Do Human Extraintestinal *Escherichia coli* Infections Resistant to Expanded-Spectrum Cephalosporins Originate From Food-Producing Animals? A Systematic Review

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To find out whether food-producing animals (FPAs) are a source of extraintestinal expanded-spectrum cephalosporin-resistant *Escherichia coli* (ESCR-EC) infections in humans, Medline, Embase, and the Cochrane Database of Systematic Reviews were systematically reviewed. Thirty-four original, peer-reviewed publications were identified for inclusion. Six molecular epidemiology studies supported the transfer of resistance via whole bacterium transmission (WBT), which was best characterized among poultry in the Netherlands. Thirteen molecular epidemiology studies supported transmission of resistance via mobile genetic elements, which demonstrated greater diversity of geography and host FPA. Seventeen molecular epidemiology studies did not support WBT and two did not support mobile genetic element–mediated transmission. Four observational epidemiology studies were consistent with zoonotic transmission. Overall, there is evidence that a proportion of human extraintestinal ESCR-EC infections originate from FPAs. Poultry, in particular, is probably a source, but the quantitative and geographical extent of the problem is unclear and requires further investigation.

Keywords. zoonosis; ESBL; *E. coli*; ST131; urinary tract; poultry.

The global spread, rapidly rising incidence, and increased mortality of expanded-spectrum cephalosporin-resistant *Escherichia coli* (ESCR-EC) infections over the past decade have made it one of the biggest threats to human health worldwide [1, 2]. In many regions, this rising incidence has coincided with a shift in the epidemiology of human infection, from healthcare associated to community acquired [1]. Discovering the origins of this shift may reveal new targets for public health intervention [3].

From as early as 1969, it has been speculated that food-producing animals (FPAs) may be a potential source of antimicrobial-resistant *E. coli* in humans [4, 5]. The use of large volumes of penicillins and cephalosporins in FPAs has been proposed as a contributing factor to the current ESCR-EC pandemic in humans [6]. Numerous studies have suggested that the use of antibiotics in FPAs directly correlates to the emergence of ESCR-EC within animal populations [7–11]. However, whether ESCR-EC from animals represents a source for human infections has been controversial [12–14].

It has been hypothesized that widespread transmission of resistant bacteria between FPAs and humans may occur via the ingestion of contaminated meat [15]. ESCR Enterobacteriaceae, residing in the gut of FPAs, may directly contaminate meat products during slaughter, or may be released into the environment and indirectly contaminate produce via an intermediary mechanism, such as soil or water. Following ingestion, resistant strains may colonize the intestinal tract and

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subsequently proceed to cause infections at extraintestinal sites, such as the urinary tract [16, 17].

Within this transmission paradigm, human ESCR-EC infections may occur via two mechanisms. First, the entire resistance harboring bacterium may be directly transmitted from animal to human. In this mechanism of whole bacterium transmission (WBT), a bacterial clone from the FPA propagates through the food production process, is ingested, and goes on to cause human extraintestinal infection with minimal genetic changes. Alternatively, the genes mediating ESCR may be transferred from Enterobacteriaceae of animal origin to a human pathogenic *E. coli*, via plasmids or other mobile genetic elements (MGEs). This may occur at any stage of the transmission paradigm, including within the human gastrointestinal tract. We termed this process MGE-mediated transmission.

In the event that FPAs are a significant source of human ESCR-EC infections, strategies incorporating the veterinary, agricultural, and retail industries may be effective at reducing the escalating global burden of ESCR-EC [18]. To address this knowledge gap, we performed a systematic review of all available published evidence that supported, or did not support, the hypothesis that FPAs are a source of extraintestinal ESCR-EC infection in humans.

METHODS

Protocol

A systematic review of published literature was undertaken, following the Preferred Reporting Items for Systemic Reviews and Meta-analyses guidelines [19]. Our initial aim was to undertake a systematic review and meta-analysis to quantify the contribution of FPA to human ESCR-EC infections, however, evaluation of the published studies indicated that only 1 study was suitable for meta-analysis.

Data Sources and Search Strategy

We developed search strategies for 3 electronic databases: Medline, Embase, and the Cochrane Database of Systematic Reviews. The most recent search was conducted in October 2013. Language of publications reviewed was not restricted. Terms included *Escherichia coli*, technical (eg, bovine) and nontechnical (eg, cow) animal descriptors, food descriptors (eg, beef), and antimicrobial resistance terminology (eg, cephalosporin resistance, extended-spectrum β-lactamase [ESBL]). Full details are included in the Supplementary Data. The bibliographies of all included publications and relevant review articles on this topic were searched for further publications.

Study Selection

Original research studies that presented a comparative analysis addressing the research question were included. We applied no exclusion criteria or limitations based on the methodology used for this comparison. Studies that reported only on animal or human data, and did not address the research question of the relationship between these 2 groups, were excluded, as were those that analyzed only enteropathogenic *E. coli*. Studies that reported only on transmission of resistance after physical contact between FPAs and humans (eg, farm or abattoir workers) were excluded, due to the limited generalizability of this phenomenon.

Data Extraction

Two authors (B. L., B. A. R.) independently reviewed all abstracts identified by the search strategy. The full text of all publications potentially meeting inclusion criteria, selected by either researcher, was obtained for review. After full independent review, any disagreement about the relevance of an article to the research question was settled by a discussion. Data were extracted from the publications by 1 author (B. L.).

RESULTS

In total, 2301 abstracts were reviewed and 34 full articles were identified with relevant data (Figure 1). The annual frequency of publications has increased markedly over the last decade (see Supplementary Data).

