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Distinguishing Pathovars from Nonpathovars: Escherichia coli*

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ABSTRACT *Escherichia coli* is one of the most well-adapted and pathogenically versatile bacterial organisms. It causes a variety of human infections, including gastrointestinal illnesses and extraintestinal infections. It is also part of the intestinal commensal flora of humans and other mammals. Groups of *E. coli* that cause diarrhea are often described as intestinal pathogenic *E. coli* (IPEC), while those that cause infections outside of the gut are called extraintestinal pathogenic *E. coli* (ExPEC). IPEC can cause a variety of diarrheal illnesses as well as extraintestinal syndromes such as hemolytic-uremic syndrome. ExPEC cause urinary tract infections, bloodstream infection, sepsis, and neonatal meningitis. IPEC and ExPEC have thus come to be referred to as pathogenic variants of *E. coli* or pathovars. While IPEC can be distinguished from commensal *E. coli* based on their characteristic virulence factors responsible for their associated clinical manifestations, ExPEC cannot be so easily distinguished. IPEC most likely have reservoirs outside of the human intestine but it is unclear if ExPEC represent nothing more than commensal *E. coli* that breach a sterile barrier to cause extraintestinal infections. This question has become more complicated by the advent of whole genome sequencing (WGS) that has raised a new question about the taxonomic characterization of *E. coli* based on traditional clinical microbiologic and phylogenetic methods. This review discusses how molecular epidemiologic approaches have been used to address these questions, and how answers to these questions may contribute to our better understanding of the epidemiology of infections caused by *E. coli*. *This article is part of a curated collection.

INTRODUCTION

A "pathovar" or "pathotype" can be defined as a pathogenic variant of a taxonomically- related group of microorganisms that asymptomatically colonizes a host. A pathovar causes disease in a host without obvious underlying medical conditions. A pathovar can cause disease at the same body site where its counterpart commensal resides (e.g., *Escherichia coli* causing diarrhea; *Helicobacter pylori* causing gastritis), or at a site outside of the commensal's natural host habitat (e.g., *E. coli* causing urinary tract infection, bloodstream infection). However, there are other microorganisms that colonize a host and cause a disease that do not fit as neatly into these classifications. For example, *Clostridium difficile* is found in mammalian intestines but it causes disease (colitis) most often when the normal intestinal microbiota is disrupted with drugs such as broad-spectrum antimicrobial agents. However, some strains of *C. difficile* have caused outbreaks of diarrhea and colitis in persons without exposure to antimicrobial drugs (1–4).

Bacteria that colonize the normal skin or mucosa (*Staphylococcus aureus*, coagulase-negative *Staphylococcus spp.*, *Streptococcus pneumoniae*) cause disease more frequently in those with underlying medical conditions (e.g., diabetes) or who undergo medical procedures (e.g., intravenous catheterization), but some strains of these organisms cause disease in people without obvious underlying medical conditions. Those organisms that cause disease in hosts with underlying medical conditions are often referred to as opportunistic pathogens, but the distinction between pathovars vs

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opportunistic pathogens may get blurred with some of these microorganisms.

The distinction of pathovar vs non-pathovar can be difficult for some other microbes of public health and clinical concern, such as *Entamoeba histolytica* and *Entamoeba dispar*, discussed in a separate chapter of this curated collection *Advances in Molecular Epidemiology of Infectious Diseases*. The traditional diagnosis based on microscopy could not distinguish these groups of protozoa. It was only when their genome sequences became available that they were classified into separate species.

This review will discuss how *E. coli* came to be prospectively differentiated as "pathovars" vs "non-pathovars" and how they retrospectively came to be recognized as potentially representing many different taxonomic groups.

WHAT IS *ESCHERICHIA COLI?*

E. coli is named after its discoverer Theodor Escherich, a German microbiologist, who in 1885 reported its isolation from infant stool and named it *Bacterium coli commune* (5, 6). It is traditionally classified as a facultative anaerobic, Gram-negative bacillus belonging to the genus *Escherichia* in the family Enterobacteriaceae. However, as will be discussed below, we now know that what is classified as *E. coli* species may not define a distinct bacterial taxonomic group, and that our understanding of pathogenic vs commensal *E. coli* may have been based on incomplete information and perhaps mistaken premises.

Methods used to classify microbes are developed to serve distinct purposes, such as making clinical or public health decisions, characterizing epidemiology of infections caused by them, studying pathogenesis, or inferring their evolutionary relationships. In most clinical settings, the steps used to identify *E. coli* include visual inspection of characteristic colony morphology and biochemical tests for lactose fermentation on MacConkey agar plates, followed by a battery of other biochemical tests, usually performed with rapid detection kits or automated systems (7). When such an identification is made in clinical settings, patient management decisions can be made based on these test results along with antimicrobial drug susceptibility test results. Further differentiation is usually not needed.

