# Extended-spectrum β-lactamase-producing *Escherichia coli* in human-derived and foodchain-derived samples from England, Wales, and Scotland: an epidemiological surveillance and typing study

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## Summary

**Background** Extended-spectrum β-lactamase-producing *Escherichia coli* isolates (ESBL-*E coli*) cause more than 5000 cases of bacteraemias annually in the UK. The contribution of the food chain to these infections is debated. We aimed to identify the most important reservoirs of ESBL-*E coli* that colonise and infect humans to identify strategic intervention points.

**Methods** Sampling for ESBL-*E coli* was done between Aug 1, 2013, and Dec 15, 2014. We used selective media to seek ESBL-*E coli* in routinely submitted samples from human faeces, and prospectively collected samples from sewage, farm slurry, and retail foodstuffs in London, East Anglia, northwest England, Scotland, and Wales. We sequenced recovered isolates and compared these isolates with 293 bloodstream and 83 veterinary surveillance ESBL-*E coli* isolates from the same regions.

**Findings** 2157 (11%) of 20 243 human faeces samples contained ESBL-*E coli*, including 678 (17%) of 3995 in London. ESBL-*E coli* also were frequent in sewage and retail chicken (104 [65%] of 159 meat samples), but were rare in other meats and absent from plant-based foods (0 of 400 fruit and vegetable samples). Sequence type (ST) 131 dominated among ESBL-*E coli* from human blood (188 [64%] of 293 isolates), faeces (128 [36%] of 360), and sewage (14 [22%] of 65) with STs 38 and 648 also widespread; CTX-M-15 was the predominant ESBL in these lineages (319 [77%] of 416). By contrast, STs 602, 23, and 117—mostly with CTX-M-1 ESBL—dominated among food and veterinary isolates (68 [31%] of 218), with only two ST131 organisms recovered. ST10 occurred in both animals and humans, being frequent in surveillance bovines (11 [22%] of 51 cattle) and representing 15 (4%) of 360 human faecal isolates (but only three [1%] of 293 from bacteraemias); however, both human and animal ST10 isolates were diverse in serotype.

**Interpretation** Most human bacteraemias with ESBL-*E coli* in the UK involve internationally prevalent human-associated STs, particularly ST131; non-human reservoirs made little contribution to invasive human disease. Any interventions that seek to target food or livestock can affect the numbers of human infections caused by ESBL-*E coli*; prevention of the spread of resistant lineages among humans is more vital.

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## Introduction

*Escherichia coli* is a Jekyll and Hyde organism; a few lineages are virulent enteropathogens whereas most are innocuous gut commensals that are harmful only if they reach other body sites—notably the urinary tract, where *E coli* is the most common pathogen. Most *E coli* urinary tract infections are uncomplicated cystitis, but some can ascend, affecting the kidneys and—at worst—causing overspill bacteraemia. Although such sequelae are rare, *E coli* is now the most common bloodstream pathogen in England, with 41 060 cases in the 2017–18 fiscal year, which was 27% more than in 2012–13 (32 309 cases).[1] Most *E coli* bacteraemias have a urinary origin[2] and, in the UK, about 60% are caused by extraintestinal pathogenic *E coli* lineages belonging to sequence types (STs) 12, 69, 73, 95, and 131.[3]

Cephalosporin resistance mediated by extended-spectrum β-lactamases (ESBLs) has proliferated in *E coli* since 2000,[4] and such resistance now occurs in 10–12% of bloodstream isolates in the UK.[5] This proportion suggests that around 4900 ESBL-producing *E coli* (ESBL-*E coli*) bacteraemias occur annually in England and more across the whole UK,[1] often due to multidrug resistant ST131 isolates.[3,6] ESBL production and multidrug resistance increases the risk that empirical treatment will fail, doubling the 17–18% mortality that is typical for *E coli* bacteraemia.[7–9]

ESBL-*E coli* are widespread in sewage, pets, meat, and food animals, but the extent of transmission between

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## Research in context

### Evidence before this study

Extended-spectrum β-lactamase-producing *Escherichia coli* (ESBL-*E coli*) are the largest group of multidrug-resistant pathogens from bacteraemias in the UK, presenting major challenges. *E coli* is also the major aerobic component of the human and animal gut biota and is a frequent contaminant of meat and the environment. Extensive literature reviews in 2011–12 were summarised in a joint 2012 report of ESBL-*E coli* by UK Government Advisory Committees. This, and subsequent publications, reported considerable uncertainly on the contribution of foodborne and environmental ESBL-*E coli* to human colonisation and invasive infection. For example, early Dutch studies suggested some similarities between ESBL-*E coli* from humans and poultry farming, whereas a larger subsequent study covering the UK, the Netherlands, and Germany did not support such a link. A meta-analysis identified six studies suggesting food-to-human transmission of ESBL-*E coli* versus 17 that argued against this view. These uncertainties led to the start of a competitive NIHR Policy Research Programme and, among various activities, this programme funded the present comparison of ESBL-*E coli* from human and animal sources.

### Added value of this study

This study shows that the ESBL-*E coli* strains from bacteraemias in the UK match those prevalent as human gut colonists and in sewage. However, with respect to strain and ESBL types, they are largely distinct from those in food animals and retail food.

### Implications of all the available evidence

In 2016, the UK Government announced its aim to achieve a 50% reduction in serious Gram-negative infections by 2020. A reduction in the numbers of infections due to ESBL-*E coli* is especially desirable, given their incidence (>5000 cases per year) and the treatment challenges. Our findings show that actions on the food chain, however desirable for animal husbandry, are unlikely to contribute to reductions in human infection. Better potential control points are prevention of transmission by good post-toilet hygiene (eg, in care homes) and prevention of severe infection through good patient care and rapid effective treatment of initial uncomplicated urinary tract infections, which precipitate most of the bacteraemias. Vaccines might also be a future solution.

these milieux and humans is uncertain, with the role of the food chain under debate.[10–12] A meta-analysis[10] identified six studies suggesting food-to-human trans-mission of ESBL-*E coli* against 17 finding foodborne transmission was unimportant. We aimed to clarify the contribution of foodborne ESBL-*E coli* to human colonisation and infection, using whole-genome sequencing to compare isolates from multiple sources across the UK.