Molecular Evidence Supporting Transmission Between Animals and Humans

Whole Bacterium Transmission

Six published articles provide data to support the hypothesis of WBT of ESCR-EC between poultry and extraintestinal human sites (Table 1). Publications originate from 3 regions: the Netherlands, Spain, and North America.

Three Dutch studies illustrating WBT of ESCR-EC between poultry and extraintestinal human infections were identified [15, 20, 21]. All 3 collected geographically and temporally matched isolates between 2006 and 2010, found a similar distribution of ESBL genes, and, using multilocus sequence typing (MLST), found that animal- and human-sourced bacteria clustered in identical clonal complexes. An extended chromosomal analysis, involving pulsed-field gel electrophoresis (PFGE) and multivariate discriminant function analysis, of the retail chicken, human rectal, and blood culture isolates found extensive similarity between *E. coli* from these sources [15, 20, 21]. Collectively, clonally related isolates were identified at all levels of the transmission paradigm, including poultry flocks, retail chicken meat, and human commensal and extraintestinal clinical sources.

The findings in all 3 studies were limited to poultry despite substantial sampling of non-poultry retail meats [21]. Significantly fewer ESCR-EC isolates were identified in non–poultry meat types [21].

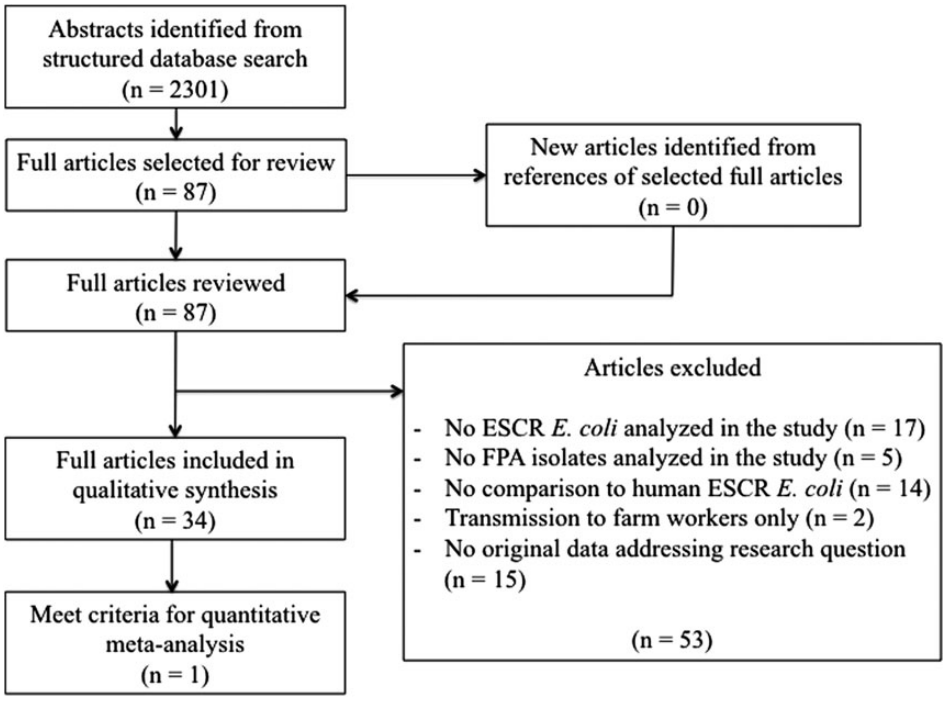

Figure 1. Flow diagram detailing study selection. Abbreviations: ESCR, expanded-spectrum cephalosporin-resistant; FPA, food-producing animal.

Two Spanish studies provide limited evidence, both based on PFGE, to suggest that some WBT of ESCR-EC between poultry and humans may occur in this country [22, 23] (Table 1). One study was conducted retrospectively sampling *E. coli* sequence type 131 (ST131) isolates selected from much larger previous samplings over a 17-year period [23].

One supportive study from North America identified genetic relatedness of isolates from FPAs and humans, albeit using molecular techniques that have a limited resolution [24] (Table 1). No distinction was made between freshly slaughtered chicken carcass samples and retail poultry products in this study.

Mobile Genetic Element-Mediated Transmission

Thirteen studies provide data to support the hypothesis of MGE-mediated transmission of ESCR between animal bacteria and *E. coli* causing human extraintestinal infections (Table 2).

The geographical setting, host animals, and host bacteria that appear to mediate MGE-mediated transmission are diverse. Studies originated from Western Europe (n = 6), North America (n = 3), and Asia (n = 2). Two additional studies were conducted across multiple continents. The animal hosts included poultry, pigs, and cattle. Whereas all MGEs were identified among *E. coli* in humans, the host Enterobacteriaceae for the MGE in animals included *Salmonella* species, *Klebsiella pneumoniae*, and *E. coli*.

The genes encoding ESCR that are described appear to vary by geographical location. ESBL genes, especially the $bla_{\text{CTX-M}}$ family, predominated in Europe, whereas $bla_{\text{CMY-2}}$ was predominant in North America, and both were prevalent in Asia.

Molecular Studies Not Demonstrating Transmission Between Animals and Humans

Whole Bacterium Transmission

Seventeen studies did not demonstrate direct WBT of ESCR-EC in North America, Europe, and Asia. These comprised 8 studies that found evidence to support MGE-mediated transmission and have already been discussed (Table 2) [25–32], and 9 further studies (Table 3).

Of the 9 studies, 3 suggest that FPAs do not appear to play the predominant role in the spread of a single clone, *E. coli* ST131, among humans [33–35]. Two studies did not isolate any ST131 from FPAs [33, 35]. One extensive study found that PFGE-defined pulsotypes of ST131 were predominantly source specific, although some pulsotypes contained isolates from both human and FPA sources [34].

