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REVIEW

Global Extraintestinal Pathogenic *Escherichia coli* (ExPEC) Lineages

Amee R. Manges,[a] Hyun Min Geum,[a] Alice Guo,[a] Thaddeus J. Edens,[b] Chad D. Fibke,[a] Johann D. D. Pitout[c,d]

[a]School of Population and Public Health, University of British Columbia, Vancouver, British Columbia, Canada
[b]Devil's Staircase Consulting, West Vancouver, British Columbia, Canada
[c]Calgary Laboratory Services, Calgary, Alberta, Canada
[d]Cumming School of Medicine, University of Calgary, Calgary, Alberta, Canada

SUMMARY Extraintestinal pathogenic *Escherichia coli* (ExPEC) strains are responsible for a majority of human extraintestinal infections globally, resulting in enormous direct medical and social costs. ExPEC strains are comprised of many lineages, but only a subset is responsible for the vast majority of infections. Few systematic surveillance systems exist for ExPEC. To address this gap, we systematically reviewed and meta-analyzed 217 studies (1995 to 2018) that performed multilocus sequence typing or whole-genome sequencing to genotype *E. coli* recovered from extraintestinal infections or the gut. Twenty major ExPEC sequence types (STs) accounted for 85% of *E. coli* isolates from the included studies. ST131 was the most common ST from 2000 onwards, covering all geographic regions. Antimicrobial resistance-based isolate study inclusion criteria likely led to an overestimation and underestimation of some lineages. European and North American studies showed similar distributions of ExPEC STs, but Asian and African studies diverged. Epidemiology and population dynamics of ExPEC are complex; summary proportion for some STs varied over time (e.g., ST95), while other STs were constant (e.g., ST10). Persistence, adaptation, and predominance in the intestinal reservoir may drive ExPEC success. Systematic, unbiased tracking of predominant ExPEC lineages will direct research toward better treatment and prevention strategies for extraintestinal infections.

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Address correspondence to Amee R. Manges, amee.manges@ubc.ca.

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INTRODUCTION

Extraintestinal pathogenic *Escherichia coli* (ExPEC) strains are versatile bacteria that can cause urinary tract, bloodstream, prostate, and other infections at nonintestinal sites. They typically occupy a niche in the intestinal microbiota of humans (and other animals), and it is from this reservoir that they emerge to cause extraintestinal infections (1). ExPEC strains are responsible for an enormous number of human infections globally, both in health care-associated and community settings (2, 3), and a limited set of ExPEC lineages are responsible for most infections (4). ExPEC strains also have the infamous distinction of being associated with the acquisition of new and troubling antibiotic resistance genes (5, 6). The clinical and economic impact of these infections and their optimal management, especially in the face of increasing antibiotic resistance, are challenging and underappreciated (7, 8).

ExPEC strains have been alternatively defined by the number and constellation of virulence genes they possess ("special pathogenicity" definition) and by their identification as predominant lineages in the gut prior to causing extraintestinal infections by mass action ("prevalence" definition) (9–11). Unfortunately, neither definition is truly adequate, nor are the definitions mutually exclusive. Despite the overrepresentation of many classic ExPEC virulence genes (12) in many lineages causing infection, there is still uncertainty about what defines or differentiates commensal *E. coli* and facultative ExPEC pathogens (13). Important differences among ExPEC strains clearly do exist, as demonstrated by the emergence of pandemic lineages such as *E. coli* sequence type 131 (ST131), along with its highly drug-resistant ST131 H30Rx (C2) sublineages (4, 14, 15). Genetic determinants of persistence, predominance, and competitiveness within the gut microbiota, which are not clear at present, may help explain the success of some of these lineages (16).

For this review, we define ExPEC based on study identification of *E. coli* as either the cause of extraintestinal infection or presence in a diagnostic, screening, or surveillance specimen in addition to membership in a major ExPEC lineage. An ExPEC ST is defined as major based on its frequency of detection (in all included studies) and by its estimated summary proportion. Multilocus sequence typing (MLST) is the most common method of identifying ExPEC-associated clonal complexes or lineages. However, whole-genome sequencing (WGS)-based lineage classification is gradually supplanting the 7-locus MLST-based sequence type (ST) and related classification systems. We define the major ExPEC lineages using the Achtman MLST classification scheme (17). Most studies included in this review lack detailed virulence gene characterizations; therefore, strict classification of ExPEC by virulence is not possible. Results will unavoidably include both commensal *E. coli* and true ExPEC.

The majority of studies investigating ExPEC linages are constrained by their geographic locations, time periods, or retrospectively assembled isolate collections and therefore cannot address questions about the global epidemiology of *E. coli* causing extraintestinal human infections. MLST databases can be leveraged to investigate the epidemiology of ExPEC lineages (18); however, strain information, location, source, collection time, and other epidemiologic information are often limited or absent. In order to describe global ExPEC lineages and leverage information from a large number of ExPEC studies conducted around the world, we performed a systematic review of the published literature examining ExPEC recovered from humans. Studies of ExPEC from the fields of molecular microbiology, molecular epidemiology, and clinical microbiology were identified. We examine the geographic and temporal distribution of major ExPEC STs. We describe the contribution of major ExPEC STs to extraintestinal infections versus intestinal colonization. We investigate differences in ExPEC ST distribution by study isolate selection or inclusion criteria. Many studies include resistance phenotype as a criterion for isolate selection or inclusion, and inclusion criteria may result in an ST

distribution bias. The purpose of this investigation is to reflect on and to harness information from many individual studies conducted to characterize the *E. coli* strains that cause human extraintestinal infections, to provide context for different ExPEC STs (e.g., temporal or geographic differences), and to help prioritize STs for future study.

METHODS

Search Strategy and Selection Criteria

We conducted a systematic review to characterize the contribution of global ExPEC lineages to human infections. This review is reported in accordance with the PRISMA statement (20). We searched Medline (including in-process and other nonindexed citations) and Embase, using Ovid for both, as well as Scopus from 1 January 1995 to 1 January 2018. All search strings were developed with the assistance of a librarian. Search strings are provided in the supplemental material. Study inclusion criteria were the following: (i) original investigation of extraintestinal pathogenic *E. coli* (including related search terms such as uropathogenic *E. coli*) but not other *E. coli* pathotypes (e.g., *E. coli* O157:H7 or EHEC); (ii) investigation of *E. coli* recovered from humans only or from humans and other reservoirs, and (iii) characterization of *E. coli* strains by MLST or WGS. Genotyping by MLST and/or WGS was required in order to standardize high-resolution lineage definitions that were comparable across the widest array of studies; image-based tools such as pulsed-field gel electrophoresis (PFGE) or other PCR-based molecular fingerprinting tools produce data that are not easily portable or comparable and were excluded. The purpose of the review was to examine the global contribution of all major ExPEC STs to extraintestinal infection; therefore, for consistency, studies that implemented full MLST protocols were included. If study results provided a breakdown of STs or if an alternate MLST method was used but results were mapped back to the Achtman scheme, they were also included. We placed no restrictions on language, year of publication, or study type. We excluded studies that included fewer than 20 unique *E. coli* isolates (unless they were WGS studies). Reviews, commentaries, or editorials were also excluded from the analysis. Studies had to include humans but could also report results for animals or other sources although MLST results only from human ExPEC isolates are reported in this review. Studies could include *E. coli* recovered from stool or *E. coli* recovered from sites of extraintestinal infections; this allowed us to compare the ST distributions in ExPEC infections and the intestinal reservoir. Risk of bias domains was not investigated in this review due to study heterogeneity. Individual patient data were not available in most studies, so ST distributions were analyzed in aggregate. Two investigators (H. M. Geum and A. Guo) independently assessed titles and abstracts for eligible publications. If eligibility could not be determined, the full article was retrieved, and the article methods were screened. We hand searched review articles that we identified for additional references. Discrepancies over study inclusion were adjudicated by consensus.

