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## *Escherichia coli* causing bloodstream and other extraintestinal infections: tracking the next pandemic



In *The Lancet Infectious Diseases*, Michaela J Day and colleagues<sup>1</sup> present the results of a large genomic epidemiology study that asks whether a food source exists for extended-spectrum  $\beta$ -lactamase-producing *Escherichia coli* isolates (ESBL-*E coli*) that cause bloodstream infections in the UK. This question is controversial, with evidence both for and against the food-source hypothesis.<sup>2,3</sup> Disagreements tend to revolve around the discriminatory power of genotyping approaches used to characterise *E coli* and on the scope and appropriateness of *E coli* sampling from human and non-human sources in past molecular epidemiology studies. Implementation of highly discriminatory genome sequencing, as in the present study, will begin to provide high quality evidence to either refute or support the hypothesis.

The study compared the number and type of multilocus sequence types (STs) and  $\beta$ -lactamase genes in ESBL-*E coli* isolates collected in 2011–14 from human and non-human sources. Human sources of ESBL-producing *E coli* (n=718) included sewage samples, human faecal samples, and bloodstream infections. Non-human sources (n=218) included veterinary diagnostic specimens, dairy cattle faeces, and food products (beef, pork, chicken, berries, vegetables, and herbs). ST131 and ST10 isolates were identified in bloodstream and non-human samples, but were found to be genetically unrelated. ST69, ST117, and ST23 were also found in bloodstream and food samples, and ST602 in faeces and chicken meat, but genome similarity and evolutionary relationships across sources were not assessed. Three

of the most common meat, slurry, and animal-source *E coli* STs in the study (ST10, ST117, and ST23) have been reported in other studies of human extraintestinal infections and were among the top 20 STs in a systematic review of human extraintestinal pathogenic *E coli* lineages.<sup>4</sup> CTX-M-1  $\beta$ -lactamase was present in both human and non-human sources, including a single bloodstream ST117 isolate containing the CTX-M-1 enzyme. Because the STs that were common across sources were relatively rare, Day and colleagues conclude that the ESBL-*E coli* causing bacteremia do not arise from food animal sources. Two practical public health questions emerge from these results.

First, timing. The authors rightly focus on bacteremia, a severe infection with the biggest impact on medical services and costs. *E coli* ST131 has increased explosively over the past 20 years as a cause of all extraintestinal infections, including bacteremia,<sup>5,6</sup> yet its original source remains unknown. *E coli* strains that are currently causing bloodstream infections, especially *E coli* ST131, might be highly host-adapted and human host-restricted, and could be more closely linked to health-care system exposure than to environmental exposures. Contemporaneous sampling of food and environmental isolates is a strength of the paper, but might have missed the period in the past when a link with food sources was measureable. The difference in ST131 clades (B, C1, and C2) by source also suggests past divergence. Similarly, the predominant ESBL genes associated with human-adapted STs probably emerged in parallel with these *E coli* lineages,

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with changing antibiotic use patterns and selective pressures over time.

Second, sampling. Day and colleagues sampled diverse reservoirs to investigate the source of bacteremia-causing *E coli*; another strength of the study. Sampling is always challenging. Studies must balance logistical feasibility with selection bias avoidance. Large numbers of *E coli* were screened to identify the predominant ESBL-producing members within each source population. Still, this finding represents a tiny fraction of the total diversity of circulating *E coli*, and ignores *E coli* isolates that are highly genetically similar across sources but have lost (or never had) ESBL-encoding mobile genetic elements. Selection for resistant-only isolates would miss any such link. Finding any genomic match between human and non-human source isolates, even between a pair of singleton STs, could be important to public health, especially in the face of extensive *E coli* diversity and finite study sample sizes. A single introduction of a highly successful resistant clone might suffice to trigger the next (non-ST131) pandemic.

The repeated emergence in *E coli* and other uropathogens of novel resistance genes, encoding not just ESBLs but also colistin and carbapenem resistance, has been linked genetically to food animal sources.<sup>7</sup> Several new lineages are emerging, some of which (eg, ST1193) might ultimately supplant ST131.<sup>8</sup> To detect newly emerging, multidrug-resistant *E coli* lineages, stand-alone research studies might not be enough. Distributed surveillance systems that involve better integrated human and animal health systems and food inspection

agencies, with sharing of carefully curated local and regional epidemiological and *E coli* genome sequencing data, will be required to counter the public health and medical threats posed by resistant and non-resistant, *E coli* causing bloodstream and other extraintestinal infections.

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I declare no competing interests.

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## Infectious disease consultation lowers candidaemia mortality

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In *The Lancet Infectious Diseases*, Carlos Mejia-Chew and colleagues report the results of a retrospective cohort study investigating the effect of infectious disease consultation on mortality and management of patients with candida bloodstream infections.<sup>1</sup> 42-day (22% vs 47%;  $p < 0.0001$ ) and 90-day mortality (29% vs 51%;  $p < 0.0001$ ) was significantly lower in the infectious disease consultation group versus the group without an infectious disease consultation. In the Cox proportional hazard model with inverse weighting by the propensity score, infectious disease consultation was associated with a hazard ratio of 0.81 (95% CI 0.73–0.91;

$p < 0.0001$ ) for mortality. Duration of antifungal therapy was longer and central line removal, echocardiography, and ophthalmological examination were more frequently done in the infectious disease consultation group. The large number of 1691 patients included and the statistical method used for survival analysis are major strengths of the study and an improvement compared with earlier studies.<sup>2–4</sup> Ishikane and colleagues<sup>5</sup> reported results from a similar setting but the number of patients included was much smaller ( $n = 275$ ). Similar results were obtained including a 46% reduction in 30-day mortality. Additionally, patients with an infectious disease