The remaining 6 studies compared a variety of isolates from animal and human sources, and did not find any significant evidence of transmission [14, 36–40]. One of these studies contained isolates from 3 European countries, including the Netherlands [40].

MGE-Mediated Transmission

Two studies did not demonstrate MGE-mediated transmission of ESCR genes between *E. coli* from FPAs and human sources

Table 1. Molecular Evidence Supporting Whole Bacterium Transmission

Location, Sampling Dates	Nature of Sample Selection	Source and No. of ESCR *Escherichia coli* Isolates			Whole Bacterium Comparison	
		Animal	Meat[a] (ESCR-EC/ Meat Samples)	Human	Methods of Comparison, No. of Human ESCR-EC Compared Using This Method	Results
The Netherlands, 2006–2010 [15]	Any ESCR-EC	Healthy poultry, n = 35	Retail chicken, n = 81/98	Urine and blood, n = 409	ESBL genotype frequency, n = 208	51 human isolates carried $bla_{CTX\text{-}M\text{-}1}$ and 14 carried $bla_{TEM\text{-}52}$. These were the 2 most common ESBL genes identified in poultry
					MLST plus plasmid typing, n = 27	8 human isolates had the same sequence type as poultry isolates (ST10, ST58 or ST117) and carried the ESBL on the same plasmid type (IncI1 CC7, 3, or 5)
The Netherlands, 2008–2009 [20, 21]	Any ESCR-EC	. . .	Retail chicken, n = 68/89 Other meats, n = 8/173	Rectal swabs (commensal), n = 45 Blood culture, n = 23	ESBL genotype frequency, n = 55	22 human rectal swab and 5 bloodstream ESCR *E. coli* contained $bla_{CTX\text{-}M\text{-}1}$ genes, the most common ESBL genes in FPA
					MLST, n = 60	25 human rectal and 9 bloodstream isolates shared the same ST group as FPA. Clonal complexes ST10, ST155, and ST117 were the most frequent groups.
					Statistical analysis[b], n = 58	23 human isolates classified as chicken meat isolates at highest level of discriminatory power (Wilks λ = 0.08)
					AFLP and PFGE, n = 14	1 human rectal isolate (B1 group) perfectly matched 1 chicken meat isolate on AFLP and PFGE. 3 human isolates (2 blood and 1 rectal) were similar to chicken meat isolates based on AFLP, but were less related on PFGE
Spain, 1993–2010 [23]	Highly selected[c]	Poultry, n = 3[d]	Retail chicken, n = 4/100	Extraintestinal, n = 5[e]	PFGE, all human and FPA isolates included	3 human $bla_{CTX\text{-}M\text{-}9}$ isolates (2007–2010) showed >90.9% similarity to 4 ESCR retail chicken isolates and 2 poultry ESCR isolates.
Spain, 2003 [22]	Any ESCR-EC	Poultry, n = 57 Pigs, n = 29	. . .	Extraintestinal, n = 80	Serotyping	55 human isolates shared serotypes identified in poultry and pig isolates, namely O2:HNM (24 isolates), O2:H6 (14 isolates), and O25 (17 isolates)
					Phylogenetic group, MLST, virulence genes and PFGE, n = 6 (O2), n = 17 (O25)	2 human O2:HNM isolates matched 3 pig isolates in terms of phylogroup (A) and MLST (ST10), but not virulence profile or PFGE 1 human O25a $bla_{CTX\text{-}M\text{-}32}$ isolate matched 1 chicken isolate in terms of phylogroup (D), MLST (ST648), virulence profile, and PFGE (96.6% match)
USA, 2002–2004 [24]	Any ESCR-EC	. . .	Slaughtered and retail poultry, n = 100/220	Rectal swabs (commensal) and extraintestinal, n = 14	Phylogenetic group and virulence genotype, n = 931[f]	Antimicrobial resistant human isolates were statistically more similar to poultry isolates than to susceptible human isolates ($P < .001$)
					Dendrogram, n = 243[f]	Antimicrobial resistant human isolates were more likely to cluster with poultry isolates than with susceptible human isolates ($P < .001$)

Abbreviations: AFLP, amplified fragment-length polymorphisms; CC, clonal complex; ESBL, extended spectrum β-lactamase; ESCR-EC, expanded-spectrum cephalosporin-resistant *Escherichia coli*; FPA, food-producing animal; MLST, multilocus sequence typing; PFGE, pulsed-field gel electrophoresis; ST, sequence type.

[a] In some studies, multiple isolates were taken per sample, so the number of isolates may not reflect the number of positive samples.

[b] Multifactorial discriminant function analysis based on phylogenetic group, ESBL genotype, plasmid replicon type, and virulence genes (Wilks λ = 0.08).

[c] Selected O25b: H4 ST131 $bla_{CTX\text{-}M\text{-}9}$ *lbe*A strains from 6 previous studies.

[d] Chicken (n = 2) and turkey (n = 1), selected from a combined pool of 1494 poultry and 408 turkey isolates collected between 1993 and 2009.

[e] Fifteen non-*lbe*A $bla_{CTX\text{-}M\text{-}non\text{-}9}$–positive strains were also compared and found not to be similar.

[f] Based on phylogenetic group and virulence genotype of isolates. Non-ESCR isolates were included in analysis, and no subgroup analysis on ESCR isolates was performed.