## Methods

### Study design

We examined ESBL-*E coli* from multiple sources, including human faeces, sewage, farm slurry, live food-producing animals, and raw meat, fruit, and vegetables. By comparing the bacteria from all of these reservoirs with ESBL-producing *E coli* from bloodstream infections in five regions of the UK, we sought to provide a comprehensive national map and to identify important reservoirs of the strains causing human disease in order to propose strategic intervention points to reduce the burden of ESBL-*E coli* in the UK.

Consecutive bloodstream ESBL-*E coli* isolates were collected between Jan 1, 2013, and Oct 12, 2014 from NHS laboratories in five UK regions, with five sites in East Anglia, two each in northwest England, Scotland, and Wales, and one in London. Identification and susceptibility testing were done according to laboratories' local protocols, with presumptive ESBL-*E coli* sent to Public Health England Colindale to a quota of 80 per region, along with brief, anonymised, patient details.

Isolates from other sources (human faeces, sewage, farm slurry, and retail foodstuffs) were collected prospectively in the five regions. Isolation involved plating samples onto CHROMagar ESBL and CHROMagar CTX (CHROMagar, Paris France) chromogenic media, prepared according to the manufacturer's directions. For human faecal sampling, which was decentralised, media were prepared at PubIic Health England Colindale and distributed weekly to laboratories. Characterisation of presumptive ESBL-*E coli* was centralised at PubIic Health England Colindale and the Animal and Plant Health Agency (APHA) Addlestone.

### Human faeces

Faecal specimens were submitted between Aug 12, 2013, and July 20, 2014, for detection of intestinal pathogens or occult blood screening at Barts Health (London), the Norfolk & Norwich University Hospital (East Anglia), Lancashire Hospitals Trust, Central Manchester University Hospitals (northwest England), Aneurin Bevan University Health Board (Wales), and NHS Greater Glasgow and Clyde (Scotland). Each laboratory was asked to randomly select and test 15–20 faecal specimens per day to a maximum of 100 per week. No guidance was given on how to select randomly.

Faeces (about 0·5 g) was mixed with 1 mL of 0·85% saline, then 50-µL aliquots were spread on the two chromogenic agars and incubated for 18–24 h. Presumptive ESBL-*E coli* (visible as pink on CHROMagar ESBL or blue on CHROMagar CTX) were retained.

### Sewage

Paired inflow and effluent sewage samples (50–1000 mL) were obtained from multiple sewage works belonging to

four water companies covering Scotland, northwest England, London, and Wales. East Anglia did not participate. Each region provided four batches of samples between Dec 9, 2013, and Dec 15, 2014, with about 80 samples per region. Samples were couriered to PubIic Health England Colindale at 2–8°C, stored at 2–10°C, and processed within 24 h. Volumes (0·01–10 mL) were filtered through 0·45-µm pore membranes, which were washed with distilled water before transfer to absorbent pads saturated with lauroyl sulphate broth for 4 h at 30°C, then to lauroyl sulphate agar for 14 h before enumeration of yellow colonies as presumptive *E coli*. Lastly, one filter per sample was transferred to each CHROMagar and incubated at 37°C for 18–24 h. Colonies that continued to develop, becoming appropriately coloured for ESBL-*E coli*, were retained at 4°C.

Sewage samples were stored for further analysis by pelleting bacteria from about 30 mL sewage, resuspended in 0·5 mL of freezing broth and retained at –70°C. Putative ESBL-*E coli* were recovered, as red colonies, after plating 100 µL of defrosted material on UTI Brilliance Agar (Oxoid, Basingstoke, UK) containing 10 mg/L of cefotaxime.

### Food

The methods and corresponding results for food isolates have been published previously.[13] We bought the following in each of the five regions: beef, pork, and chicken (n=397 samples in a 2:1:2 ratio, reflecting market share), grapes (n=50), strawberries (n=38), raspberries (n=35), blueberries (n=27), celery (n=50), carrots (n=50), onions or spring onions (n=50), lettuce (n=50), coriander (n=43), and basil (n=7).[13] Retailers included leading supermarkets, discount stores, convenience stores, and local butchers and greengrocers, in proportion to market share. Beef and chicken were obtained on five occasions between Aug 1, 2013, and Feb 28, 2014; pork on four occasions between Oct 1, 2013, and Feb 28, 2014; and vegetables on 15 occasions between Jan 1, and March 31, 2014. Meat samples were processed by the UK APHA; fruit, vegetables, and herbs were done by PubIic Health England, with the two chromogenic agars used to recover presumptive ESBL-*E coli*.

### Slurry

97 slurry samples were collected from dairy farms across the five regions between Jan 13, and March 24, 2014, after milking and before cleaning. Samples were taken from five different areas at each farm on the route that the cows followed when leaving the milking parlour. London was represented by the Home Counties (Berkshire, Buckinghamshire, Essex, Hertfordshire, Kent, Surrey, and Sussex). 1-g samples were incubated overnight at 37°C in 9 mL of buffered peptone water before plating 10-µL amounts on the two chromogenic agars.

### Veterinary diagnostic surveillance

We assessed veterinary diagnostic submissions to APHA or its predecessor laboratories from prospective sur-veillance across the five regions and from scanning surveillance of food animals. The latter entails laboratory investigations of animal disease, largely post-mortem or through sample submission. Investigation aims to find the cause of disease, and *E coli* might be recovered and characterised. The isolates we studied comprised all ESBL-*E coli* submitted across the five regions during 2011–13, irrespective of their contribution to disease.

