travellers can be updated to incorporate the healthiest behaviours for one's gut microbiome.

How the gut microbiome is altered in healthy people during invasion of ESBL-E highlights the ways in which some travellers are seemingly resistant to colonisation. Results outlined in this thesis show how acquiring ESBL-E seemingly has little effect on the gut microbiome as a whole, instead the onset of travellers diarrhoea is the most significant perturbation. The large, longitudinal data set used in this study allowed us to carry out robust statistics which are lacking from this field of research, meaning that other research can refer to these results or access the sequencing data that was made publicly available. This thesis explores methods that can be utilised in future research on the pre-travel risk of developing diarrhoea. There is therefore a high potential to discover a gut microbiome structure or composition that is more resilient to diarrhoeal perturbation, and in turn resilient to ESBL-E taking advantage of an inflamed environment. Especially with the increased potential behind faecal microbiome transplantation, discovering a protective microbiome would lead to intervention strategies that minimise transmission of AMR bacteria, and the research in this thesis helps focus future research in this field.

Finally, we increased the resolution on the gut microbiome and focussed on the relationship that individual species have with ESBL-E during travel. Until the work in this thesis, this area of research remained understudied due to the lack of species-level technologies and sufficient number of samples. The outcome from this research highlights that members of Bacteroidaceae or other members of Enterobacteriaceae are potential targets of probiotic research against ESBL-E. We also discovered how the *E. coli* population itself is very dynamic in a travel-dependent manner and this provides strong leads for future research to better understand how this may be utilised to counteract the acquisition of ESBL-E.

To conclude, this thesis contributes to the field of research on the gut microbiome during travel by explaining the roles, of lack thereof, that the gut microbiome or its individual components play in the acquisition of ESBL-E. The results provide the groundwork for various future research endeavours, but also emphasise the need to increase the resolution of the analysis technology and to incorporate more components

of the gut microbiome, in order to fully understand how to exploit this to prevent the spread of AMR.