Table 2. Molecular Evidence Supporting Mobile Genetic Element–Mediated Transmission

Location, Sampling Dates	Nature of Sample Selection	Source and No. of ESCR *Escherichia coli* Isolates			Major ESCR Mechanism	Methods Used to Exclude Whole Bacterium Transmission	Comparison of MGEs Across Sources	
		Animal	Meat	Human			Methods	Results
United Kingdom, 2006–2010 [30]	Selected $bla_{CTX\text{-}M\text{-}14}$ isolates only	Cattle, n = 9 Poultry, n = 9	. . .	Clinical, n = 7	$bla_{CTX\text{-}M\text{-}14}$	PFGE and virulence genotype	PBRT, genetic environment (of ESBL) and ISEcp1, *nikB* sequence and RFLP with PstI	4 human isolates carried $bla_{CTX\text{-}M\text{-}14}$ on IncK, pCT-like plasmid, highly related to plasmids from 9 cattle and 8 poultry isolates
Sweden, 2010 [25]	Selected $bla_{CMY\text{-}2}$ isolates only	Broilers, n = 22	. . .	Clinical, n = 72 Healthy, n = 6	$bla_{CMY\text{-}2}$	PFGE and MLST	PBRT	19 human clinical isolates carried CMY-2 on IncK, which was also the case in 21/22 FPA isolates
France, 2007–2009 [55]	Any ESCR-EC from FPA but no human isolates	Cattle, n = 9	. . .	Clinical, reported in UK, 2003 and Italy, 2006 [65–67]	$bla_{CTX\text{-}M\text{-}15}$	No human isolates for direct comparison	PBRT, molecular size, pMLST, and RFLP with EcoRI	3 cattle isolates carried $bla_{CTX\text{-}M\text{-}15}$ on IncFII plasmids similar to those previously reported in human *E. coli* infections [65–67]
Spain, 2006–2007 [27]	Highly selected, all $bla_{CTX\text{-}M\text{-}15}$, ST410, and retrospective	. . .	Turkey, n = 2	Clinical, n = 5	$bla_{CTX\text{-}M\text{-}15}$	PFGE[a]	PBRT, molecular size, genetic environment (of ESBL) including ISEcp1. HpaI plasmid digestion	All 7 isolates carried $bla_{CTX\text{-}M\text{-}15}$ on IncF1B plasmids of similar size, with IS26 located 64 bp upstream of ISEcp1. Digestion profiles differ
Portugal, 2006–2007 [56]	Any ESCR-EC from animals but no human isolates	Pigs, n = 22	. . .	Clinical, reported in Portugal, 2003 [68]	$bla_{TEM\text{-}52}$	No human isolates for direct comparison	PBRT, plasmid MLST, and RFLP	8 pig isolates carried $bla_{TEM\text{-}52c}$ on 90kB IncI1 plasmid identified as ST3. Previously identified in human clinical isolates in Portugal
Belgium, 2001–2007 [29]	Highly selected, all plasmids previously analyzed	Poultry, n = 4 Pigs, n = 2 Non-EC, n = 5[b]	. . .	Nonclinical (fecal), n = 3	$bla_{TEM\text{-}52}$ $bla_{CTX\text{-}M\text{-}2}$ $bla_{CTX\text{-}M\text{-}15}$	Performed but method not disclosed	Conjugative resistance transfer, size, PBRT, RFLP, southern blot hybridization	1 human isolate carried $bla_{TEM\text{-}52}$ on IncI1 plasmid with similar size and RFLP profile as 4 FPA isolates. 2 remaining human isolates did not share the same RFLP pattern
International[c], 1995–2006 [53]	Highly selected, only $bla_{TEM\text{-}52}$ isolates over 10-y period	Poultry, n = 2 Non-EC, n = 5[d]	Chicken, n = 3 Beef, n = 1	Clinical, n = 9	$bla_{TEM\text{-}52}$	None performed	PBRT, plasmid size, ESBL gene location relative to Tn3 transposon, RFLP with EcoRI	1 human isolate carried $bla_{TEM\text{-}52}$ on IncX1A plasmid highly related to 4 meat isolates and 4 FPA isolates (*Salmonella*)
Spain, 2006–2007 [26]	Any ESCR-EC	. . .	Mixed, n = 55[e]	Urine and blood, n = 80	$bla_{SHV\text{-}12}$ $bla_{CTX\text{-}M\text{-}9}$ $bla_{CTX\text{-}M\text{-}1}$	PFGE	Distribution of genes mediating ESCR between meat and human isolates	78 human isolates carried $bla_{SHV\text{-}12}$, $bla_{CTX\text{-}M\text{-}9}$ or $bla_{CTX\text{-}M\text{-}1}$ genes, which were identified in 45, 6, and 4 FPA isolates, respectively
USA, 2006–2007 [26]	Any ESCR-EC	. . .	Mixed, n = 34[f]	Urine and blood, n = 47	$bla_{CMY\text{-}2}$	PFGE[g]	Distribution of genes mediating ESCR between meat and human isolates	21 human isolates carried $bla_{CMY\text{-}2}$ gene, which was identified in 34 FPA isolates

Table 2 continued.

