

Antimicrobial resistance genes and clonal success in *Escherichia coli* isolates causing bloodstream infection

We read with interest the study by Gladstone and colleagues¹ describing a large, longitudinal survey of *Escherichia coli* bacteraemia isolates from Norway from 2002 to 2017. The authors' central hypothesis is that antimicrobial resistance does not explain clonal success, using the example of the early and sustained growth of the predominantly antimicrobial susceptible clonal complex 131 (CC131) clade A versus the multidrug resistant clade C2. However, the authors characterised clade A as being drug susceptible based on the presence or absence of *bla*_{CTX-M} and fluoroquinolone resistance mechanisms only. The authors did not investigate the effect of antimicrobial resistance genes conferring resistance to other classes of antibiotics in their published analysis, some of which (particularly β -lactams and aminoglycosides) are more widely used in Norway.²

We commend the authors for making their data available, enabling a re-analysis and comparison with our longitudinal survey of *E coli* bacteraemia isolates in Oxfordshire, UK, from 2008 to 2018.³ We used stacked negative binomial regression to estimate the incidence rate ratio per year (IRRY) for each CC131 sub-clade and compared trends between these (ie, through using Wald tests for heterogeneity). We mapped raw reads

to the EC958 reference (GenBank HG941718.1) using Snippy (version 4.6.0) and produced recombination-corrected phylogenies using GUBBINS (version 2.4.3). Reads were assembled using the Shovill⁴ bioinformatics software and antimicrobial resistance genes presence/absence called using the NCBI AMRFinder⁵ database.

We found 61 (81%) of 75 of the Norwegian CC131 sub-clade A isolates carry non-CTX-M β -lactamase genes compared with 15 (29%) of 51 sub-clade C2 isolates ($p < 0.001$). Furthermore 17 (23%) of 75 sub-clade A isolates carry a gentamicin antimicrobial resistance gene, with some evidence that the rate of increase of these (IRRY 1.26, 95% CI 1.12–1.41; $p < 0.001$) was greater than that of sub-clade A isolates not carrying these genes ($p_{\text{heterogeneity}} = 0.0496$). Sub-clade A isolates also carried numerous other antimicrobial resistance genes (appendix); only 6 (8%) of 75 had no known antimicrobial resistance genes.

Excluding sub-clades C0 and B0 (≤ 4 isolates sequenced), the greatest incidence increases were observed in sub-clades C1 and C2 (both multidrug resistant [appendix]; C1 IRRY 1.26, 95% CI 1.20–1.32; $p < 0.001$; C2 1.25, 1.17–1.34; $p < 0.001$). In comparison, the rate of increase was significantly lower ($p_{\text{heterogeneity}} = 0.003$) in the most drug-susceptible sub-clade B (1.08, 1.03–1.12; $p = 0.001$). Results were similar using Oxfordshire data³ (C1 1.30, 1.20–1.42; $p < 0.001$; C2 1.18, 1.13–1.23; $p < 0.001$; B 1.11, 1.06–1.16; $p = < 0.001$, $p_{\text{heterogeneity}} < 0.001$).

We agree with Gladstone and colleagues¹ that antimicrobial resistance gene acquisition is not the only factor explaining the expansion of particular

E coli CC131 sub-clades and could be variably relevant. However, given that these two independent, large, longitudinal studies show the incidence of resistant CC131 sub-clades is increasing faster than susceptible ones, we believe the role of antimicrobial resistance in clonal expansion should not yet be discounted.

We declare no conflicts of interest.

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- 1 Gladstone RA, McNally A, Pöntinen AK, et al. Emergence and dissemination of antimicrobial resistance in *Escherichia coli* causing bloodstream infections in Norway in 2002–17: a nationwide, longitudinal, microbial population genomic study. *Lancet Microbe* 2020; published online May 10. [https://doi.org/10.1016/S2666-5247\(21\)00031-8](https://doi.org/10.1016/S2666-5247(21)00031-8).
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- 3 Lipworth S, Vihta K-D, Chau K, et al. Molecular epidemiology of *Escherichia coli* and *Klebsiella* species bloodstream infections in Oxfordshire (UK) 2008–2018. *medRxiv* 2021; published online Jan 6, 2021. <https://doi.org/10.1101/2021.01.05.20232553> (preprint).
- 4 Seemann T. Shovill. 2020. <https://github.com/tseemann/shovill> (accessed May 18, 2020).
- 5 National Library of Medicine. NCBI AMRFinderPlus. <https://www.ncbi.nlm.nih.gov/pathogens/antimicrobial-resistance/AMRFinder> (accessed May 20, 2020).



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See Online for appendix