### Characterisation of presumptive ESBL-*E coli*

Presumptive ESBL-*E coli*, isolated as explained from blood, faeces, sewage, food, animals and slurry were received at PubIic Health England and screened for $bla_{CTX\text{-}M}$, $bla_{TEM}$, $bla_{SHV}$ and $bla_{OXA}$ by multiplex PCR.[14] $bla_{CTX\text{-}M}$-positive isolates were accepted as ESBL producers, whereas isolates that were positive for one of the other β-lactamase genes underwent double disc ESBL tests using amoxicillin–clavulanate (20 µg+10 µg) discs about 20 mm apart (centre to centre) from cefotaxime (30 µg), ceftazidime (30 µg), and cefepime (30 µg) discs. Expansion of an oxyimino-cephalosporin zone towards the amoxicillin–clavulanate disc suggested ESBL production.[15] Isolates positive by these methods were confirmed as *E coli* by MALDI-ToF (Bruker Maldi-Biotyper, Bremen, Germany); any isolates flagged as shigella were confirmed as *E coli* based on *o*-nitrophenyl-β-D-galactosidase activity and a 603-bp PCR product for *ipaH*.[16] Definitive confirmation as ESBL-*E coli* was done by whole-genome sequencing (HiSeq 2500; Illumina, San Diego, CA, USA). STs were assigned and β-lactamase genes sought using the in-house Genefinder pipeline.[17] ST131 isolates were assigned to clades based on *fimH* sequences.[18] Serotypes of ST10 isolates (which crossed among host species) were deduced from sequence data.[19]

### Statistical analysis

Our analysis was primarily descriptive, with proportions shown as percentages and continuous variables as mean and SD. We used Pearson's $\chi^2$ test to compare proportions. We used R (version 3.5.0) for all analyses.

### Role of the funding source

The funder of the study had no role in study design, data collection, data analysis, data interpretation, or writing of the report. The corresponding author had full access to all the data in the study and had final responsibility for the decision to submit for publication.

## Results

ESBL production was confirmed in 293 (90%) of 327 bloodstream isolates received as ESBL-*E coli* (table 1). Case record forms were available for 244 (83%) of 293 isolates, with fewer forms available for London isolates (18 [33%] of 55; p<0·001). The mean age was

| | East Anglia | London | Northwest | Scotland | Wales | All |
|---|---|---|---|---|---|---|
| Cases, n | 66 | 55 | 61 | 37 | 74 | 293 |
| Cases with data, n | 55 | 18 | 61 | 37 | 72 | 244 |
| Age, mean (SD) | 71·5 (24·0) | 58·9 (20·4) | 65·7 (20·2) | 73·3 (17·0) | 74·3 (13·9) | 70·0 (18·7) |
| Sex, n (%) | | | | | | |
| Women | 30 (55%) | 7 (39%) | 34 (56%) | 16 (43%) | 32 (44%) | 119 (49%) |
| Men | 25 (45%) | 11 (61%) | 27 (44%) | 21 (57%) | 40 (56%) | 125 (51%) |
| Source of isolate, n (%) | | | | | | |
| Community or outpatient* | 2/25 (8%) | 10 (56%) | 6/55 (11%) | 0 | 2/48 (4%) | 20/184 (11%) |
| Inpatient | | | | | | |
| >48 h | 5/25 (20%) | 4 (22%) | 21/55 (38%) | 12 (32%) | 29/48 (60%) | 71/184 (39%) |
| ≤48 h | 18/25 (72%) | 4 (22%) | 28/55 (51%) | 25 (68%) | 17/48 (35%) | 93/184 (50%) |
| Specialty, n (%) | | | | | | |
| Accident and emergency | 13 (24%) | 6 (33%) | 12/53 (23%) | 20 (54%) | 16/46 (22%) | 67/209 (32%) |
| Intensive care | 0 | 3 (17%) | 3/53 (6%) | 2 (5%) | 2/46 (3%) | 10/209 (5%) |
| Medical | 29 (53%) | 8 (44%) | 24/53 (45%) | 9 (24%) | 25/46 (35%) | 95/209 (46%) |
| Paediatrics | 2 (4%) | 0 | 3/53 (6%) | 0 | 0 | 5/209 (2%) |
| Surgical | 11 (20%) | 0 | 4/53 (8%) | 2 (5%) | 2/46 (3%) | 19/209 (9%) |
| Other | 0 | 1 (6%) | 7/53 (13%) | 4 (11%) | 1/46 (1%) | 13/209 (6%) |
| Origin, n (%) | | | | | | |
| Gastrointestinal or biliary | 7/40 (18%) | 5/15 (33%) | 3/27 (11%) | 6/31 (19%) | 1/7 (14%) | 22/120 (18%) |
| Genitourinary tract | 27/40 (68%) | 6/15 (40%) | 14/27 (52%) | 23/31 (74%) | 2/7 (29%) | 72/120 (60%) |
| Line related | 0 | 1/15 (7%) | 2/27 (7%) | 1/31 (3%) | 2/7 (29%) | 6/120 (5%) |
| Respiratory | 4/40 (10%) | 1/15 (7%) | 1/27 (4%) | 1/31 (3%) | 2/7 (29%) | 9/120 (8%) |
| Skin or soft tissue | 0 | 0 | 2/27 (7%) | 0 | 0 | 2/120 (2%) |
| Surgical site infection | 0 | 2/15 (13%) | 0 | 0 | 0 | 2/120 (2%) |
| Other | 2/40 (5%) | 0 | 5/27 (19%) | 0 | 0 | 7/120 (6%) |

Denominators are given when the value is not consistent with the number of cases with data. Overall completeness of each variable for East Anglia, London, northwest, Scotland, Wales, and all was: age 38%, 33%, 97%, 100%, 97%, and 72%; sex 83%, 33%, 100%, 100%, 97%, and 83%; source of isolate 38%, 33%, 90%, 100%, 65%, and 62%; and origin 61%, 27%, 44%, 84%, 9%, and 41%. ESBL-*E coli*=extended-spectrum β-lactamases-producing *Escherichia coli*. *This category underestimates community onset infection, as evidenced by the much larger proportion of patients in the accident and emergency category. Patients presenting at Accident and Emergency with suspected bacteraemia and sepsis are likely to be admitted, with their isolates recorded under the inpatient, <48 h category. Figures in the table are shown as percentages of available data.