Location, Sampling Dates	Nature of Sample Selection	Source and No. of ESCR *Escherichia coli* Isolates			Major ESCR Mechanism	Methods Used to Exclude Whole Bacterium Transmission	Comparison of MGEs Across Sources	
		Animal	Meat	Human			Methods	Results
Canada, 1999–2006 [28, 46]	Retrospectively selected human bla_{CMY-2} isolates	Cattle, n = 26	. . .	Clinical, n = 22 [69]	bla_{CMY-2}	PFGE	PBRT, RFLP with Bg1II	5 human clinical isolates carried bla_{CMY-2} on IncA/C plasmids that were >85% similar to those from 14 cattle on RFLP. 1 was >95% and 2 were > 90% similar
USA, 1998–2000 [31]	Any ESCR-EC from multiple sampling sites	Cow or pig, n = 59 Non-EC, n = 4[h]	. . .	Urine, n = 5 Blood, n = 1	bla_{CMY-2}	PFGE of all 65 ESCR *E. coli* isolates[i]	RFLP with EcoRI, BamHI and or PstI; Southern blot with bla_{CMY-2} probe	1 human isolate carried bla_{CMY-2} on a plasmid with highly similar restriction and Southern blot profiles to those from FPAs (*E. coli* and *Salmonella* spp)
Hong Kong, 2002–2010 [54]	Retrospectively collected $bla_{CTX-M-14}$ isolates	Pigs, n = 14 Chickens, n = 16 Cattle, n = 8 Pets, n = 20	. . .	Clinical (UTI), n = 37 Commensal (fecal), n = 65	$bla_{CTX-M-14}$	None performed	PBRT, size, RFLP, $bla_{CTX-M-14}$ genetic environment, plasmid sequencing	5 clinical and 4 commensal isolates carried $bla_{CTX-M-14}$ on IncFII plasmids with matching restriction profiles (pHK01) to at least 1 FPA isolate from each animal source
Taiwan, 2001–2002 [32]	Any ESCR-EC from multiple sampling sites	Poultry stool, n = 1 Pig stool, n = 7	Ground chicken, n = 14 Ground pork, n = 1	UTI, n = 11	bla_{CMY-2}	RAPD and ribotyping with EcoRI and HindIII	Plasmid size, RFLP with EcoRI, co-transferred resistance	7 human isolates carried bla_{CMY-2} on a 70–110 kb plasmid that had the same RFLP profile as 3 ground pork isolates. 2 of the human isolates also had identical pattern of co-transferred resistance

Abbreviations: EC, *E. coli*; ESBL, extended-spectrum beta-lactamase; ESCR, expanded-spectrum cephalosporin resistant; FPA, food-producing animal; MGE, mobile genetic element; PBRT, PCR-based replicon typing; PFGE, pulsed-field gel electrophoresis; pMLST, plasmid multilocus sequence typing; RAPD, randomly amplified polymorphic DNA; RFLP, restriction fragment-length polymorphism analysis; UTI, urinary tract infection.

[a] Identified 81.2% similarity between clinical (n = 3) and both meat isolates.

[b] *Klebsiella pneumoniae* (n = 1) and *Salmonella* spp (n = 4) isolates from healthy poultry feces.

[c] Isolates collected from Denmark, France, Netherlands, Belgium, Spain, Korea, and Canada.

[d] *Salmonella* spp from poultry.

[e] Poultry (n = 15), pork (n = 3), beef (n = 1).

[f] Exact number of isolates not mentioned, sourced from poultry (n = 31), pork (n = 2), and beef (n = 1) samples.

[g] One clonal $bla_{CTX-M-1}$–producing isolate in chicken meat and human sources was identified by PFGE; however, this was in the context of no other bla_{CTX-M} being identified in poultry and the single isolate being a perfect match, so the authors reasoned that this may have been a contaminant.

[h] *Salmonella* spp from bovine (n = 3) and porcine (n = 1) sources.

[i] Eight FPA and 2 human isolates underwent plasmid analysis.

Table 3. Molecular Evidence That Does Not Support Whole Bacterium Transmission

Location, Sampling Dates	Nature of Sample Selection	Source and Number of ESCR*Escherichia coli* Isolates			Whole Bacterium Comparison	
		Animal	Meat	Human	Methods	Results
International[a], 1967–2009 [34]	Highly selected	Source not specified, n = 45	Source not specified, n = 6	Source not specified, n = 486	Source distribution of PFGE pulsotypes	Of 170 pulsotypes, 65 contained multiple isolates, of which 5 contained isolates from FPA and humans. Pulsotypes containing FPA isolates were negatively associated with those containing human isolates in the UK
UK, 2008 [33]	No human isolates	. . .	Chicken, n = 141	None, cf UK study [70]	ESBL genotype	Meat isolates carry $bla_{\text{CTX-M-2/8}}$ genes, which are rare in human clinical isolates in the UK [70]
					MLST	None of the isolates were ST131
Hungary, 2006–2007 [35]	Any ESCR-EC	Poultry, n = 5 Pigs, n = 4 Calves, n = 7 Turkey, n = 1	. . .	Clinical, n = 45	ESBL genotype	Human isolates mostly carried $bla_{\text{CTX-M-15}}$, whereas FPA isolates carried $bla_{\text{CTX-M-1}}$
					Phylogenetic group	Human isolates were mostly B2 or D groups, whereas FPA isolates were mostly A or B1 groups
					Serotype	2/17 FPA isolates were typeable (O168, O8), whereas human isolates were predominantly O25b-ST131
					PFGE	Human and FPA isolates did not share pulsotypes
International[b], 2005–2009 [40]	Any ESCR-EC	Poultry, n = 133 Cattle, n = 35 Turkey, n = 17 Pig, n = 16	. . .	Clinical, n = 157[c]	Virulence genotype based on microarray	At 40% similarity threshold, 15/42 (36%), 1/10 (10%), and 3/26 (12%) of the clusters containing human isolates also contained animal isolates
					MLST and virulence genotype	1 human isolate from the Netherlands shared the MLST clonal complex (ST23) and virulence cluster with a poultry isolate from the same country; however, overall most human and FPA isolates of the same ST type did not belong to the same virulence cluster
UK, 2006–2009 [14]	Highly selected	Poultry: Healthy, n = 26 Sick, n = 3	. . .	Clinical, n = 10	ESBL genotype	$bla_{\text{CTX-M-1}}$, which was the main ESBL gene among FPA, is not the predominant ESBL in UK hospitalized patients [71]
					Virulence genotype	6/10 of virulence genes in human isolates were not identified in FPA
Spain, 2005 [38]	Sampled environmental waste	Poultry waste, n = 9	. . .	Urban waste, n = 1	Phylogenetic group	Isolates from poultry waste belonged to groups A and B1, whereas the isolate from urban waste belonged to group D
China, 2010–2013 [36]	Any ESCR-EC	Pigs, n = 31	. . .	Commensal, n = 46 Clinical, n = 36	ESBL genotype	$bla_{\text{CTX-M-3}}$ and $bla_{\text{CTX-M-15}}$ found in human but not FPA sources[d]
					Phylogenetic group	Group D prevalent in human isolates, whereas groups A and B1 prevalent in pigs
					MLST	ST10 group found in both human and FPA isolates
					PFGE	Isolates that belong to ST10 group were not clonal by PFGE
Japan, 2010 [37]	No human isolates	. . .	Chicken, n = 52[e]	None, compared with published studies [72, 73]	ESBL genotype	Meat isolates carry $bla_{\text{CTX-M-2/8}}$ genes, which are rare in human clinical isolates in Japan [73]
					Serotype	Meat isolates that carry $bla_{\text{CTX-M-15}}$ were not O25b, the main serotype in human isolates [72]

