



## Commentary

## Quantifying the impact of COVID-19-related restrictions on antibiotic resistance

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The COVID-19 pandemic, declared by WHO on March 11, 2020, caused monumental changes in health and social care delivery globally. Restrictions varied by country, but many could plausibly affect rates of bacterial antibiotic resistance. There is limited published research to date robustly evaluating this impact.

During the pandemic, reductions in elective procedures, hospital admissions, and lengths of hospital stay [1], could have resulted in decreased bacteraemia cases. The proportion that was hospital-acquired could also have decreased, with community-acquired infections typically less antibiotic-resistant [2]. Antibiotic prescribing changed significantly in community and hospital settings [3], altering selection pressure. There were fewer general practice appointments and decreased antibiotic prescribing for respiratory infections overall, but more consultations were remote, with higher antibiotic prescription rates than face-to-face [4]. Opportunities for transmission of antibiotic-resistant bacteria were reduced in many community, and healthcare and social care settings by isolation measures and with the increased use of personal protective equipment. Quantifying the impact of these changes, individually or in combination, on antibiotic resistance is extremely challenging. Such analyses necessarily use observational, often routine administrative, data with inherent difficulty in adjusting for

confounders. The timing of any resulting change in antibiotic resistance could vary, with important analytical considerations.

Stanley et al. [5] reported a welcome analysis of changes in antibiotic resistance among *Escherichia coli* bacteraemia associated with COVID-19 restrictions across a large population in southwest England, United Kingdom. They used 19 055 *E. coli* bacteraemia episodes in a routine NHS reporting system 2016–2021, reporting monthly proportions resistant to six antibiotics—amoxicillin-clavulanate, ciprofloxacin, piperacillin-tazobactam, gentamicin, third-generation cephalosporins, and carbapenems. They hypothesized that antibiotic resistance would be lower after the introduction of COVID-19 restrictions (i.e. lockdown), but did not consider the changes in antibiotic consumption. Analyses to test their hypothesis involved segmented binomial regression modelling of interrupted time series data, a robust quasi-experimental analytical approach when randomization is not possible [6]. The authors prespecified the intervention time point as March 23, 2020—the start of the first national UK COVID-19 restrictions [7]. Temporal trends in *E. coli* resistance before and after COVID-19 restrictions were reported as odds ratios (ORs, with 95% high-density intervals [HDI]) representing the annual change in odds of antibiotic resistance. Comparisons between preintervention and postintervention trends quantified the difference between slope ORs, and used a Bayesian approach, returning a Bayesian Factor (BF, where >1 supports the proposed hypothesis, and higher values indicate stronger evidence) [8]. Step-changes at the intervention time point were the absolute differences in percentage resistance between the final preintervention and the first postintervention points.

Resistance ranged from 0.15% (0.04–0.27) for carbapenems to 40.9% (37.8–44.0) for amoxicillin-clavulanate immediately before the intervention (which aligns with consumption rates in UK clinical practice). Preintervention, monthly resistance rates were increasing for all antibiotics except ciprofloxacin, although increases were small for gentamicin (OR 1.01 [0.97–1.07]) and carbapenems (1.01 [0.71–1.44]). The overall pattern of change postintervention was that increasing preintervention trends became less steep or switched to decreasing trends, but with considerable uncertainty (all 95% HDI's cross the null). Estimates from the Bayesian approach were all in the direction of the resistance being lower postintervention, with moderate evidence of lower postintervention rates for gentamicin, third-generation

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cephalosporins, and carbapenems. There were downward immediate step-changes for all antibiotics except carbapenems, although 95%HDIs crossed the null except for ciprofloxacin ( $-2.40\%$  [ $-4.35$  to  $-0.48$ ]) and piperacillin-tazobactam ( $-2.90\%$  [ $-4.51$  to  $-1.16$ ]). The upward step-change in carbapenem resistance was numerically small ( $+0.17\%$  [ $-0.07$  to  $-0.45$ ]) but proportionately high. It was balanced by the largest reduction in OR for trend ( $-0.29$  [ $-1.21$  to  $-0.46$ ]), although all changes in carbapenem resistance have considerable uncertainty.