***Table 1:*** **Sources of ESBL-*E coli* isolates from bloodstream infections**

70 years (SD 18·7) overall, although participants were younger in London (58·9 years; Kruskal-Wallis rank sum test p=0·002). 240 (69%) of 347 patients with data were community presentations, or stayed in hospital for fewer than 48 h. Data on the origin of bacteraemia were available for 120 (49%) of 244 patients, with genitourinary (72 [60%] of 120) and gastrointestinal or hepatobiliary sources (22 [18%] of 120) being the most common. Few patients were identified as post-surgical (19 [9%] of 209 with data), but post-discharge re-presentations might be under-recorded.

20 243 faecal samples were screened, comprising 3995–4112 per region (table 2). 2107 (10%) gave colonies of the appropriate colour for *E coli* on CHROMagar ESBL, 1302 (6%) on CHROMagar CTX, and 1252 (6%) on both. If appropriately coloured growth on either medium—as was true for 2157 (11%) of 20 243 faecal specimens—the samples were deemed to be positive. Regional ESBL prevalence was 8·5–9·8%, except for London, where prevalence was 17·0% (p<0·001; table 2). 400 of the presumptive ESBL-*E coli* (80 per region) were forwarded to Public Health England, and whole-genome sequencing found ESBL genes in 360 (90%) of these. The 40 isolates lacking ESBL genes were split between cephalosporin-susceptible *E coli* (n=20), *E coli* with other resistance mechanisms (n=18), and non-*E coli* isolates (n=2). Accordingly, ESBL prevalence could be up to 10% lower than suggested in table 2; although some detection failures might reflect plasmid loss, reducing this correction factor.

Data were available for 355 (99%) of 360 carriers (table 2). Their age distribution peaked at less than 5 years and at 75–79 years. 50–64% of carriers were men, according to region, and in-patients accounted for 30% (London) to 65% (Scotland) of carriers. Overseas travel was reported for 99 (28%) of 360 patients, with south and southeast Asia being the most common destinations (n=33); recent travellers (defined as within the past 12 months) accounted for 58% of the patients in Wales, 42% in London, and less than 20% elsewhere. Clinically significant gastrointestinal pathogens were identified by local laboratories in 40 (11%) of 360 patients. 72 (20%) of 360 patients had recently (defined as within

| | East Anglia | London | Northwest | Scotland | Wales | Overall |
|---|---|---|---|---|---|---|
| Faecal samples that gave colonies of the appropriate colour for *E coli*, n/N (%) | | | | | | |
| CHROMagar ESBL | 309/4107 (7·5%) | 678/3995 (17·0%) | 366/4019 (9·1%) | 393/4010 (9·8%) | 361/4112 (8·8%) | 2107/20 243 (10·4%) |
| CHROMagar CTX | 169/4107 (4·1%) | 363/3995 (9·1%) | 258/4019 (6·4%) | 282/4010 (7·0%) | 230/4112 (5·6%) | 1302/20 243 (6·4%) |
| Either medium | 349/4107 (8·5%) | 678/3995 (17·0%) | 366/4019 (9·1%) | 393/4010 (9·8%) | 371/4112 (9·0%) | 2157/20 243 (10·6%) |
| Isolates reviewed in detail and sequenced, n | 64 | 77 | 75 | 66 | 73 | 355 |
| Mean age, years (SD) | 56·9 (26·1) | 33·4 (25·7) | 48·3 (28·5) | 60·3 (24·5) | 64·2 (22·9) | 52·1 (27·8) |
| Sex | | | | | | |
| Female | 32 (50%) | 41 (53%) | 38 (51%) | 42 (64%) | 42 (58%) | 195 (55%) |
| Male | 32 (50%) | 36 (47%) | 36 (48%) | 24 (36%) | 31 (42%) | 159 (45%) |
| Missing data | 0 | 0 | 1 (1%) | 0 | 0 | 1 (<1%) |
| Overseas travel | | | | | | |
| Yes | 6 (9%) | 32 (42%) | 13 (17%) | 6 (9%) | 42 (58%) | 99 (28%) |
| No | 58 (91%) | 45 (58%) | 62 (83%) | 60 (91%) | 31 (42%) | 256 (72%) |
| Source of isolate | | | | | | |
| Community | 44 (69%) | 54 (70%) | 42 (56%) | 23 (35%) | 36 (49%) | 199 (56%) |
| Inpatient (>48 h) | 9 (14%) | 20 (26%) | 20 (27%) | 32 (48%) | 26 (36%) | 107 (30%) |
| Inpatient (≤48 h) | 9 (14%) | 3 (4%) | 7 (9%) | 11 (17%) | 11 (15%) | 41 (12%) |
| Missing data | 2 (3%) | 0 | 6 (8%) | 0 | 0 | 8 (2%) |
| Recent use of antibiotics | | | | | | |
| Yes | 5 (8%) | 20 (26%) | 12 (16%) | 1 (2%) | 15 (21%) | 72 (20%) |
| No | 13 (20%) | 43 (56%) | 0 | 2 (3%) | 14 (19%) | 53 (15%) |
| Missing data | 46 (72%) | 14 (18%) | 63 (84%) | 63 (95%) | 44 (60%) | 230 (65%) |

Data are n (%) unless otherwise specified. Recent use of antibiotics was defined as use within the past 3 months. ESBL-*E coli*=extended-spectrum β-lactamases-producing *Escherichia coli*.