Data Abstraction

Two reviewers (H. M. Geum and A. Guo) performed data abstraction for included publications. Data were abstracted using a standardized form. The following study-level characteristics were abstracted: number of *E. coli* isolates investigated (the total and the number characterized by MLST or WGS), geographic region, sample collection dates, antimicrobial susceptibility testing (if available), outpatient or inpatient population, genotyping method (MLST or WGS), MLST method (Achtman, Whittam, or Pasteur) (18, 21, 22), and number of isolates by specific ST. Age and sex were not individually abstracted as age range and sex distribution varied widely by study and were frequently not reported. Some new ST assignments and a small number of rare STs were excluded from our final review data set. For certain studies, it was not clear whether the specific ST or ST complex was being reported. Ultimately, 215 specific STs were selected from the published studies and are reported here. The distribution of STs was investigated by study isolate source, selection criteria, geographic region, and start of sample collection by year.

Study isolate source was classified as follows in our data set: (i) colonization (either isolates from surveillance cultures or isolates from healthy individuals, primarily recovered from stool), (ii) any source (inclusion of ExPEC from multiple infections or sources), (iii) bloodstream infection or blood source (including true bloodstream infections, sepsis or bacteremia, or blood source isolate), (iv) urinary tract infection (UTI) (including cystitis, pyelonephritis, or urine source isolate), (v) respiratory tract infection (including *E. coli* from lung or sputum cultures), and (vi) other sources, which included studies of *E. coli* recovered from cases of orthopedic infections, cystic fibrosis, inflammatory bowel disease (IBD), meningitis, and necrotizing enterocolitis.

Many studies included a preselection strategy in their sampling scheme, which was captured during data abstraction. For example, a study might provide MLST data on extended-spectrum β-lactamase (ESBL)-producing *E. coli* isolates only or on sepsis-associated *E. coli* only, meaning that the results are representative only of that particular subset of resistant *E. coli*, infection type, or source. We investigated the distribution of STs in studies that selected isolates for inclusion based on ESBL-producing, carbapenem- or fluoroquinolone-resistant, or multidrug-resistant (MDR) phenotypes versus studies that included isolates based on isolate availability or source without regard to resistance phenotype. To augment conclusions from the systematic review, results from selected WGS studies and larger MLST studies are included in the final part of the Results section as these studies provide a deeper perspective on ExPEC epidemiology, evolution, and pathogenesis.

Statistical Analyses

A meta-analysis was performed including all studies identified in the systematic review. The 20 most common STs, based on frequency of detection and by estimated overall summary proportion, were defined as major ExPEC STs. Calculation of overall proportions, 95% confidence limits, and I^2 (study heterogeneity) values were estimated using meta-analysis random-effects models, implemented through the meta package, version 4.9-2, using the metaprop function in R, version 3.5.2. Summary proportions by ST are reported by study characteristics, including study isolate selection criteria, geographic area, source, and isolate collection start date. Estimation of summary proportion by study characteristic was not performed if fewer than three studies were available for analysis. The I^2 statistic describes the percentage of variation across studies that is attributable to study heterogeneity rather than random variation. The results for each model include Cochran's Q (analogous to a chi-square test), which indicates heterogeneity in summary proportions for each ST within a subgroup (e.g., geographic region) analysis. All summary proportions, I^2 estimates, confidence limits, and Cochran's Q are reported for each model in supplemental files.

RESULTS

The search resulted in the identification of 1,964 nonduplicate published articles. The titles and abstracts were reviewed, and 1,508 did not meet the inclusion criteria and were excluded (Fig. 1). Full-text documents were retrieved for 456 articles. After full-text review, 217 articles were included for data abstraction, including 173 articles that reported results for MLST only or MLST plus WGS. A further 44 articles were identified that reported WGS results only. The investigation of ExPEC lineages is based on these 217 studies.

Summary of Articles

MLST results were reported in 173 articles (21–194). Almost all of the studies implemented the Achtman MLST scheme. Two studies used the Whittam MLST scheme and were excluded from the review (109, 157). Six studies implemented the Pasteur Institute's MLST scheme (21). The ST results of four (21, 130, 170, 176) of these six studies were partially, but unambiguously, converted to STs corresponding to the Achtman scheme (195). Therefore, the distribution of human ExPEC STs was derived from 169 studies. The full review data set is provided in Table S1 in the supplemental material. These 169 studies include MLST data for 15,538 isolates and represent a very

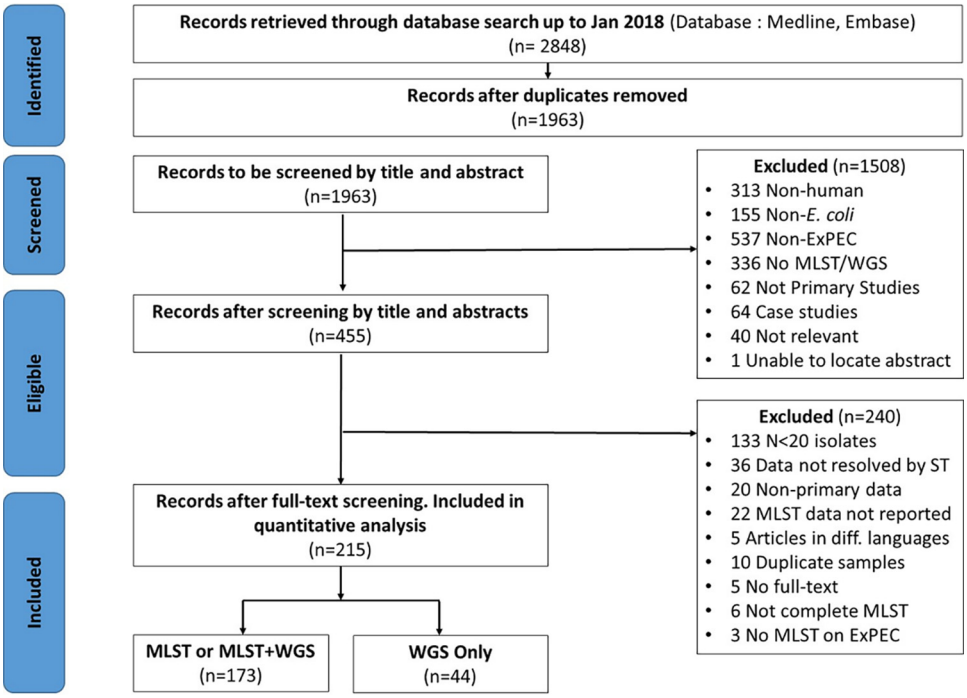

FIG 1 PRISMA flow diagram for this systematic review. This diagram shows the selection of studies included in the systematic review of ExPEC lineages (20).

wide range of scientific disciplines and diverse research questions, sampling methods, study populations, time periods, and regions. Studies including whole-genome sequencing of ExPEC isolates are listed in Table S2.

Studies reported *E. coli* sample sizes of anywhere between 20 and 3,060 isolates. Multiple studies selected isolates from large national or regional collections of *E. coli* based either on specimen source (e.g., urine or stool), infection type (e.g., urinary tract or bloodstream infection), or resistance screening, so the initial *E. coli* sample sizes were larger than the final number of genotyped *E. coli* isolates. Therefore, we included the number of *E. coli* isolates from each study that were eligible for MLST or WGS testing. The sample sizes of *E. coli* characterized by MLST ranged from 5 to 2,166 isolates. A summary of study characteristics is provided in Table 1. Many studies ($n = 112$, 66%) preselected ExPEC isolates for study inclusion based on a specific antibiotic resistance phenotype or genotype. Seventy-two (64%) of these studies restricted their MLST analyses to ESBL-positive ExPEC. *E. coli* isolates from a wide range of extraintestinal infections were represented in the studies, including 35 (21%) studies that investigated UTIs and 26 (15%) studies that included isolates recovered from bloodstream or meningitis cases. The patient population was split between inpatient and outpatients, with many ($n = 73$, 43%) studies including isolates from both inpatients and outpatients. Europe was overrepresented, with 82 (49%) studies, followed by Asia (24%) and North America (11%). This review covers the period since 1995 when MLST was first introduced (196) although the majority of studies were conducted since 2000. Five studies (3%) included ExPEC recovered from the 1990s, 31 (18%) included isolates from 2000 and 2005, 76 (45%) included isolates from 2006 to 2010, and 44 (26%) included isolates from 2011 to 2016. Two studies examined ExPEC collections retrospectively, one examined ExPEC recovered from 1956 to 2000 (45), and another study examined isolates from 1988 to 2003 (28). Eleven studies did not report the date or year in which they started collecting specimens or isolates.