Table 3 continued.

Location, Sampling Dates	Nature of Sample Selection	Source and Number of ESCR*Escherichia coli* Isolates			Whole Bacterium Comparison	
		Animal	Meat	Human	Methods	Results
China, 2006–2009 [39]	Any ESCR-EC	Pigs, n = 167	. . .	Commensal, n = 280	ESBL genotypes	$bla_{CTX-M-1}$ and bla_{CMY-2} detected less frequently among FPA compared with human isolates
					PFGE	No evidence of clonal transmission among 59 bla_{CMY-2} isolates

Abbreviations: ESBL, extended-spectrum β-lactamase; ESCR-EC, expanded-spectrum cephalosporin-resistant *Escherichia coli*; FPA, food-producing animal; MLST, multilocus sequence typing; PFGE, pulsed-field gel electrophoresis.

[a] United States, Canada, Australia, Chile, France, South Korea, Lebanon, India, Italy, Peru, Portugal, Spain, and Switzerland.

[b] United Kingdom, Germany, and the Netherlands.

[c] All human isolates from the Netherlands (n = 108) were published previously [15].

[d] Study reported that ESBL distribution differed between FPAs and humans but no further specific data were provided.

[e] Eighty-five samples of retail beef and pork were also sampled but no ESCR *E. coli* was cultured.

[41, 42] (Table 4). Resistance plasmids of the same replicon type were identified in FPAs and humans; however, higher-resolution comparison by plasmid-MLST and PFGE found them to be heterogeneous.

Observational Epidemiological Studies

Four observational epidemiological studies fulfilled our inclusion criteria (Table 5). One ecological study and 2 case-control studies supported the hypothesis of FPAs as a source of ESCR-EC infections in humans [6, 43, 44]. One other case-control study found that urinary tract infections caused by the ST131 strain of ESCR-EC was negatively associated with frequent consumption of poultry, as compared to infections caused by non-ST131 ESCR-EC [45].

DISCUSSION

Through the use of a systematic review, we present scientific data related to the hypothesis that a proportion of human ESCR-EC infections may originate from an FPA source. Specifically, poultry in the Netherlands have been implicated as a likely source of human infections. A variety of FPA and geographical regions have also been investigated, but the evidence is mixed. Whole bacterium and MGE-mediated mechanisms of transmission may both play a role.

At a population level, WBT is a phenomenon that is most well characterized in the Netherlands, with 3 geographically and temporally matched molecular epidemiological studies being conducted there [15, 20, 21]. Unlike in other regions, the evidence in the Netherlands is consistent across studies, which used widespread and representative sampling methodologies and a range of well-validated molecular epidemiological methods. These studies also consistently demonstrated an unusually high proportion of human clinical extraintestinal infections that could have resulted from a poultry source.

One recent study does not support these findings, but the authors of that study highlight some limitations in their data, when compared to previous work [40]. Perhaps the most significant of these is that genetic relatedness was evaluated by comparing similarity of virulence genotypes, which is a less stable method than MLST and PFGE, because virulence genes are acquired by horizontal transfer rather than spontaneous mutations to the genetic backbone.

In the future, whole genome sequencing may be the most methodologically sound and cost-effective way of conducting molecular epidemiological analysis. In addition to providing the highest possible discriminatory power, this method also results in a permanent data output that can be made easily accessible for comparison between researchers.

Outside the Netherlands, 3 studies supported WBT, however, all have limitations that precluded stronger conclusions being

Table 4. Molecular Evidence That Does Not Support Plasmid-Mediated Transmission

Location, Sampling Dates	Nature of Sample Selection	Source and No. of ESCR *Escherichia coli* Isolates			Major ESCR Mechanism	Comparison of MGEs Across Sources		
		Animal	Meat	Human		Methods Used to Exclude Whole Bacterium Transmission	Methods Used to Exclude MGE Transmission	Results
Switzerland, 2009–2011 [42]	Prospectively selected 32 of 87 ESCR *E. coli* for analysis[a]	Poultry, n = 8 Calf, n = 5 Pig, n = 4 Lamb, n = 1	. . .	Commensal (fecal), n = 14	$bla_{CTX\text{-}M\text{-}1}$ $bla_{CTX\text{-}M\text{-}15}$	Phylogenetic group, serotype, and MLST	Plasmid PFGE with S1 nuclease	No relationship between plasmids from FPAs and human isolates
Italy, 2009 [41]	Highly selected from pool of previously analyzed isolates and plasmids	Poultry, n = 8	. . .	Clinical, n = 6	$bla_{CTX\text{-}M\text{-}1}$ $bla_{CMY\text{-}2}$	Phylogenetic group and MLST from prior study [49]	pMLST and RFLP with PstI	No relationship between plasmids from FPAs and human isolates

Abbreviations: ESCR, expanded-spectrum cephalosporin-resistant; FPA, food-producing animal; MGE, mobile genetic element; MLST, multilocus sequence typing; PFGE, pulsed-field gel electrophoresis; pMLST, plasmid multilocus sequence typing; RFLP, restriction fragment-length polymorphism analysis.