***Table 2:*** **Faecal carriage of ESBL-*E coli* by patient demographics**

| | Bacteraemia | | Faeces | | Sewage | | Meat | | Slurry | | Animals | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | ST | Representatives, n | ST | Representatives, n | ST | Representatives, n | ST | Representatives, n | ST | Representatives, n | ST | Representatives, n |
| 1 | 131 | 188 | 131 | 128 | 131 | 14 | 602 | 21 | 10 | 6 | 23 | 16* |
| 2 | 38 | 17 | 38 | 29 | 38 | 6 | 23 | 8 | 641 | 3 | 117 | 11† |
| 3 | 648 | 16 | 10 | 15 | 10 | 3 | 117 | 8 | 0 | 0 | 10 | 11‡ |
| 4 | 405 | 9 | 648 | 11 | 0 | 0 | 155 | 6 | 0 | 0 | 6284§ | 6¶ |
| 5 | 73 | 6 | 69 | 10 | 0 | 0 | 57 | 4 | 0 | 0 | 602 | 4‖ |
| 6 | 69 | 4 | 405 | 10 | 0 | 0 | 371 | 4 | 0 | 0 | 88 | 4** |
| 7 | 636 | 4 | 410 | 10 | 0 | 0 | 3776 | 4 | 0 | 0 | 0 | 0 |
| 8 | 95 | 3 | 636 | 7 | 0 | 0 | 6285 | 4 | 0 | 0 | 0 | 0 |
| 9 | 1193 | 3 | 162 | 6 | 0 | 0 | 665 | 3 | 0 | 0 | 0 | 0 |
| 10 | 10 | 3 | 443 | 6 | 0 | 0 | 2040 | 3 | 0 | 0 | 0 | 0 |
| Number included in above major types | .. | 253 | .. | 232 | .. | 35 | .. | 65 | .. | 9 | .. | 52 |
| Total number of isolates for all STs | .. | 293 | .. | 360 | .. | 65 | .. | 111†† | .. | 24 | .. | 83‡‡ |

The top ten STs are listed, except where a group has fewer than three representatives. ST=sequence type. ESBL-*E coli*=extended-spectrum β-lactamases-producing *Escherichia coli*. *14/16 from chickens. †9/11 from cattle. ‡11/11 from cattle. §Single locus variant of ST117; if these were grouped collectively, they would be the top ST from livestock. ¶6/6 from cattle. ‖4/4 from chicken. **2/4 from chicken and 2/4 from cattle. ††106 chicken, 3 beef, and 2 pork. ‡‡51 cattle, 29 chicken, and 3 other.

***Table 3:*** **Major STs among ESBL-*E coli* found, by sample type and rank**

the past 3 months) taken antimicrobials, of whom 11 had received piperacillin or tazobactam.

163 inflow and 162 effluent samples from sewage were submitted. Failure of the selective media to adequately suppress developing colonies of ESBL-negative *E coli* on the transfer membranes prevented the accurate calculation of ESBL prevalence. Nevertheless, a panel of 65 sewage ESBL-*E coli* was assembled, 41 from Wales, 18 from London, and three each from Scotland and northwest England.

| | CTX-M ESBLs | | | | | | | | | SHV | TEM: known or possible ESBLs | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | –15 | –27 | –14 | –1 | –24 | –2 | –3 | –9 | Other | | –52 | –117 | –191 | Other |
| **Bacteraemia** | | | | | | | | | | | | | | |
| 131 | 159 | 24 | 5 | 0 | 0 | 0 | 2 | 0 | 0 | 0 | 0 | 0 | 4 | 0 |
| 38 | 8 | 0 | 8 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 |
| 648 | 16 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 1 | 0 |
| 405 | 8 | 0 | 1 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 |
| 73 | 4 | 0 | 0 | 1 | 0 | 0 | 0 | 1 | 0 | 0 | 0 | 0 | 0 | 0 |
| All | 229 | 27 | 20 | 10 | 1 | 2 | 2 | 1 | 0 | 4 | 0 | 1 | 8 | 0 |
| **Faeces** | | | | | | | | | | | | | | |
| 131 | 98 | 18 | 7 | 1 | 0 | 0 | 0 | 0 | 4* | 0 | 0 | 1 | 0 | 2 |
| 38 | 11 | 1 | 15 | 1 | 0 | 0 | 0 | 0 | 0 | 1 | 0 | 0 | 0 | 0 |
| 10 | 8 | 0 | 1 | 3 | 0 | 0 | 0 | 0 | 1 | 0 | 0 | 1 | 0 | 1 |
| 648 | 10 | 0 | 1 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 |
| 69 | 6 | 0 | 2 | 0 | 0 | 0 | 0 | 0 | 1 | 0 | 0 | 0 | 0 | 0 |
| All | 256 | 24 | 38 | 21 | 0 | 0 | 0 | 0 | 20 | 11 | 1 | 6 | 2 | 5 |
| **Sewage** | | | | | | | | | | | | | | |
| 131 | 13 | 1 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 1 | 0 | 3 |
| 38 | 2 | 0 | 5 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 5 |
| 73 | 1 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 1 | 0 | 0 |
| 648 | 2 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 1 |
| 10 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 2 | 0 | 1 |
| All | 21 | 1 | 5 | 0 | 0 | 0 | 0 | 0 | 3 | 3 | 0 | 6 | 0 | 14 |
| **Meat** | | | | | | | | | | | | | | |
| 602 | 0 | 0 | 0 | 21 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 |
| 23 | 0 | 0 | 0 | 8 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 1 | 0 | 4 |
| 117 | 0 | 0 | 0 | 8 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 |
| 155 | 0 | 0 | 0 | 6 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 |
| 57 | 0 | 0 | 0 | 1 | 0 | 0 | 0 | 0 | 0 | 3 | 0 | 0 | 0 | 0 |
| All | 0 | 0 | 0 | 82 | 0 | 2 | 0 | 0 | 4 | 13 | 8 | 3 | 2 | 4 |
| **Slurry** | | | | | | | | | | | | | | |
| 10 | 1 | 0 | 2 | 1 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 1 | 0 | 0 |
| 641 | 0 | 0 | 1 | 2 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 1 |
| All | 4 | 1 | 4 | 6 | 0 | 0 | 0 | 0 | 4† | 0 | 0 | 2 | 0 | 1 |
| **Animals** | | | | | | | | | | | | | | |
| 23 | 1 | 0 | 1 | 12 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 9 |
| 117 | 1 | 0 | 3 | 2 | 0 | 0 | 3 | 0 | 2‡ | 0 | 0 | 1 | 1 | 0 |
| 10 | 3 | 0 | 7 | 0 | 0 | 1 | 0 | 0 | 0 | 0 | 0 | 1 | 0 | 0 |
| 6284 | 0 | 0 | 6 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 |
| 602 | 0 | 0 | 0 | 4 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 |
| All | 13 | 0 | 31 | 32 | 0 | 1 | 3 | 1 | 2 | 0 | 0 | 2 | 2 | 9 |
| Chicken | 0 | 0 | 0 | 29 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 9 |
| Cattle | 12 | 0 | 30 | 3 | 0 | 1 | 3 | 1 | 2 | 0 | 0 | 2 | 2 | 0 |

Some totals exceed the numbers of isolates belonging to the ST because some isolates had more than one ESBL. The top five STs are included, except those with fewer than three representatives. ST=sequence type. ESBL-*E coli*=extended-spectrum β-lactamases-producing *Escherichia coli*. *Includes one isolate with Asn173Ser variant of CTX-M-27. †Includes one isolate with novel Ser205Arg variant of CTX-M-1. ‡All with CTX-M-214.