ExPEC Sequence Types

A summary of all 215 MLST STs detected in one or more studies is provided in Table S1. Twenty major ExPEC STs, as defined by the number of positive studies and

TABLE 1 Characteristics of included ExPEC studies

Study characteristic	No. of studies (%)
Total studies	169 (100)
Study ExPEC selected based on resistance[a]	112 (66)
Extended spectrum β-lactamase	72 (64)
Fluoroquinolone/quinolone	10 (9)
Multidrug resistance	9 (8)
Beta-lactamase	8 (7)
Carbapenem	7 (6)
Fosfomycin	2 (2)
Nitrofurantoin	2 (2)
Colistin	1 (1)
Fully susceptible	1 (1)
ExPEC source[a]	
Any infection	72 (43)
Urinary tract infections	49 (29)
Bloodstream infection	26 (15)
Colonization	17 (10)
Orthopedic infection	2 (1)
Cystic fibrosis	1 (0.6)
Irritable bowel disease	1 (0.6)
Necrotizing enterocolitis	1 (0.6)
Patient population	
Any inpatients	110 (65)
Any outpatients	103 (61)
Both in- and outpatients	73 (43)
Not reported	28 (17)
Geography	
Europe	82 (49)
Asia	41 (24)
North America	18 (11)
Africa	12 (7)
Middle East	5 (3)
South America	3 (2)
Central America	2 (1)
Oceania	2 (1)
Global	3 (2)
Not reported	1 (0.6)

[a]Some studies selected for more than one type of resistance phenotype or included a combination of infections or sources.

estimated summary proportions, are shown in Table 2. These include ST131, ST69, ST10, ST405, ST38, ST95, ST648, ST73, ST410, ST393, ST354, ST12, ST127, ST167, ST58, ST617, ST88, ST23, ST117, and ST1193 (by decreasing study positivity). These top STs accounted for 85% of *E. coli* isolates for which ST results were reported in all included studies. Not surprisingly, ST131 was detected in over 90% of studies, while the next most common STs (ST69 or ST10) were detected in 50% of studies overall. The maximum number of STs identified in any one study was 84, while some studies reported information on a few STs. If a study investigated only a single ST, it was excluded from analysis. As expected, the study heterogeneity estimated by I^2, which assesses heterogeneity beyond random variation, was large and ranged from 0.37 to 0.94 (Table 2). An I^2 of over 0.75 is generally considered to indicate that study results are very heterogeneous.

ExPEC Sequence Types by Isolate Inclusion Criteria

Most studies included ExPEC isolates based on the presence of specific antimicrobial resistance phenotypes, largely ESBL production (Fig. 2; Table S3). This inclusion criterion may influence the identification of important STs in a given study. Other studies, those that did not select based on resistance phenotype, selected isolates based on infection type or specimen source (e.g., UTI isolates) or were convenience samples of ExPEC

TABLE 2 Summary proportions for the top 20 ExPEC STs: meta-analysis results[a]

Sequence type	No. of positive studies	Summary proportion (95% CI)	I^2 (95% CI)
ST131	133	0.24 (0.21, 0.27)	0.94 (0.94, 0.95)
ST69	87	0.05 (0.05, 0.06)	0.68 (0.60, 0.74)
ST10	85	0.05 (0.04, 0.06)	0.81 (0.77, 0.84)
ST405	81	0.04 (0.04, 0.05)	0.74 (0.68, 0.79)
ST38	72	0.06 (0.04, 0.07)	0.83 (0.79, 0.86)
ST95	71	0.07 (0.06, 0.09)	0.87 (0.84, 0.89)
ST648	67	0.04 (0.03, 0.05)	0.71 (0.63, 0.77)
ST73	62	0.08 (0.07, 0.10)	0.86 (0.83, 0.89)
ST410	45	0.03 (0.03, 0.05)	0.69 (0.58, 0.77)
ST393	42	0.03 (0.02, 0.03)	0.75 (0.66, 0.81)
ST354	40	0.02 (0.01, 0.03)	0.63 (0.49, 0.74)
ST12	37	0.04 (0.03, 0.05)	0.56 (0.36, 0.70)
ST127	36	0.03 (0.03, 0.04)	0.46 (0.19, 0.63)
ST167	35	0.03 (0.02, 0.04)	0.69 (0.57, 0.78)
ST58	35	0.02 (0.01, 0.03)	0.73 (0.62, 0.80)
ST88	34	0.03 (0.02, 0.04)	0.84 (0.79, 0.88)
ST617	34	0.02 (0.01, 0.03)	0.53 (0.30, 0.68)
ST23	31	0.03 (0.02, 0.05)	0.87 (0.83, 0.90)
ST117	30	0.02 (0.01, 0.02)	0.37 (0.01, 0.59)
ST1193	28	0.03 (0.02, 0.05)	0.85 (0.79, 0.89)

[a]Summary proportions (95% CI) and I^2 (95% CI) were estimated using meta-analysis random-effects models, implemented through the meta package, version 4.9-2, using the metaprop function in R, version 3.5.2. The I^2 statistic describes the percentage of variation across studies that is attributable to study heterogeneity rather than random variation. Summary proportions were calculated across multiple, diverse studies, including very different study populations, multiple specimen types, and clinical outcomes and should not be interpreted as population-level estimates of an individual ST's contribution to the global burden of infection.

isolates available to study investigators. Figure 2 shows the estimated overall proportion for the most common 20 ExPEC STs stratified by whether studies selected isolates based on a resistance criterion ($n = 112$) or not ($n = 57$). Six studies were excluded from this analysis as they selected for isolates exhibiting resistance to amdinocillin and/or nitrofurantoin (2 studies), colistin (1 study), or fosfomycin (2 studies).

The primary resistance phenotypes used for isolate selection in these 163 studies included beta-lactam resistance or ESBL production, quinolone or fluoroquinolone resistance, and any multidrug resistance. A small number of studies included carbapenem-resistant ExPEC. Selection based on ESBL production was by far the most common resistance criterion used, and importantly all of the top 20 STs were detected in multiple collections of ESBL-positive isolates (Table 1; Table S3). The estimated overall proportion of ST131 in studies varied by the resistance selection criterion used in the study design. Estimated summary proportions for MDR, ESBL-producing, and carbapenem- and fluoroquinolone-resistant ST131 isolates were 0.62 (95% confidence interval [CI], 0.40, 0.80), 0.29 (95% CI, 0.25, 0.34), 0.18 (95% CI, 0.10, 0.31), and 0.32 (95% CI, 0.21, 0.45), respectively. In contrast, the ST131 prevalence was only 0.17 (95% CI 0.14, 0.20) in studies without resistance selection (Q test $P < 0.001$). In general, studies selecting on resistance phenotype produced higher estimated summary proportions (in at least one resistance category) than studies that employed no resistance inclusion criterion. This was true except for ST95 (Q test $P < 0.001$) and ST73 (Q test $P < 0.001$) and, to a lesser extent, ST69 (Q test $P = 0.001$), ST12 (Q test $P = 0.009$), and ST127 (Q test $P = 0.003$) (Fig. 2; Table S3). Selection for carbapenem-resistant isolates resulted in higher estimated summary proportions for ST38, ST648, and ST410 isolates. Interestingly, these data suggest that summary proportions for ST10, ST58, ST88, ST617, ST23, and ST1193 do not differ between studies employing ESBL-positive selection and studies without resistance selection. In one study of fully susceptible ExPEC isolates, ST131 was not identified at all. Of the 80 isolates characterized by MLST, 35 (44%) belonged to the ST69, ST95, ST73, ST12, and ST127 lineages (80). This suggests that the infection burden of ExPEC lineages such as ST131 (especially MDR ST131) and ST38 may