For the purpose of epidemiologic, microbiologic, pathogenesis and phylogenetic characterizations, however, a microorganism biochemically identified as *E. coli* needs to be further differentiated or subtyped. Such subtyping tests have included serogrouping/serotyping, multilocus enzyme electrophoresis (MLEE), pathotyping/virulence factor typing, multilocus sequence typing (MLST), pulsed field gel electrophoresis (PFGE), 16S rDNA sequencing, and whole genome sequencing (WGS), reviewed in detail in other parts of this curated collection *Advances in Molecular Epidemiology of Infectious Diseases*.

E. coli pathovars were first recognized when *E. coli* strains came to be subtyped by serologic tests (8). In 1947, Kauffmann proposed a serologic typing scheme based on the organism's somatic or polysaccharide side chains (O antigen), capsular antigen (K) and flagellar protein (H) (8). Currently there are about 200 different *E. coli* O-groups and 53 H-types recognized (9). Subtyping *E. coli* by serogroups (based on O antigens) and serotypes (based on combination of O, K, and H antigens) has been traditionally performed to describe outbreaks and conduct surveillance of *E. coli* associated with enteric diseases. In fact, serogrouping is still performed by many clinical laboratories to screen *E. coli* isolates for common disease-associated serotypes such as *E. coli* O157:H7, a causative agent of hemorrhagic colitis and hemolytic-uremic syndrome (10–13). However, for outbreak investigations and surveillance, *E. coli* serotyping is largely confined to reference laboratories, due to the labor-intensive requirement for maintaining a large panel of quality-assured antibodies directed at O, K and H antigens. For this and other reasons, serotyping tests are now being replaced by nucleic acid sequencing methods, such as WGS in most major reference laboratories.

WGS analyses of *E. coli*, however, have raised new questions about what we call *E. coli*. The first complete genome sequence of an *E. coli* strain (K12, MG1655) was published in 1997 (14). This non-pathogenic laboratory *E. coli* strain, belonging to phylogenetic group A, was found to contain 4,639,221 bases comprised of 4,288 protein-coding genes. When this genome sequence was compared to that of a pathogenic *E. coli* strain (*E. coli* O157:H7, strain EDL933) in 2001, it was found that EDL933 contained 5,416 genes, of which 1,387 were unique to this strain—that is, these genes were not found in MG1655 (15). Seven years later in 2008, Rasko et al. reported comparison of WGS of 17 *E. coli* genomes, which included those from commensal and pathogenic *E. coli* strains (16). They found that 2,200 genes were estimated to be conserved across all isolates (16). In 2012, Kaas et al. described WGS of 186 *E. coli* genomes and found that 1702 genes were found in 100% of all the genomes and 3051 gene clusters/families were found in 95% of them (17). Most recently (2018),

Yang et al. analyzed genome sequences of 491 *E. coli* isolates archived at NCBI (ftp://ftp.ncbi.nih.gov/genomes/all/) from 37 countries and five continents and found that only 867 genes were shared by all (18).

These WGS analyses of *E. coli* and other bacterial strains have led to the introduction of a taxonomic term "**pan-genome**" (19). Pan-genome is a sum of all genes shared among multiple strains belonging to a "species" (called core genes) plus genes found in only one strain (unique genes) or two or more but not all strains (dispensable genes). Table 1 shows the number of genes found in core and pan-genomes of *E. coli* reported over the last 20 years (15, 16, 18, 20, 21). Based on the most recent report, the pan-genome of *E. coli* "species" contains 43,415 genes (18). *E. coli* is thus considered to have an "open" pan-genome because with each new genome that is sequenced, new unique genes are identified.

So, what then is *E. coli*? All of the above genomes share their 16S rDNA sequences, and the strains all exhibit identical biochemical characteristics. However, the genomes of some pairs of *E. coli* strains can differ by as much as 80%! How can bacterial strains with this much difference in their genome sequences be grouped into the same species? It has become clear from WGS data that what we designate as "species" is built on different consensus definitions agreed upon by clinicians, epidemiologists, taxonomists, and microbiologists used to facilitate ready communication among themselves, and that "*E. coli*" does not really define a distinct taxonomic entity. What has been described as *E. coli* by these different disciplines is reminiscent of an Indian fable in which six blind wise men try to describe an elephant (https://americanliterature.com/author/james-baldwin/short-story/the-blind-men-and-the-elephant). The terms "pathovar" or "pathotype" are, thus, derivatives of these consensus definitions of "species". These terms had to be "invented" because we did not have all the information. If we had the WGS information we now have many years ago, the above strains of "*E. coli*" would have been classified into multiple distinct taxonomic groups and given names other than *E. coli*.