***Table 4:*** **ESBL types among major STs of *E coli* from different sources**

Results of screening foodstuffs have been published separately.[13] ESBL-*E coli* were recovered from 104 (65%) of 159 chicken samples, with positivity rates from 41% (13 of 32 samples in Scotland) to 81% (25 of 31 samples in northwest England; p<0·0001). Contamination could arise from the original bird or be acquired during slaughter and processing. Even with enrichment, only three (2%) of 159 beef samples and two (3%) of 79 pork samples yielded ESBL-*E coli*, based on growth on either of the two chromogenic agars. No ESBL-*E coli* were recovered from 400 fruit and vegetable samples, many of which were of international origin.

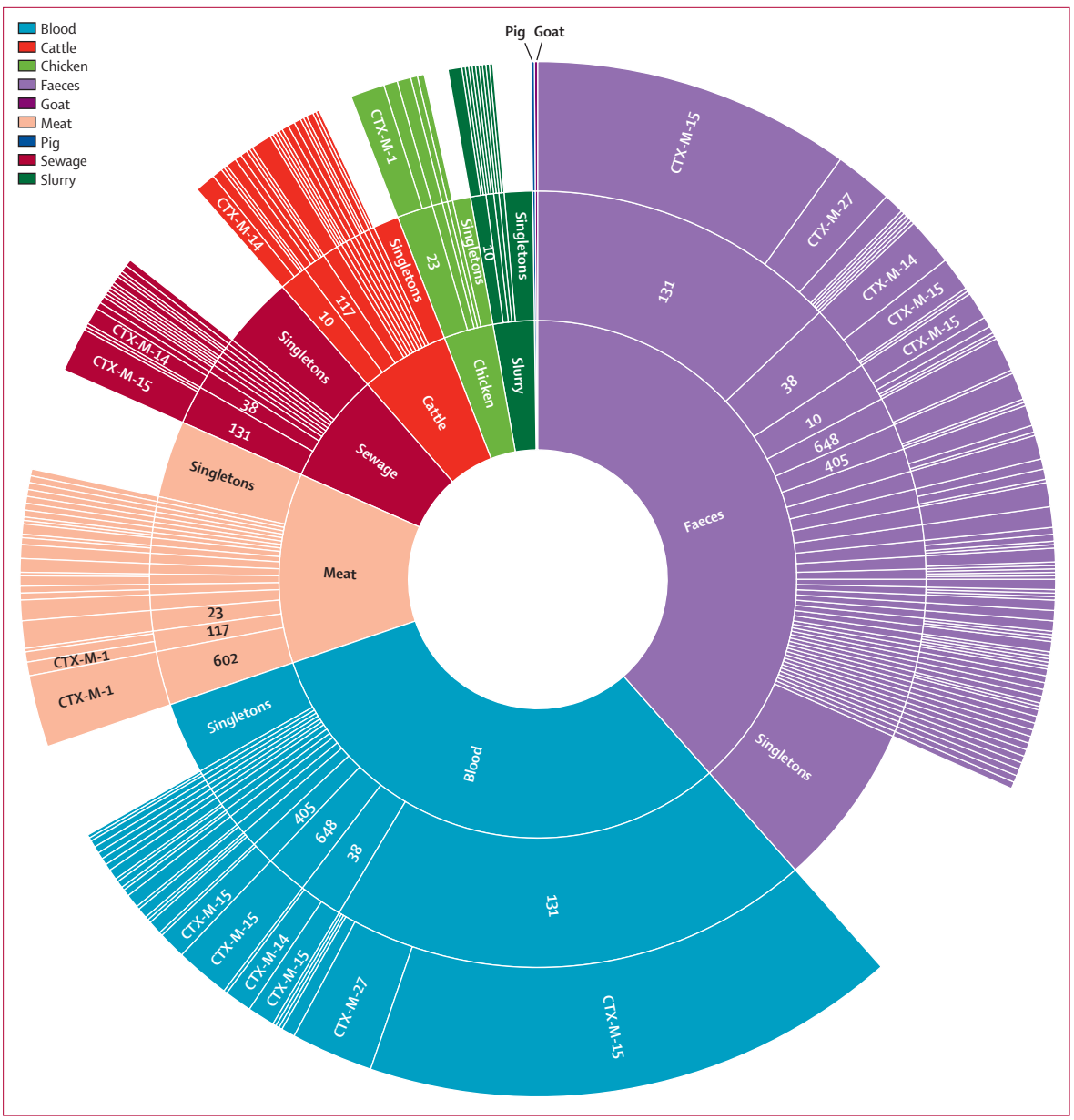


***Figure: Escherichia coli* strains and ESBL types dominating in specimen types that relate to humans and animals**
The inner circle presents the sources of ESBL-*E coli*; segments are scaled according to the numbers of isolates found and single representatives of an ST are aggregated into the singleton category. The middle circle represents the numbers of isolates from each ST in relation to each ESBL. The outer circle represents the number of isolates with an ESBL type. ST=sequence type. ESBL-*E coli*=extended-spectrum β-lactamases-producing *E coli*.

19–20 dairy farm slurry samples were tested per region, with 27 (28%) of 97 samples positive for ESBL-*E coli*, based on growth on either medium. Regional rates ranged from 15% (three of 20 samples in Scotland) to 40% (eight of 20 samples in northwest England).

These prospective collections were supplemented with 83 ESBL-*E coli* from the APHA's scanning surveillance of food animals. These were from the same regions as the other series, with London again including the Home Counties; 51 isolates were from cattle, 29 from chickens with single isolates from other species.