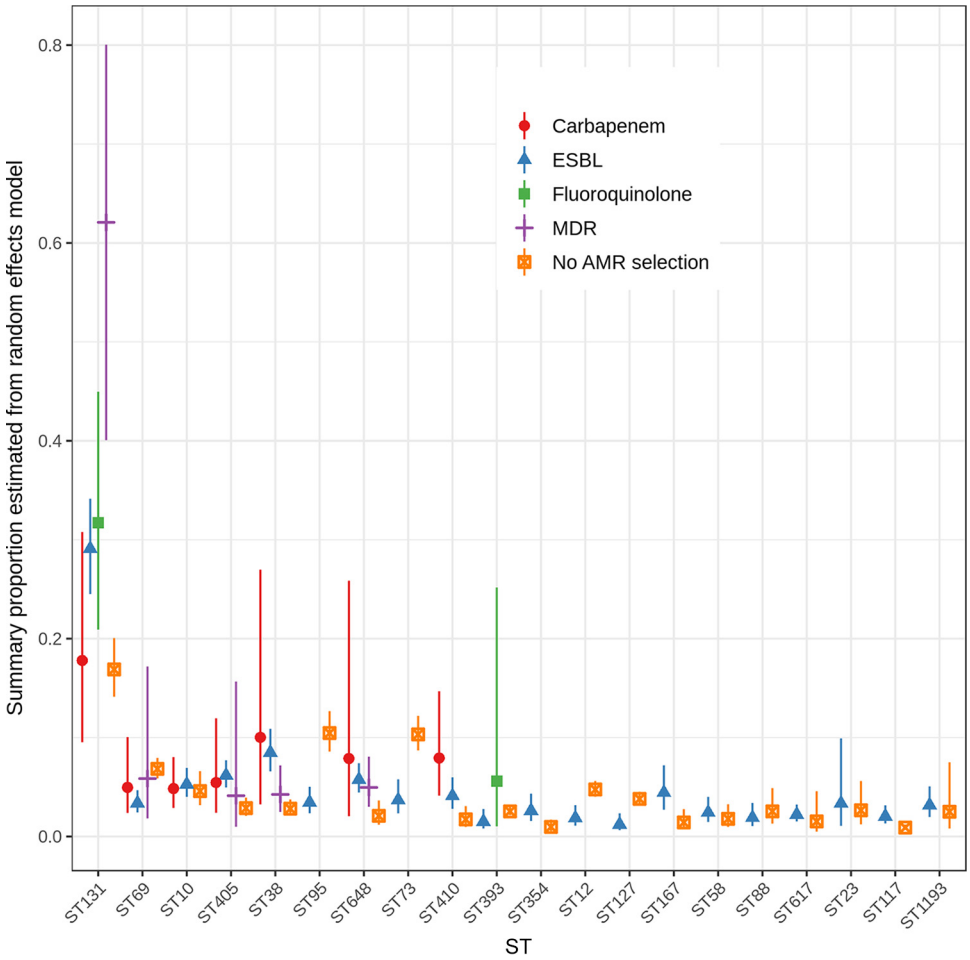

FIG 2 Summary proportions from random-effects models for the most common ExPEC STs by study isolate inclusion criteria. Six studies were excluded from this analysis as they selected for isolates exhibiting specific drug resistance phenotypes, including amdinocillin and nitrofurantoin (1 study), nitrofurantoin alone (1 study), colistin (1 study), and fosfomycin (2 studies), or only for fully susceptible *E. coli* isolates (1 study). AMR, antimicrobial resistance.

be overestimated, while that of ST95 and ST73 may be underestimated if selection is based on antimicrobial resistance phenotype or genotype. These differences in estimates across studies suggest that inferences about the clinical and public health importance of specific ExPEC STs need to consider study inclusion criteria.

ExPEC Sequence Types by Geographic Area

As expected, the summary proportions for ST131 were elevated for each geographic region compared to those for other major STs. Summary proportion estimates for ST131 were higher for studies from Asia (0.23; 95% CI, 0.19, 0.28) and Europe (0.25; 95% CI, 0.21, 0.30) and lower in African (0.19; 95% CI, 0.12, 0.28) and North American (0.21; 95% CI, 0.13, 0.31) studies. However, these summary proportions were not significantly different (Q test $P = 0.57$) (Fig. 3; Table S4). ST648 and ST617 were the only other STs for which sufficient data from African studies were available; the summary proportion for ST617 (0.10; 95% CI, 0.03, 0.28) (Q test $P = 0.004$) was considerably higher than for studies from Asia and Europe. Notably, common STs, including ST95, ST393, and ST354, were absent from, and the summary proportion for ST73 was especially low in, the African studies (Table S1). Underrepresentation of these STs might be the result of isolate selection criteria as a high proportion (83%) of African studies selected isolates based on resistance phenotype. Summary proportions may also underestimate African

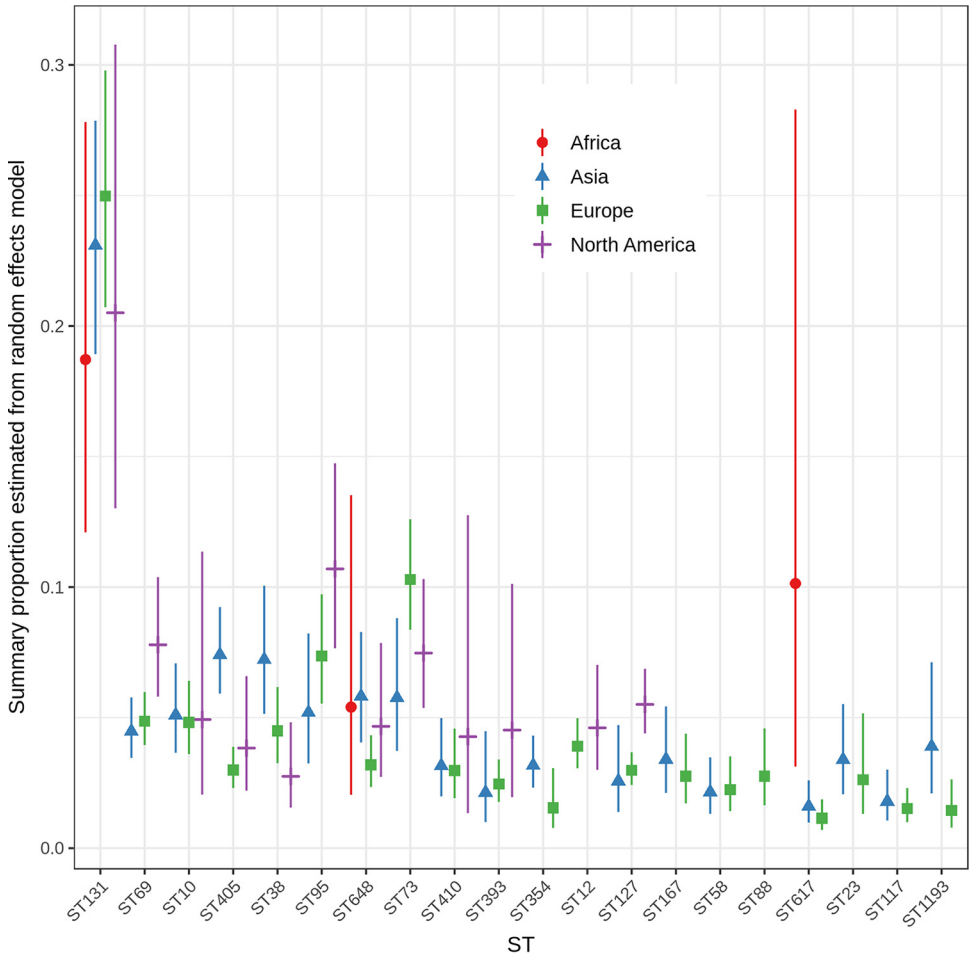

FIG 3 Summary proportions from random-effects models for the most common ExPEC STs by geographic region. Six studies were not included: three included global collections of ExPEC, two studies were from Australia only, and one study did not report the geographic source of isolates analyzed.

ExPEC ST diversity due to MLST reference database limitations or due to the scope or sampling methods of included studies.

In 41 studies conducted in Asia, 71% selected isolates based on resistance phenotype. In addition to ST131, Asian studies yielded the highest summary proportions, by region, for ST405 (0.07; 95% CI, 0.06, 0.09) (Q test $P < 0.001$), ST38 (0.07; 95% CI, 0.05, 0.10) (Q test $P = 0.01$), ST1193 (0.04; 95% CI, 0.02, 0.07) (Q test $P = 0.024$), and possibly ST648 (0.06; 95% CI, 0.04, 0.08) (Q test $P = 0.08$), while Asian studies exhibited a lower overall estimate for ST73 (0.06; 95% CI, 0.04, 0.09) (Q test $P = 0.03$) (Fig. 3; Table S4). ST12 and ST88 were identified in fewer than 3 studies of the 41 studies from Asia.