[a] Of the 32 isolates analyzed for ability to transfer ESCR gene, only 9 (4 poultry, 1 lamb, 4 human) were confirmed to be able to do so.

drawn in these locations. Specifically, 2 Spanish studies found only a very small number of related isolates [22, 23]. One of these studies analyzed a highly selected population of bacteria that had been collected over 17 years [23]. The North American study relied on molecular techniques with limited discriminatory power, did not distinguish between ESCR-EC and other forms of resistance, and lacked samples from human infection [24].

A considerable body of work conducted outside of the Netherlands has not demonstrated WBT. Seventeen publications, mostly from Spain, North America, the United Kingdom, and China, found evidence that did not support WBT using contemporary molecular epidemiological techniques [14, 25–28, 30–40, 46]. Supporting the validity of these negative findings, 8 of the studies identified MGE-mediated transmission instead of WBT [25–32] (Table 2).

It is not clear whether the concentration of evidence supporting WBT in the Netherlands represents a truly geographically defined phenomenon or relates to the limited breadth and methodology of research in other parts of the world. If a geographical finding is real, the relatively high rates of antimicrobial use in animal husbandry in the Netherlands may be a contributing factor [15]. Other potential factors, including differences in farming practice, the food production and supply chain, and human population dynamics, may warrant further investigation.

One area of concordance among the molecular epidemiological evidence of WBT is the identification of poultry as the most likely FPA source of ESCR-EC in humans. In several studies, retail meat samples from beef, pork, and other FPAs either did not harbor ESCR-EC [21, 37], or harbored strains clonally unrelated to human infections (Tables 2 and 3). Certain multilocus sequence types (ST10, ST155, and ST177), which have been found in poultry and poultry products, appear to be most frequently associated with a zoonotic risk [15, 20, 21]. Conversely, ST131, a common cause of human ESCR-EC infections, seems less likely to originate from poultry or other FPA sources [34].

This apparent host specificity to poultry, and identification of ST10 as a high-risk strain, is consistent with existing studies investigating zoonotic transmission of non-ESCR-EC [47–50]. It is also consistent with all 4 observational epidemiological studies (Table 5), which collectively suggest that poultry is the primary FPA host and that non-ST131 ESCR-EC strains may be more likely to mediate this zoonotic potential [6, 43–45]. The consistent identification of poultry as a source, rather than other FPAs, further supports the hypothesis of transmission.

Genomic data offer some explanation for this finding. Studies have demonstrated that human extraintestinal pathogenic *E. coli* and avian pathogenic *E. coli* share numerous virulence factors [51, 52]. Therefore, resistant strains that are able to infect

Table 5. Observational Epidemiological Studies

Location, Dates	Study Design	Data From Food-Producing Animals	Data From Human Isolates	Data for Comparison	Method of Association and Results
Europe[a], 2005–2008 [6]	Ecological	Prevalence of AMR among *Escherichia coli* from poultry, pigs, and cattle, using surveillance data[b]	Prevalence of AMR in human bloodstream *E. coli* infections, using surveillance data[c]	Correlation of ESCR between FPAs and human sources in 11 European countries	Statistical correlation between poultry and human ESCR across 11 European countries. $r = 0.76$ ($P < .05$, Spearman correlation coefficient)
Germany, 2011–2012 [43]	Case-control	None	Cases = hospitalized patients colonized with CA-ESCR *E. coli* Controls = patients colonized with CA non-ESCR *E. coli*	Verbal questionnaire including dietary habits in the past 12 mo; multivariate analysis	Frequently eating pork (≥3 meals per week) was independently associated with ESCR *E. coli* colonization (OR = 3.5; 95% CI, 1.8–6.6). Frequent consumption of poultry, beef, veal, and fish were not associated
USA, 2003–2004 [44]	Case-control	None	Cases = women with antimicrobial-resistant *E. coli* UTI Controls = women with fully susceptible *E. coli* UTI	Verbal questionnaire including dietary habits in the past 6 mo prior to UTI; adjusted OR	Women with UTI caused by ampicillin or cephalosporin-resistant *E. coli* reported more frequent consumption of pork (adjusted OR = 4.0; 95% CI, 1–15.5) Women with multidrug-resistant *E. coli* UTI more likely to report chicken exposure (adjusted OR = 3.7; 95% CI, 1.1–12.4)
Paris, 2008–2009 [45]	Case-control	None	Cases = inpatients with clinical sample positive for $bla_{CTX\text{-}M}$ positive ST131 *E. coli*[d] Controls = inpatients with clinical sample positive for $bla_{CTX\text{-}M}$ positive non-ST131 *E. coli*[d]	Evaluated consumption of poultry, beef, and raw meat; exposure to livestock using unreported method; multivariate analysis	Regular consumption of poultry products was negatively associated with ST131 ESCR *E. coli* infections (OR = 0.2; 95% CI, .1–.6); regular consumption of beef, consumption of raw meat, and exposure to livestock were not statistically associated

Abbreviations: AMR, antimicrobial resistant; CA, community acquired (identified <72 hours after admission); CI, confidence interval; ESCR, expanded-spectrum cephalosporin resistant; FPA, food-producing animal; OR, odds ratio; UTI, urinary tract infection.