The findings are, at least partly, consistent with observational European data. The 2023 English Surveillance Programme for Antimicrobial Utilisation and Resistance report, comparing 2022 with 2018, found statistically significant differences in resistance in *E. coli* bacteraemia, with decreases for ciprofloxacin ( $-2.0\%$ ) and co-amoxiclav ( $-2.0\%$ ) but increases for piperacillin-tazobactam ( $+1.5\%$ ) and amikacin ( $+1.5\%$ ) [3]. Data from the Scottish One Health Antimicrobial Usage and Antimicrobial Resistance (SONAAR) comparing 2018 with 2022 indicated that resistance in *E. coli* bacteraemia remained stable for most antibiotics, except for co-amoxiclav (which had increased from 41.5% to 46.1%) and temocillin (2.9% to 6.8%) [9]. Similarly, the European Centre for Disease Prevention and Control reported, from 2017 to 2021, decreases in resistance in invasive *E. coli* isolates for all antibiotics except carbapenems, and carbapenem resistance remained  $\leq 0.3\%$  [10]. These observed changes cannot confidently be attributed to COVID-19 interventions due to multiple potential confounders, such as underlying temporal trends. There are very few relevant published analytical studies, but one interrupted time series analysis in a single Italian hospital found no significant change in the incidence of *E. coli* bacteraemia or associated antibiotic resistance between pre-COVID-19 and post-COVID-19 periods [11]. A systematic review and meta-analysis of observational studies reported a nonstatistically significant pooled increase in the proportion of antibiotic-resistant gram-negative organisms associated with the COVID-19 pandemic (RR 1.08 [0.91–1.29]) [12]. Another systematic review of observational studies reported high rates of antibiotic resistance among *E. coli* during COVID-19, but most included studies involved intensive care units, and there was no pre-COVID-19 comparison [13].

In addition to the robust analytical approach by Stanley et al. [5], a key strength is the almost complete coverage of a geographic population with little missing data overall. Missing antibiotic susceptibility data were, however, unevenly distributed, with missing ciprofloxacin data potentially biasing that analysis. A key limitation of the study is that antibiotic consumption data were not examined. This changed dramatically during the pandemic [3] with, arguably, a higher potential than changes in transmission to influence population-level antibiotic resistance, given widely established country-level associations between consumption and resistance.

The authors examined underlying trends in *E. coli* bacteraemia incidence and concluded that there was no significant difference preintervention versus postintervention; hence, did not adjust for incidence. This is contrary to reported *E. coli* bacteraemia rates across England rising before the pandemic, with 9.2 more cases per 100 000 population in 2019 than in 2015, then falling to below 2015 rates from 2020 to 2021 [3,14]. In addition, likely changes in the distribution of cases across settings, i.e. community-acquired versus hospital-acquired, and patient demographics, might impact resistance rates and this was not accounted for [3]. The authors claim that the severity of *E. coli* bacteraemia means presentation to hospital would not be influenced by COVID-19 restrictions. However, the threshold for admission for young, otherwise well, patients with pyelonephritis, for example, would have been higher, meaning that some people managed at home would likely have bacteraemia that was not detected.

A final weakness in their interpretation is the attribution of immediate downward step-changes in resistance to decreased transmission of antibiotic-resistant *E. coli* [5]. *E. coli* outbreaks do not occur as clusters of bacteraemia cases. Rather, transmitted resistant isolates become part of the recipient's flora and may or may not be associated with subsequent bacteraemia, with varying lag times. Also, they do not consider the role of selective competition between bacterial species. Studies including gram-negative bacteria more broadly, report overall increases in resistance during COVID-19 [12]. There is evidence that close proximity interactions (and therefore interrupting these) are more relevant to the transmission of extended spectrum beta-lactamase (ESBL) producing *Klebsiella pneumoniae* than *E. coli* [15]. The inclusion of additional organisms could, therefore, be more informative on the relative contributions of COVID-19-related changes, e.g. healthcare contacts and procedures versus antibiotic consumption. The observed step-changes are likely an artefact of enforcing a breakpoint in the trend lines, supported by their supplementary analyses without breakpoints not changing their overall conclusions.

Although the analyses by Stanley et al. [5] shed some light on the potential impact of COVID-19 restrictions on antibiotic resistance among *E. coli* bacteraemia, uncertainty remains. Data covering a larger population or over a longer period would increase analytical power and inform on whether changes are sustained. Analyses should account for changes in bacteraemia rates, composition of the patient population, changes in hospital activity (e.g. admissions), and antibiotic consumption. Statistical methods that are more data-driven, allowing changes in these factors to determine interruption time points, may be more informative than enforcing a prespecified time point. Finally, analyses that estimate the difference between observed rates and modelled rates that would be expected had the intervention not happened can be used to incorporate changes in trend and step-changes.

The implications for clinical practice and policy are not straightforward. The COVID-19-associated disruption could not be replicated in other circumstances, even if there were more definitive or larger reductions in resistance. A robust examination of the impact of changes in antibiotic consumption during the pandemic on antibiotic resistance is warranted and may be applicable to informing future interventions.

## Author contributions

The first author is lead and corresponding author. Writing—original draft: C.M.; review and editing: L.C.; conceptualization: C.M. and L.C.; investigation: L.C. and C.M.

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