In 82 studies from Europe, 67% selected isolates based on resistance phenotype. European studies reported the highest overall proportion of ST131 (0.25; 95% CI, 0.21, 0.30) and a higher overall proportion of ST73 (0.25; 95% CI, 0.21, 0.30) (Q test $P = 0.03$). The estimated proportions for ST405 (0.03; 95% CI, 0.02, 0.04) and ST648 (0.03; 95% CI, 0.02, 0.04) tended to be lower than point estimates from other regions (Fig. 3; Table S4).

In 18 studies set in North America, 44% selected isolates based on resistance phenotype. Reports from North America yielded higher overall proportions of ST95 (0.11; 95% CI, 0.08, 0.15) (Q test $P = 0.037$), ST69 (0.08; 95% CI, 0.06, 0.10) (Q test $P = 0.031$), and ST127 (0.06, 95% CI, 0.04, 0.07) (Q test $P < 0.001$). The proportion of ST38 (0.03; 95% CI, 0.02, 0.05) appears to be lower in North America than elsewhere, and ST354, ST167, ST58, ST88, ST617, ST23, ST117, and ST1193 were identified in fewer than three North American studies (Fig. 3; Table S4). Detection of these STs may be

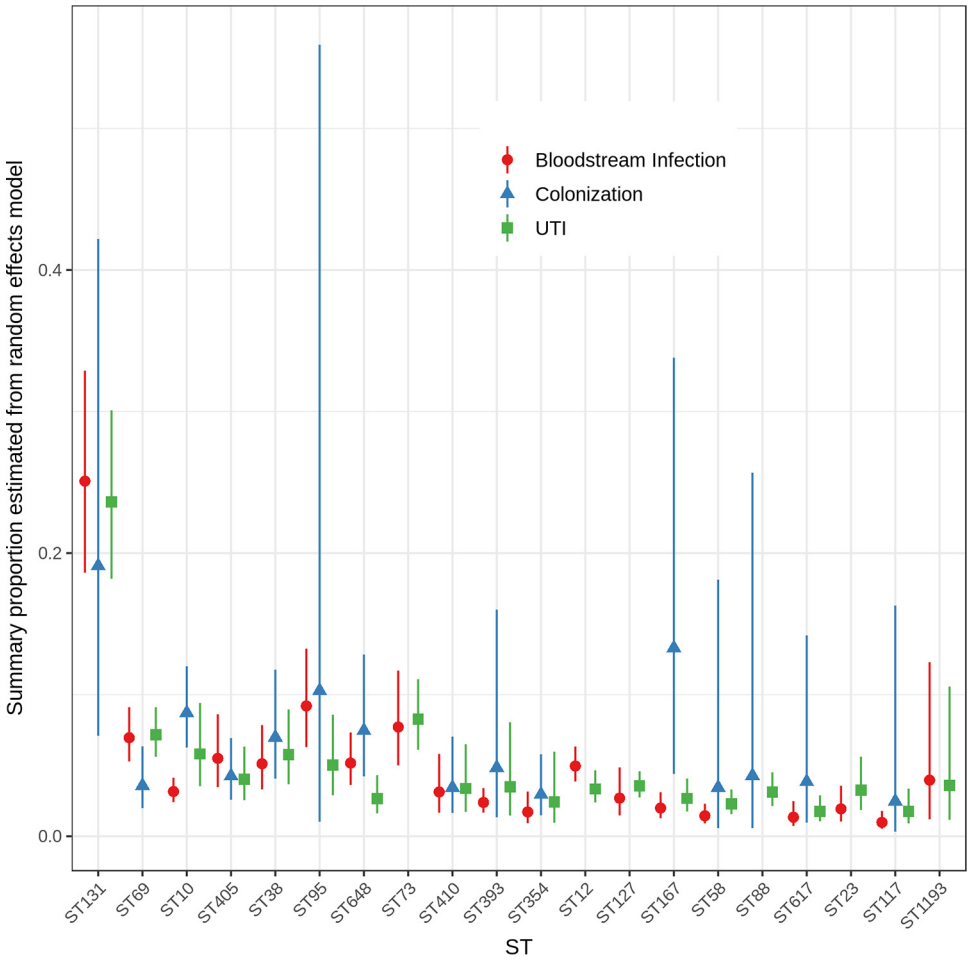

FIG 4 Summary proportions from random-effects models for the most common ExPEC STs by source. Only those studies that examined isolates recovered exclusively from one source category were included. One study of bloodstream isolates also included isolates from orthopedic infections and was included in the bloodstream/meningitis group.

influenced by the limited number of studies undertaken in North America. Interestingly, the summary proportions for ST10 were similar for all regions.

Five studies each recovered isolates from the Middle East and from Central or South America. Studies originating from Central and South America detected ST131, ST69, ST73, and ST62 most commonly, while studies originating from the Middle East detected ST131, ST38, ST410, ST10, and ST617 most commonly. As the sample sizes for these regions are small, they are not included in the data shown in Fig. 3. Two studies included isolates from Australia only, and one study did not report the geographic source of isolates analyzed.

ExPEC Sequence Types by Source

Of the 169 included ExPEC studies, only 79 studies included isolates from a single specimen source or infection type (Table 1). Even though we restricted our analyses to a single reported source, there will be an unavoidable mixture of ExPEC and non-ExPEC in these results. In the 90 studies that included isolates from multiple sources, detailed ST breakdowns by source were not provided in their reports, so these studies could not be included in the meta-analysis. Only 17 studies focused specifically on colonization or surveillance isolates.

The presence of specific STs in the studies varied only modestly by *E. coli* source (Fig. 4; Table S5). All 20 major STs were identified in three or more studies examining UTI (or

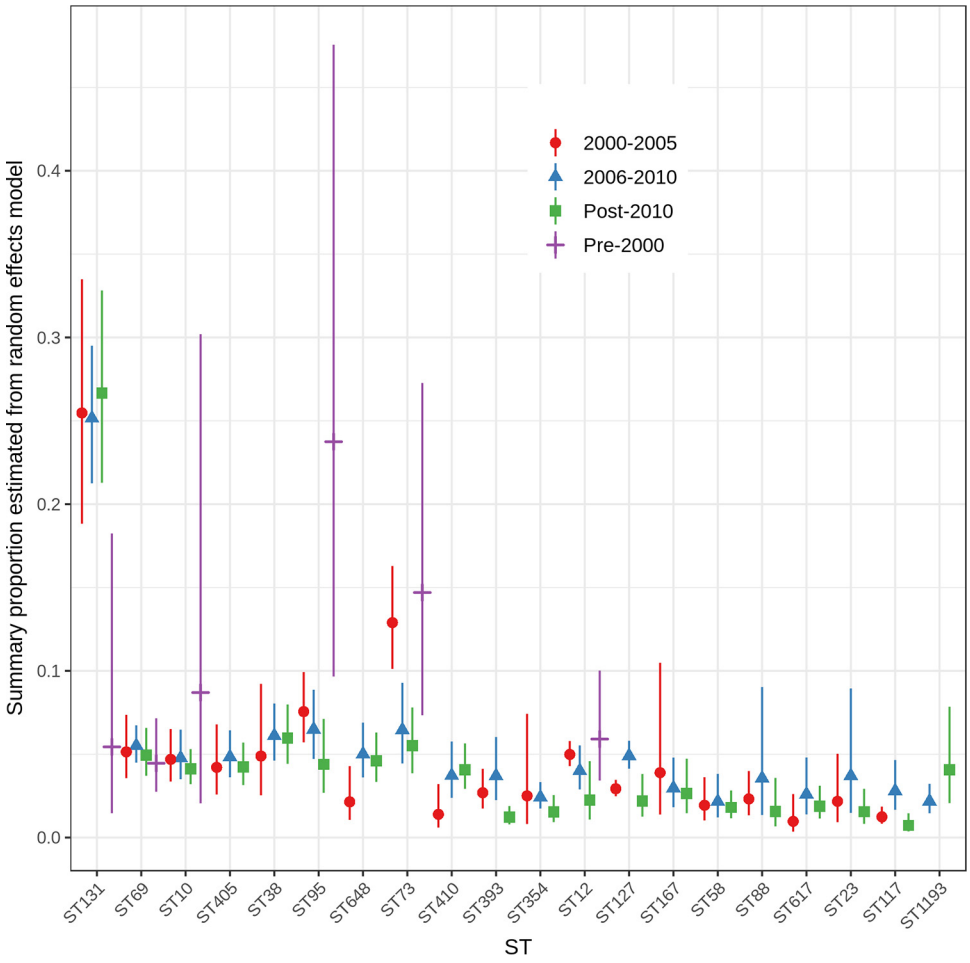

FIG 5 Summary proportions from random-effects models for the most common ExPEC STs by start date of study isolate collection. Dates were determined based on the reported start date for sample collection for each study. In some cases, isolate collection ended in a different period, which makes categories overlap for some studies. Moreover, the number of STs included in databases has grown over time. The absence of some STs might reflect the fact that these STs had not yet been added to the MLST allele database.