The important epidemiologic question now is, how does one designate a group of microorganisms with characteristic genome sequences as pathogens, commensals, or saprophytes? Phylogenetic differentiation by itself cannot determine which strains called *E. coli* are pathogenic. We discuss below how bacteria called *E. coli* came to be differentiated into pathovars vs commensals, and how molecular epidemiologic methods contributed to this differentiation that led to new understanding of the epidemiology of intestinal and extraintestinal infections caused by these organisms. Information derived from these molecular epidemiologic investigations have contributed to several new and focused public health intervention strategies.

E. COLI ASSOCIATED WITH DISEASE

In 1945, John Bray in London described cases of "summer diarrhea" in infants associated with *E. coli*, which, at the time, was called *Bact. coli neapolitanum* (22). This was the first time *E. coli* was epidemiologically linked to a human illness. Today, we know that *E. coli* (as defined biochemically or by 16S rDNA sequences) can cause a wide spectrum of human diseases, but that they also occur as a member of the intestinal commensal flora of many warm-blooded vertebrate animals. In this review, *E. coli* groups that cause diarrhea will be referred to as intestinal pathogenic *E. coli* or **IPEC** (23), while those that cause illness at an extraintestinal site (urinary tract, bloodstream, abdomen, joint, meninges, skin and soft tissue) will be designated as extraintestinal pathogenic *E. coli* or **ExPEC**, using the term first proposed by Russo and Johnson (24).

Intestinal Pathogenic *E. coli* (IPEC)

While *E. coli* organisms were suspected to cause human illness even shortly after its discovery by Escherich (25),

TABLE 1 Pangenome analysis of *E. coli*, 1997-2018. Core genes are all genes shared among all strains belonging to the species *E. coli* as defined by the 16S rDNA sequence.

Reference	Number of *E. coli* strains sequenced	Number of core genes	Number of pan-genome genes
Blattner et al. (1997)	1	–	4,288
Perna et al. (2001)	2	4,029	5,416
Rasko et al. (2008)	17	2,200	>13,000[a]
Sun et al. (2016)	26	2,168	6,797
Her et al. (2018)	59	2,874	15,950
Kaas et al. (2012)	186	1,702	16,373
Yang et al. (2018)	491	867	43,415

[a]Extrapolated.

it was the series of epidemiological investigations in the 1940s of outbreaks of infantile diarrhea and their association with particular *E. coli* serogroups and serotypes that convincingly provided evidence that some subgroups of *E. coli* can cause disease (26). These diarrhea outbreak investigations subsequently led to volunteer studies in adults with the outbreak-implicated serotypes of *E. coli*, which, for some of them, fulfilled the Henle-Koch postulates of disease causation (27–29). By the mid-1950s, these *E. coli* serotypes associated with infantile diarrhea outbreaks came to be termed enteropathogenic *E. coli* (EPEC) (30). This was thus the first time a subgroup of *E. coli* "species", based on serotype classification, was differentiated into pathovars.

Further differentiation of *E. coli* as pathovars required animal pathogenicity studies and in vitro bioassays. A subset of *E. coli* strains grouped earlier as EPEC was later shown to express enterotoxins (31–35). These toxigenic strains of *E. coli* came to be known as enterotoxigenic *E. coli* (ETEC). ETEC strains express two major types of enterotoxins—heat labile (LT) and heat stable (ST) toxins (35), which are the defining virulence factors of this group of IPEC. LT is related to the cholera toxin expressed by toxigenic *Vibrio cholerae* O1 (36). These enterotoxins mediate production of watery (secretory) diarrhea, and the genes that encode the toxins are located on a plasmid (37).

ETECs are commonly associated with traveler's diarrhea (37, 38). ETECs have also been implicated in outbreaks, which, recently, have included those associated with kimchi in Korea, a crowded restaurant in Osaka, Japan, scrambled egg served at a Christmas buffet in Norway, and sushi restaurants in Nevada, United States (39–42).