[a] Eleven European countries: Austria, Denmark, Finland, France, Germany, Italy, the Netherlands, Norway, Spain, Sweden, and Switzerland.

[b] The Data from Animals originates from European Food Safety Authority.

[c] The Data from Humans originates from European Antimicrobial Resistance Surveillance.

[d] Consecutive inpatients across 10 hospitals in France with clinical *E. coli* sample positive for $bla_{CTX\text{-}M}$.

avian sources are also more likely to possess the cellular machinery required to infect humans.

The dynamics of MGE-mediated transmission of ESCR, between FPAs and humans, appear quite different to that of WBT. Studies that support MGE-mediated transmission are characterized by an extraordinary degree of diversity. Positive findings originate from many regions, collectively encompassing all major forms of livestock, across different species of Enterobacteriaceae with different ESCR resistance genes, plasmid types, and MGEs [27–32, 46, 53–57].

Data also suggest some differences between ESCR gene classes. MGE-mediated transmission of ESBL genes may be primarily mediated by whole plasmids [27, 29, 30, 53–55, 58], whereas bla_{CMY-2} may move within a smaller MGE owing to its close relationship with ISEcp1 [31], as described previously [10, 59].

The wide range of host Enterobacteriaceae and host FPA observed in this form of transmission reflect a more flexible and ubiquitous phenomenon, where transmission of resistance can occur independently of host bacterium specificity. There are, however, some limitations with the studies that support MGE-mediated transmission. Only a relatively small number of isolates underwent comprehensive plasmid sequence analysis, perhaps owing to high labor-intensity of this work. Most studies are based on lower-resolution measures of plasmid similarity, such as plasmid replicon types. Two recent European studies have demonstrated a poor correlation between plasmid replicon typing and higher-resolution techniques [41, 42]. However, the interpretation of these 2 studies is unclear, because only a small number of isolates underwent high-resolution comparison. Thus, the lack of support may reflect an insufficient sample size rather than a true absence of relatedness.

The strengths of our systematic review include a comprehensive search strategy, a structured approach to selecting articles, and integration of data from multiple fields, including molecular and observational epidemiology.

Our review has a number of limitations. First, many molecular epidemiology studies included in the review used inherently biased sampling methodologies, and only analyzed a small number of isolates. Selection bias, and the associated heterogeneity of sampling methodologies, limits the conclusions that can be drawn regarding the extent of the problem. Only 1 study was able to provide meaningful quantitative assessment of the burden of FPA-associated ESCR-EC within a population [15]. On the other hand, underpowered studies that did not find evidence of transmission can be difficult to interpret, because the absence of evidence may be due to an insufficient sample size rather than a true absence of relatedness.

Second, molecular epidemiological techniques have inherent limitations, with considerable variability in the discriminatory power afforded by the technique utilized [60]. Underlying this limitation is the fact that genetic relatedness exists on a spectrum. Dichotomous conclusions about "transmission" between 2 sources frequently require an element of subjective judgment. The emerging use of whole-genome sequencing in molecular epidemiology of Enterobacteriacae has already confirmed the inherent limitations of older techniques [61, 62], and will certainly shape future research on this topic. Furthermore, genetic similarity also does not necessarily prove the origin of transmission. For example, an external source that contaminates FPAs and humans would also result in genetic similarity. The potential for transmission mechanisms external to the food chain deserves further research.

Research bias and publication bias may have influenced our results. Most research effort has focused on a limited number of geographical areas, almost all within the developed world. The impact of publication bias is harder to ascertain, but likely present. We identified a considerable number of negative studies in this area, although approximately half of these results were presented in publications with other positive findings.

Owing to the specificity of the research question, we have also limited the review to evaluate human infections caused by ESCR-EC. Extraintestinal and intestinal human infection with other species of ESCR Enterobacteriaceae of zoonotic origin, such as *Salmonella* species, also appears to be a problem [31, 46].

Similarly, we have investigated only unidirectional transmission from animal to humans. Transmission in both directions is possible, and may be responsible for the original incursion of resistance into animal species [63]. A recent study from the Netherlands indicates that the dynamics of the secondary spread of FPA-associated resistant strains within human communities are complex, and will require further research [64].

In conclusion, there is evidence that a proportion of human extraintestinal ESCR-EC infections originate from FPAs. Poultry appears to be a more likely source than other FPAs based on current evidence. Transmission of whole ESCR-EC and mobile ESCR genetic elements from poultry to humans probably occurs, but the specific parameters surrounding this, including the magnitude and geographical extent of the problem, remain inadequately understood. A broader sampling methodology, including environmental and human commensal samples, and higher-resolution molecular comparisons are required. Such research would also lend insight into the specific mechanisms involved in transmission and potentially offer a means for public health intervention.

Supplementary Data

Supplementary materials are available at *Clinical Infectious Diseases* online (http://cid.oxfordjournals.org). Supplementary materials consist of data provided by the author that are published to benefit the reader. The posted materials are not copyedited. The contents of all supplementary data are the sole responsibility of the authors. Questions or messages regarding errors should be addressed to the author.

Note

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All authors have submitted the ICMJE Form for Disclosure of Potential Conflicts of Interest. Conflicts that the editors consider relevant to the content of the manuscript have been disclosed.

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