ST131 greatly predominated in human bacteraemias, comprising 188 (64%) of 293 isolates. It was also the most prevalent ST, though less overwhelmingly so, in faeces (128 [36%] of 360 isolates) and sewage (14 [22%] of 65). Regional proportions of ST131 among bloodstream isolates were 36 (65%) of 55 in London, 40 (60%) of 66 in East Anglia, 29 (48%) of 61 in northwest England, 28 (76%) of 37 in Scotland, and 55 (74%) of 74 in Wales

(p=0·011). Corresponding proportions among faecal isolates were 16 (21%) of 77 in London, 16 (24%) of 67 in East Anglia, 27 (36%) of 75 in northwest England, 37 (54%) of 68 in Scotland, and 32 (44%) of 72 in Wales (p<0·0001).

Other common bloodstream STs, in descending order of frequency, were 38, 648, 405, 73, 69, 636, 95, 1193, and 10. Several of these were also prominent in other human-related sources. STs 38, 405, 636, and 648 were among the top ten types among faecal isolates, with ST38 in second rank and ST648 in fourth; ST38 was the second ranked ST from sewage, followed by ST10. By contrast, the top-ranked STs from meat and animals were 602, 23, 117 (or its single locus variant ST6284), and ST10. Collectively, STs 23, 117, and 602 accounted for 68 (31%) of 218 food-derived and animal-derived ESBL-*E coli* samples collected, whereas ST10 accounted for 11 (22%) of 51 bovine ESBL-*E coli* samples. There was species specificity within the animal isolates, with STs 23 and 602 dominating for chickens and chicken meat, whereas STs 10, 117 and 6284 dominated in cattle and their slurry (table 3).

The top-ranked human types were rare in meat, animals, and slurry. Just two ST131 isolates were recovered from animal-related sources: one from chicken meat and another from a surveillance chicken; both isolates belonged to ST131 clade B whereas over 95% of bloodstream, faecal, and sewage ST131 isolates belonged to clades C1 and (mostly) C2. STs 38, 648, 405, 73, 636, 95, and 1193 were not found in animal-associated sources, and ST69 was found in just one isolate from chicken meat and one from a cow. Only ST10, which accounted for 15 (4%) of 360 human faecal isolates and three (1%) of 293 isolates from blood was widely seen in bovines and their slurry, though not in meat (table 3). This human and animal overlap for ST10 was more apparent than real; we found that 38 ST10 isolates belonged to 26 different combinations of O (somatic) and H (flagellar) serotype, with the three human bloodstream isolates and 12 (87%) of 15 human faecal isolates belonging to serotypes that were not seen from animal sources.

The predominant animal-related STs were infrequent in humans. ST602, the top ST from meat (specifically chicken), was not found in human bacteraemias and had only two representatives from human faeces. Among all 293 human bacteraemia isolates, only five (2%) belonged to top-ranked types from any animal-related source, specifically the three ST10 isolates and single representatives of STs 23 and 117.

CTX-M-15 enzyme was most common in human bloodstream, faecal, and sewage isolates (table 4). This finding reflected CTX-M-15's association with ST131, but it remained the most prevalent ESBL in other major STs from these sources except ST38, where CTX-M-14 narrowly dominated. 24 (14%) of 188 ST131 isolates had CTX-M-27, not CTX-M-15. Overall, CTX-M-15 accounted for 319 (77%) of 416 ESBLs found in the predominant human-linked lineages: ST131, ST38, and ST648.

CTX-M-1 was the most common ESBL found in meat (chicken) isolates, whereas CTX-M-15 was not found and most other ESBLs were SHV or TEM types. CTX-M-1 also dominated (20 of 29 cases) in surveillance chickens, whilst CTX-M-14 dominated in cattle, with 30 examples versus 12 for CTX-M-15, three for CTX-M-27, and seven for other CTX-M types. STs 23 and 602 were the major hosts of CTX-M-1 enzyme in chickens and their meat, whereas ST10 and ST117/ST6284 were the frequent hosts of CTX-M-14 among bovines. Despite its frequency in *E coli* from chickens and their meat, CTX-M-1 enzyme was found in only ten (3%) of 293 human bloodstream isolates, 21 (6%) of 360 from faeces, and seven (11%) of 65 from sewage. CTX-M-1 enzyme mostly occurred in minor human STs, with only one or two representatives each. The only exception was ST10, for which CTX-M-1 was found in three (60%) of 15 human faecal isolates. The ST23/CTX-M-1 and ST602/CTX-M-1 combinations, which were widespread in chickens and their meat, were found only in single human faecal isolates and were never found in blood. CTX-M-14, the most frequent ESBL from the bovine isolates, was widely found in major human blood and faecal isolates, including ST131 and ST38, but the ST10/CTX-M-14 combination, frequent in cattle, had only single representatives from human faeces and blood, whereas ST117/ST6284 CTX-M-14 was not detected. There was a single bloodstream ST117 isolate with CTX-M-1 enzyme, matching a combination seen in ten isolates from chickens or their meat.

## Discussion

We compared ESBL-*E coli* from human bacteraemias with those from human faeces, sewage, food, slurry, and animals across five regions in the UK. Bloodstream isolates followed expected patterns; they were mostly found in older patients with community-associated infection of genitourinary or gastrointestinal origin.[2] Faecal ESBL-*E coli* were often linked to foreign travel (particularly to south or southeast Asia) or previous use of antibiotics, which is consistent with the literature.[20,21] Greater contamination of chicken than other meats concurs with previous findings.[22]

Typing and ESBL results showed commonality between human bloodstream ESBL-*E coli* and those from faeces and sewage, with STs 131 (especially), 38, and 648 prominent in all these sources, largely with CTX-M-15 enzyme. There was also commonality between the lineages from surveillance chickens and chicken meat, with STs 23 and 602 dominating, often with CTX-M-1 ESBL, and between cattle and their slurry, where ST10 (with CTX-M-14 or CTX-M-15) dominated. There was little crossover between types from humans, chickens, and bovines, with only serotype diverse ST10 among the top ten most common types from humans, animals, and meat (figure). ST117 was widely found in isolates from both bovines and chickens. Little contamination was seen for foodstuffs other than chicken.