urine specimens) and bloodstream infections (or blood specimens). ST73, ST12, ST127, ST23, and ST1193 were each detected in fewer than three studies of colonization or surveillance isolates. ST131 was found at a higher overall proportion in studies that investigated UTI (or urine) (0.24; 95% CI, 0.18, 0.30) and bloodstream infections (or blood isolates) (0.25; 95% CI 0.19, 0.33) but was lower in colonization or surveillance studies (0.19; 95% CI, 0.07, 0.42). These differences were not significant (Q test $P = 0.84$). ST69 also exhibited this pattern (Q test $P = 0.08$). Compared to the levels of all of the other STs, ST73 was generally found at elevated levels in UTI (or urine) (0.08; 95% CI, 0.06, 0.11) and bloodstream infections (or blood) (0.08; 95% CI, 0.05, 0.12) (Fig. 4). In contrast, ST10 (0.09; 95% CI 0.06, 0.12) (Q test $P < 0.001$), ST648 (0.08; 95% CI, 0.04, 0.13) (Q test $P = 0.02$), and ST167 (0.13; 95% CI, 0.04, 0.34) appeared to be identified at higher proportions in studies looking at colonization or surveillance isolates. Most of the other major STs were identified at similar levels in studies of UTI, bloodstream infections, or stool. Relatively few studies specifically investigated stool isolates, which may explain why a number of STs had low detection rates.

ExPEC Sequence Types by Start Date of Study Isolate Collection

To examine timing of ExPEC ST emergence or persistence, we investigated the distribution of STs by the start date of study isolate collection; time periods were grouped as follows: pre-2000,2001 to 2005, 2006 to 2010, and 2011 or later (Fig. 5; see

also Table S6 in the supplemental material). All predominant STs were identified from the inception of MLST testing around 1995; however, there were only 11 pre-2000 studies that were eligible for inclusion in the systematic review and meta-analysis. Aside from the pre-2000 period, virtually all 20 major STs were detected in studies that collected isolates after the year 2000.

The overall estimated proportion of ST131 was low prior to 2000 (0.05; 95% CI, 0.02, 0.18) but increased, and summary proportions were approximately 0.25 in studies from 2000 onwards (Q test $P = 0.08$) (Table S6). ST73 (Q test $P < 0.001$), ST95 (Q test $P = 0.013$), and ST12 (Q test $P = 0.1$) were all detected more commonly in the pre-2000 period, and the summary proportions gradually declined from 2000 onwards (Fig. 5; Table S6). This suggests that these STs have been long-standing ExPEC lineages and may have ceded ground to newly emerging lineages, such as ST131. Summary proportions for some STs appeared to rise and fall over the time periods (ST88, ST127, ST393, and ST117) although this could just reflect study variability (Fig. 5). There is some evidence that ST1193 increased from 2006 (Q test $P = 0.1$) although there was only a single study that detected ST1193 in sampling prior to 2006. The summary estimates for ST69, ST58, ST167, ST38, ST405, and ST10 remained remarkably stable over time. Changes in ST detection over time may be influenced by multiple factors, including the following: (i) the emergence and recognition of new ST lineages; (ii) dynamic changes in ST detection due to shifts in ExPEC sources, transmission, or selective pressures; (iii) an expansion in the number of MLST allele profiles contained in the databases (where new STs defined later would be underrepresented at earlier time periods); and (iv) the specific selection of certain STs or lineages in some studies (e.g., ST131).

Whole-Genome Sequencing of ExPEC Lineages

Twenty-eight (16%) of the 173 MLST studies included whole-genome sequencing of *E. coli* isolates. Forty-four additional studies employed WGS to study ExPEC but did not include information on the distribution of STs and so were not summarized in the systematic review (Table S2). Many of these additional WGS-focused studies examined a small number of genomes or previously deposited genomes or were draft genome announcements. Several WGS studies investigated ST131 specifically (14, 197–201) or examined the evolution, resistance, and virulence gene distributions of ExPEC in general. To complement and augment the meta-analysis results, we provide a narrative summary of results from WGS studies focusing on the molecular epidemiology, evolution, and drivers of the emergence of ExPEC lineages, starting with ST131.

Emergence of ST131 and drivers of success. The study by Kallonen et al. (166), conducted over an 11-year period, noted a single rapid expansion of ST131 beginning around 1995 in the United Kingdom. Ben Zakour et al. investigated the evolution of 185 previously deposited ST131 genomes, which suggested that the emergence of fluoroquinolone-resistant fimH30 ST131 (clade C) occurred in the 1980s, followed by the rapid expansion of the ST131 lineages, probably originating in North America (197). A split into clades C1 (H30R; fluoroquinolone resistant) and C2 (H30Rx; fluoroquinolone resistance in combination with CTX-M-15 ESBL production) then occurred around 1990. This is generally consistent with other studies that have investigated ST131 genomes and the acquisition of resistance genes and plasmids by the H30R and H30Rx lineages (14, 166, 201).

McNally et al. compared core and accessory ST131 genomes and found that the phylogenetic clustering of ST131 is driven to a large extent by accessory genome content. This provides support for the theory that ST131 has benefited from compensatory mutations that make carriage of multidrug resistance and virulence plasmids possible without a fitness cost. Furthermore, comparison of human and nonhuman source isolates suggests that ST131 has a wide host range (198). Alqasim et al. took a different approach and investigated capsular variation within the ST131 H30Rx C2 clade (13). They show evidence for multiple recombination events at capsular loci in ST131 genomes over time. Capsular variation did not appear to be related to virulence in *in vitro* testing but may still contribute to the widespread dissemination of this ST131 sublineage (13).

Comparative genome analysis of ST131 versus other ExPEC STs was performed by Kallonen et al. to identify potential drivers of ST131 success in causing a large fraction of total infections. They showed that the SPATE (serine protease autotransporters of *Enterobacteriaceae*) virulence gene (*espC*) was strongly associated with ST131, which has been linked to other *E. coli* pathotypes. This observation was echoed in the study by Shaik et al. that compared ST131 *E. coli* to other ESBL-producing *E. coli* lineages (ST38, ST405, and ST648) and found that SPATE was identified exclusively in ST131 isolates (199). In contrast, Clark et al. conducted a WGS-based virulence gene analysis and did not find any genome regions that explained ST131 increased fitness compared to that of non-ST131 ExPEC genomes (202). Kallonen et al. also argue that antimicrobial resistance does not appear to be a major driver in the success of resistant ST131 or other drug-susceptible ExPEC lineages, such as ST73, as these groups were equally maintained in the population over time; this was also shown in the study by Ben Zakour (166, 197). These analyses suggest that the success of ST131 and other major ExPEC lineages may be linked to selection and expansion in *E. coli* reservoirs, primarily the intestinal tract (166).