Our findings do not support the assertion that invasive ESBL-*E coli* are disseminating via the food chain. Rather, they suggest that host-adapted ESBL-*E coli* lineages are circulating, with infrequent interspecies transmission. This conclusion agrees with most studies included in a 2015 meta-analysis.[10] ST131, which dominated among human-related isolates, is well known and often multidrug resistant.[6,23] Although ST131 occasionally occurs in food animals (as was seen in two instances in our analysis), the animal ST131 clades are generally different.[24] At the upper edge of the reported prevalence range, Johnson and colleagues[25] in the USA found five of 25 ESBL-*E coli* from chickens or chicken meat belonged to ST131. By contrast, we—and a previous investigation covering the UK, Germany, and the Netherlands[22]—found only occasional ST131 isolates from food and animals. This rarity is supported by a major review,[6] cataloguing many individual detections of ST131 from food or food animals, but no dissemination.

Other common types from bacteraemia—ST38 and ST648, each accounting for about 5% of cases versus 64% for ST131—were absent from food or animals. ST38 (with CMY-2, rather than ESBLs) has been found in poultry, humans, and wildlife;[26] ST648 is also largely reported from humans, although carriage was seen in horses and dogs.[27] Among the major meat and animal types, ST23 was reported from an outbreak in a French hospital,[28] with various further one-off reports but, as we report here, is mostly found in poultry,[29] as is ST117,[23] which has spread in Nordic broiler production.[30] ST602, although common in our study, has not been widely reported in previous studies.[22] ST10, as the sole lineage to appear in the top ten of both human bloodstream and meat-associated groups has been repeatedly noted by other studies[22] in both animals and humans. Nonetheless, the serotype diversity seen in our analysis argues against simple direct flows of ST10 along the food chain. Our results are consistent with those of a comparison of ESBL-*E coli* from human bacteraemias and livestock in the east of England, one of the regions we surveyed, which also found that these isolate groups and their resistance determinants are largely distinct.[31]

Rather than the food chain, the human to human oral-faecal route is likely to be the most frequent route of transmission for human-adapted ESBL-*E coli*. This route would account not only for the strain and enzyme distributions we have summarised, but also the regional variation in gut carriage of ESBL-*E coli* with higher rates in London than elsewhere, where sampling was solely from the Royal London Hospital, which predominantly serves poor, crowded areas and populations with frequent travel to and from south Asia. A study in the West Midlands, UK, similarly showed that human gut carriage of ESBL-*E coli* was more prevalent in inner city conurbations (ie, around Birmingham) than in rural Shropshire.[32] We cannot exclude the possibility that some small minority of human infections might have a direct origin from food, nor that local clusters can occur. In Canada,[33,34] near-identical ST131 and ST117 *E coli* (ESBL-producing or not) have been found in both retail chicken meat and human infections; nevertheless these putative crossovers accounted for only a small minority of all the human and animal *E coli* collected. Further, we cannot exclude the possibility that some future multidrug resistant *E coli* lineage from one or more food animal species will also prove adept at colonising and infecting humans. One further caveat remains: we do not know when, where, or how often $bla_{CTX\text{-}M}$ genes escaped from *Kluyvera* spp (where they are endogenous and chromosomal) to mobile DNA, nor the chain of transmission to human-adapted *E coli* lineages. However, it seems logical that the hazard of such gene escape will multiply with the range of animal species and intestinal microbiotas exposed to selective antibiotics.[35]

Our findings suggest that efforts to stop the rise of ESBL-*E coli* in invasive infections should concentrate upon disrupting oral-faecal transmission by good post-toilet hygiene (eg, in care homes), on prevention of urinary tract infections by good hydration and catheter care, and on prompt effective treatment of preceding urinary tract infections. Vaccines could provide a solution in the future, with promising early results for cystitis in younger women.[36] Efforts to counter the spread of ESBL-*E coli* in food production seem unlikely to affect greatly the tally of invasive human infections but remain important in ensuring that veterinary infections remain tractable.

#### Contributors

MJD, KLH, MT, LR, CT, and CW designed the study. MJD also led the central laboratory processing and sequencing of isolates from all sources. KLH was also overall project manager. DWW led the design, analysis, and co-ordination of the faecal screening programme and managed local aspects of the project in London. MT also managed the project in Wales and led analysis of the sewage data. NE managed all non-meat food sampling and sewage analyses. LR and CT also managed the meat and slurry work, and sourced the veterinary surveillance isolates. PC designed and undertook all statistical analyses and managed the project in northwest England. CW also managed all aspects of the study in Scotland. MD and MJE did the bioinformatic analyses of whole genome sequencing data. NW wrote the original funding application and led the overall project design and co-ordination. DML co-ordinated the project in East Anglia and led the writing and revising of this paper. All authors commented on the draft manuscript and contributed to the final version.

#### Declaration of interests

DML reports advisory board or ad-hoc consultancy fees from Accelerate, Allecra, Antabio, BioVersys, Centauri, Entasis, Integra-Holdings, Meiji, Melinta, Menarini, Mutabilis, Nordic, ParaPharm, Pfizer, QPEX, Roche, Shionogi, Taxis, T.A.Z., Tetraphase, VenatoRx, Wockhardt, and Zambon; lecture fees from Accelerate, Astellas, bioMerieux, Beckman Coulter, Cepheid, Correvio, Merck, Menarini, Pfizer, and Nordic; and shares in Dechra, GSK, Merck, Perkin Elmer, Pfizer, and T.A.Z, amounting to less than 10% of portfolio value. NW reports grants from Momentum Bioscience, Tetraphase Pharmaceuticals, Bio-Rad, bioMerieux, Meiji Seika Pharma, Accelerate Diagnostics, Wockhardt, Check-Points, Helperby Therapeutics, Merck Sharpe & Dohme, Roche, VenatoRx, AstraZeneca, Paratek, Shionogi, Neem Bioteck, GlaxoSmithKline, Innovate UK, Kalidex Pharmaceuticals, Melinta, Mobidiag, Rokitan, Trius Therapeutics, and Rabiotics Rx. KLH, on behalf of Public Health England's AMRHAI Reference Unit, has received financial support for

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