Emergence of other major ExPEC STs and drivers of success. Relatively few studies investigated the genomic basis for non-ST131 ExPEC success. ST73 phylogenies from the Kallonen et al. study exhibited multiple divergent clades, suggesting that ST73 is an older lineage (166). Alhashash et al. investigated 22 isolates of MDR ST73 and also found considerable genome heterogeneity, suggesting a longer period of evolution. The authors reported similar levels of virulence gene carriage and a diverse pool of plasmids containing resistance genes that did not differ between isolates recovered from UTI and bacteremia cases. The authors concluded that the increase in ST73 resistance was not due to the spread of one or more specific clones. So, unlike the highly clonal ST131, ST73 is also highly successful but for reasons that are still unclear (152). A few small studies investigated ST95 (203) and ST69 (166) by WGS but provided few details on the emergence of these STs. Shaik et al. examined ST38, ST405, and ST648 and contrasted these with ST131. ST131 possessed a greater total number of virulence genes, while the non-ST131 isolates shared similar, albeit lower, numbers of virulence genes, but the composition of genes varied (199). Salipante et al. showed no real differences in virulence factors between urine and blood source STs (75). Despite the significant role these major STs have in global infections, we still know fairly little about the apparent differences in performance by the different lineages at different extraintestinal sites and in the gut.

Genomic epidemiology of major ExPEC STs. Several genomic epidemiology studies were identified that assessed potential ExPEC transmission routes and identified clusters of closely related ExPEC isolates in diverse clinical settings. Salipante et al. investigated the genomic epidemiology of ExPEC recovered from urine and blood at a single health care institution. They observed genetically identical urine and blood source isolates, differing by 0 to 1 single nucleotide polymorphisms (SNPs), collected over short periods. Another pair of isolates exhibiting indistinguishable genomes occurred more than a year apart, without any evidence of an epidemiological link (75). ExPEC genome clusters were also observed in Brodrick et al., where related ESBL-positive *E. coli* ST131 genomes were identified in 17 patients (112). Clark et al. identified genetically monomorphic ST131 isolates from 10 subjects (202). Finally, Roer et al. studied 552 cephalosporin-resistant ExPEC isolates recovered from bloodstream infections between 2014 and 2015 in Denmark and found evidence of 15 national outbreaks (defined as fewer than 10 SNPs) comprised of seven ST131 outbreaks, with three due to ST12, two due to ST410, and one each due to ST3666, ST58, and ST69 (72).

ExPEC has been associated with many different environmental reservoirs and potential foodborne and other transmission routes (204). Sexual and household transmission has been demonstrated previously using non-WGS molecular methods, but household clustering of ST131 ExPEC has recently been confirmed using WGS (161). Berg et al. identified ST38 human and retail chicken isolates that differed by fewer than 15 SNPs (91). ESBL-positive ST410 isolates from a study by Falgenhauer et al. recovered from

human, companion animal, livestock, and farm sources differed by fewer than 70 SNPs (138). Clusters of ESBL-producing *E. coli*, including ST131, ST2003, ST354, ST38, ST405, and ST410, from clinical and water sources in Thailand also differed by only 3 to 23 SNPs (74). *E. coli* ST131 has also been shown to have a potentially large host range and has been identified in wild birds, food, and companion animals (198). However, in one study by de Been et al. which examined human and poultry isolates that were considered to be indistinguishable by less discriminatory genotyping methods, genome sequences were more divergent than expected (205). Musicha et al. investigated ExPEC isolates associated with bacteremia and meningitis infections in Malawi and found *E. coli* to be more diverse than in other regions (34), reinforcing the results from this systematic review. The extent of global differences in ExPEC molecular epidemiology is still not well understood.

A few studies investigated the link between the human intestinal reservoir for ExPEC and development of infection in the same host. This relationship has been known for a long time, but WGS has confirmed the link (41, 121, 161). A study by Nielsen et al. examined fecal and UTI isolates by WGS (41). Multiple *E. coli* isolates per fecal specimen were investigated, providing information on the predominance of ExPEC ST carriage in the stool. ST95 was associated with fecal predominance in multiple subjects, whereas ST131 was predominant in the gut in only two cases. The authors found no differences in phylogenies of *E. coli* isolates recovered from feces and those from UTI cases. ST73 and ST12 were overrepresented among the UTI cases; however, no closely related genomes were discovered. The main difference between the fecal and UTI isolates was in their accessory genomes. Moreover, healthy women who had never had a UTI carried fecal *E. coli* isolates in their gut that were similar to the fecal *E. coli* isolates recovered from women who went on to develop UTI (41). Intriguingly, one study with detailed assessments of urine and fecal isolates confirmed shared clones between the gut and the urinary tract and showed that the metabolic properties of ExPEC are crucial to fitness in both environments. In fact, isolates that exhibited greater fitness at both sites were most successful (121). These data begin to suggest that the dichotomy between the special pathogenicity and prevalence explanations for ExPEC success be revisited. Identification of genes that contribute to persistence and predominance in the intestinal reservoir, and possibly to host specificity and environmental dissemination, should be the focus of future investigations.

DISCUSSION

In the absence of systematic, large-scale, public health reporting or surveillance systems for ExPEC, reviews of the literature can help capture information on important ExPEC lineages. Leveraging data from a systematic review can depict a more complete picture of the type, evolution, distribution, and characteristics of ExPEC. As expected, ST131 was the undisputed winner. ST131 was detected in 91% of all reviewed studies and exhibited the highest summary proportions, regardless of study isolate selection criteria, geographic region, source, or time period. The other major STs were ST69, ST10, ST405, ST38, ST95, ST648, ST73, ST410, ST393, ST354, ST12, ST127, ST167, ST58, ST617, ST88, ST23, ST117, and ST1193 (in decreasing study positivity) across all 169 studies (Table 2). Other narrative reviews of ExPEC point to a largely overlapping list of important STs (4).

The results of this systematic review are heavily influenced by the selection criteria employed by study authors. The role of certain ExPEC lineages in the global spread of antimicrobial resistance is undisputed; however, the overall contribution of ExPEC to antimicrobial-susceptible extraintestinal infections is also enormous. A large fraction of studies (66%) sampled isolates based on antibiotic resistance phenotype, especially ESBL production. This inclusion criterion influenced the distribution of STs detected and most likely overestimated the importance of certain lineages associated with multidrug resistance and ESBLs, such as ST131, ST405, ST38, ST648, ST410, and ST354, whereas ExPEC lineages exhibiting lower multidrug resistance levels, such as ST95, ST73, ST12, and ST127, may have been underreported.

It is likely that the high estimated proportions of certain MDR lineages globally are due to the large number of studies that included only resistant isolates. Two large retrospective studies that included all isolates irrespective of their susceptibility profiles, conducted in the United Kingdom and Ireland from 2001 until 2010/2011, showed that ST73 was the most common cause of bloodstream infections due to ExPEC (132, 166). This was reinforced in studies from Germany (84) and Canada (187). In contrast, studies that included only MDR isolates (primarily ESBL producers) described ST131 as the most prevalent ST among ExPEC responsible for bloodstream infections (72, 154, 193).

Certain longstanding or "classic" ExPEC STs, such as ST73 and ST95, are successful extraintestinal pathogens but are also persistent intestinal colonizers (4). Interestingly, most of the other major STs were identified at similar proportions in studies of UTI, bloodstream infections, and stool. Such classic STs are often responsible for higher proportions of extraintestinal infections than the MDR lineages, as illustrated in the large studies from the United Kingdom and Ireland (132, 166). The introduction of highly resistant lineages, such as ST131, does not necessarily displace these classic lineages (166). However, constant selection pressures created by antimicrobials can drive the selection and emergence of MDR ExPEC lineages, as noted with ST131. All major STs have now been linked to multidrug resistance gene carriage or ESBL production, and an increasing number of the major STs have been associated with carbapenemase production.

The largest number of ExPEC genomic studies were conducted in Europe and North America and showed similar distributions of ExPEC lineages; however, data from Asia and Africa suggest that different STs may be associated with infections in these regions. This could have resulted from the influence of selection criteria used in these studies or could represent real differences due to distinct selection pressures in these regions. In 2014, a report from the World Health Organization (WHO) showed that when antimicrobial resistance surveillance data are available, appropriate treatment regimens can be selected, resistance trends can be understood, priority areas for interventions can be identified, and the impact of interventions to reduce resistance can be monitored (206). The report revealed the lack of adequate surveillance programs in many parts of the world. This systematic review supports the WHO report conclusions and specifically points to the lack of systematic and unbiased information about ExPEC lineage incidence, especially the absence of this information for many regions of the world, including Africa, Central and South America, the Middle East, and Oceania. Understanding these underrepresented regions will be vital to detecting the emergence of newly successful lineages, especially those harboring extensive drug resistance plasmids.

This review highlights that the epidemiology and population dynamics of ExPEC are complex and variable. Recently, investigators have identified blooms of specific STs over multiple years (207, 208) and have reported an increase in the prominence of other STs, such as MDR ST1193 (209). Other STs appeared to decrease over time (e.g., ST95). This may be due to actual increases in different lineages or could be the result of a heightened focus on MDR ExPEC lineages. Other STs exhibited nearly identical proportions over all periods (e.g., ST10), suggesting that some lineages may be less influenced by selection pressures on ExPEC population dynamics. This is a significant concern for public health, infection prevention, antimicrobial stewardship, and vaccination programs. We need continuous, large-scale global genomic studies that include ExPEC isolates, irrespective of their susceptibility profiles, to fully elucidate the population structure of these successful groups of pathogens.

The results of this review question the absolute distinction between commensal fecal isolates and ExPEC isolates as two separate *E. coli* pathotypes as isolates from colonization and infection studies share substantial parts of their genetic cores, which for some lineages cannot be distinguished in SNP-based phylogeny. Nielsen et al. make the case that ExPEC bacteria exist equally in the intestinal reservoir and urinary tract, as there were few differences in the core genomes between these pathotypes, except possibly in the accessory genome (41). This has also been supported by data from other

non-WGS studies (210, 211). This reinforces the idea that the *E. coli* in the intestinal reservoir serves as the primary source of the *E. coli* that gives rise to extraintestinal infections and that there may be no clear distinction between commensal *E. coli* and ExPEC. Kallonen et al. point to the importance of competition, persistence, and predominance in the intestinal reservoir to the dominance of ST131 and ST73 ExPEC lineages as the cause of infections (166). However, currently there is limited evidence of this distinction in other lineages as most WGS-based studies have focused primarily on ST131. Despite the lack of differences in virulence gene profiles between infection and intestine source isolates, phylogenetic group, as a marker of evolution, clearly distinguishes lineages that contribute most to extraintestinal infections (166). It is also possible that disturbances to the microbiota, as the result of travel or antibiotic use, contribute to transient intestinal acquisition of and colonization with successful ExPEC lineages. This could explain why it could be challenging to differentiate commensal *E. coli* and ExPEC strains around the time of infection; however, this hypothesis requires testing. The research community still does not fully understand the role of different adaptations in ExPEC that contribute to fitness in the intestinal reservoir and at extraintestinal infection sites.

ExPEC bacteria are transmitted via fecal-oral, household, sexual, and foodborne routes. Local clusters of closely related ExPEC isolates, as shown by WGS, have been detected in multiple settings. Almost all major ExPEC STs have been identified in at least one nonhuman host or environmental source. Understanding the transmission mechanisms for these common and successful STs could go a long way in reducing ExPEC carriage and infection. Multiple factors, from both the host and the environment, shape the genomics of ExPEC. Therefore, the need for a "one-health" (i.e., spanning ExPEC isolates among humans, animals, and their environments) strategy for surveillance and containment across the different sectors will clarify ExPEC transmission routes.

There are multiple limitations to this systematic review. Study populations were very different. The studies included *E. coli* isolates from a range of sources, including surveillance specimens, UTIs, and bloodstream infections, and from both community-based and health care settings. The values of I^2 in the supplemental tables show that study heterogeneity was substantial. Different definitions of "ExPEC" were used in the various studies. In many cases, the patient or isolate sampling procedures and denominators were incompletely described or were not listed. Given the breadth of the literature and the multiple disciplines contributing to ExPEC research, we likely missed some relevant reports and manuscripts. The review adhered to a modified Cochrane review strategy; however, variation in the indexing of studies in publication databases may have influenced our ability to identify relevant studies. It can be a common practice to include the same isolates in more than one study so that different research questions can be addressed. We did our best to exclude studies that used the same or part of the same collection of *E. coli* isolates although some isolates may have been counted twice in this review. We also acknowledge that there were rare STs that were detected in some of studies but were not captured and abstracted into our review data set. However, we feel confident that the 215 STs included represent the STs contributing most to the burden of human extraintestinal infections around the world. Given the large number of studies that selected their study isolates by resistance phenotype, the ExPEC lineages associated with multidrug resistance (e.g., ST131) will be significantly overrepresented, while lineages not associated with resistance are likely to be underrepresented.

A discrete set of ExPEC lineages contributes to the enormous burden of human extraintestinal infections. Despite the limited number, these STs are highly diverse in genetic background, virulence, and resistance gene carriage. There is mounting evidence that ExPEC success as a pathogen of extraintestinal sites may be mediated by its persistence, adaptation, and predominance or function in the intestinal reservoir. The emphasis on MDR ExPEC ST131 has unfortunately created a gap in our knowledge about other important ExPEC lineages, such as ST73 and ST95. Additional whole-

genome sequencing-based studies, using a one-health approach, are urgently needed to understand the phylogeny, function, population dynamics, and molecular epidemiology of these 20 major ExPEC STs. This gap will gradually be filled as genome sequencing becomes part of routine research and public health practice. ExPEC contributes to an enormous infectious disease burden around the world and serves as a reservoir for the development and mobilization of new resistance genes or novel combinations of resistance genes in the gut and at infected extraintestinal body sites. Interventions to tackle the most common ExPEC lineages would go a long way in reducing the burden of disease caused globally by these *E. coli* strains.

SUPPLEMENTAL MATERIAL

Supplemental material for this article may be found at https://doi.org/10.1128/CMR.00135-18.

SUPPLEMENTAL FILE 1, PDF file, 0.5 MB.

SUPPLEMENTAL FILE 2, XLSX file, 0.9 MB.

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A.R.M. and J.D.D.P. conceived of and designed the review. A.R.M., H.M.G., and A.G. performed the systematic review. C.D.F. and T.J.E. analyzed the data. A.R.M. and J.D.D.P. wrote the manuscript.

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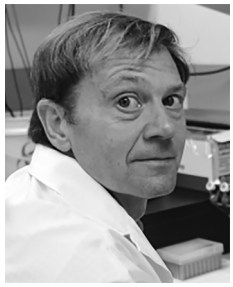
Amee R. Manges is an Associate Professor at the University of British Columbia, School of Population and Public Health, and an Adjunct Scientist at the British Columbia Centre for Disease Control, where she supervises a research laboratory. Her primary research interests are in public health and molecular epidemiology, specifically the application of genomics and metagenomics to questions in infectious disease epidemiology and human microbiome research.

Hyun Min Geum received her bachelor of science degree in microbiology and immunology (2016) at the University of British Columbia and is now pursuing her M.D. Her current research interests include infectious diseases, addiction medicine, and public health.

Alice Guo is a public health professional who holds a B.Sc. in microbiology and immunology from the University of British Columbia and an M.Sc. in global population health from the London School of Economics and Political Science. Currently, she is a consultant in the Department of Essential Medicines and Health Products at the World Health Organization. Her interests are in improving population health outcomes globally.

Thaddeus J. Edens is a bioinformatician and scientific computing consultant and holds a Ph.D. in mathematics from the University of California at Davis. His research interests include processing, managing, and analyzing high-dimensional metagenome sequencing data. He also provides consulting services in biostatistics and scientific software development.

Chad D. Fibke is a current M.Sc. student in the University of British Columbia, School of Population and Public Health. His research interests are in molecular and genomic epidemiology and public health bioinformatics.



Johann D. D. Pitout is a Professor at the Cummings Medical School, University of Calgary, and Medical Microbiologist at Calgary Laboratory Services, Alberta, Canada. His main research interests are resistance to antimicrobial agents among Gram-negative bacteria, especially the laboratory detection, characterization, molecular epidemiology, and evolution of bacteria with newer β-lactamases such as AmpC, extended-spectrum β-lactamases, and carbapenemases. He has also been involved in population-based surveillance studies and the role of high-risk clones and mobile genetic elements (such as plasmids) among bacteria producing these newer types of β-lactamases. He serves on the editorial boards of several journals has published over 160 peer-reviewed manuscripts in this field.