Some of the so-called EPEC strains were later found to cause dysentery in children and adults similar in clinical manifestations to a disease caused by Shigella, first described as *Bacillus dysentericus* by Kiyoshi Shiga in Japan in 1897 (43, 44). They were demonstrated to invade mammalian tissue culture cells (45, 46) or cause keratoconjunctivitis in guinea pig (Serény test) (47); they came to be described as enteroinvasive *E. coli* (EIEC) (48). Today, we know that Shigella species are phylogenetically included among *E. coli* species, based on their 16S rDNA sequences (49, 50). Shigella species classification, therefore, was based on the characteristic type of enteric illness the organism caused (inflammatory diarrhea), in addition to biochemical characteristics, such as their distinct sugar fermentation properties.

EIEC is the prototypic intracellular *E. coli* pathogen. The defining virulence feature of EIEC is its ability to invade mammalian cells, which is mediated by a set of proteins encoded by genes located on a plasmid (51, 52). Additional virulence factors are encoded by genes in a pathogenicity island, a cluster of genes in the chromosome that collectively regulates and mediates bacterial organism's characteristic adaptive behavior or pathogenicity (53).

Although less common than ETEC diarrhea, outbreaks of diarrhea caused by EIEC have been reported from different regions of the world. Recent examples include those associated with lettuce, kindergarten, and canteen (54–56). Multiple outbreaks in Europe caused by a rare EIEC serotype O96:H19 was suggested to have resulted from acquisition of the invasion plasmid by a commensal *E. coli* strain (57). Temporal occurrence of EIEC infections suggestive of epidemics was described in Ecuador (58).

Despite the separation from "EPEC" of ETEC and EIEC subgroups, a subset of so-called EPEC strains remained that did not exhibit the characteristic virulence properties of ETEC or EIEC. This remaining set of *E. coli* was thus tested for their pathogenicity in a series of volunteer studies conducted by Levine et al.in the late 1970s, which conclusively showed that nontoxigenic and non-invasive "EPEC" organisms were indeed pathogenic (28). The term EPEC then came to be more narrowly used to refer to this subgroup of *E. coli*.

The EPEC subgroup underwent further differentiation when some of them were discovered to be cytotoxic to Vero cells (59, 60). The cytotoxin expressed by these *E. coli* strains, initially named verotoxin (VT), was found to have structural and functional similarity to the Shiga toxin expressed by *Shigella dysenteriae* type 1, and came to be known as Shiga-like toxin (SLT) and later shigatoxin (Stx) (60–62). *E. coli* strains expressing Stx associated with diarrhea are now grouped into shigatoxin-producing *E. coli* or STEC (Table 2).

In the early 1980s, multiple large outbreaks of bloody diarrhea (hemorrhagic colitis) were reported in the United States (10), which were shown to be associated with one serotype of *E. coli* (O157:H7), first described by Wells et al.at the Centers for Disease Control and Prevention (63). The *E. coli* strain was labeled enterohemorrhagic *E. coli* or EHEC (10, 63). *E. coli* O157:H7 was subsequently shown to express two types of shigatoxin (Stx1, Stx2) and is thus classified as a member of STEC (64–66).

In addition to demonstrating cytotoxicity, the study of the interaction (attachment, invasion) of microbes with cultured mammalian cells has contributed to further differentiation of *E. coli* into pathovars. Cravioto et al. showed that EPEC strains but not non-pathogenic *E. coli*

TABLE 2 Intestinal pathogenic *E. coli* (IPEC)-associated virulence genes targeted for PCR-based detection.

Escherichia coli group	Gene target	References
Enteropathogenic *E. coli* (EPEC)	*bfpA, eae*	56, 93, 94
atypical EPEC (aEPEC)	*eae*	56
Enterotoxigenic *E. coli* (ETEC), heat stable (ST) producer	ST gene	56, 93, 94, 96, 97, 98
ETEC, heat labile (LT) producer	LT gene	56, 93, 94, 96, 97, 98
Enteroinvasive *E. coli* (EIEC)	*ipaC, ipaH*	56, 93, 94, 99
Shigatoxin-producing *E. coli* (STEC)	*stx1, stx2*	56
Enterohemorrhagic *E. coli* (EHEC)	*stx1, stx2, eae,*	56
Enteroaggregative *E. coli* (EAEC)	*aatA*	56
Enteroaggregative-Enterohemorrhagic *E. coli* (EAEC-EHEC)	*aatA, eae, stx2*	56, 92

adhered to the surface of Hep-2 cells (67). Scaletsky et al. went on to show that EPEC but not ETEC or EIEC attached to HeLa cells in a distinct pattern called localized adherence (LA), where the bacteria formed microcolonies on the mammalian cell surface (68).

Although clinical presentations of the enteric illnesses caused by IPEC often overlap, prototypically, ETEC cause watery diarrhea while EIEC are linked to inflammatory or invasive diarrhea. EPEC cause watery diarrhea but also another distinct type of diarrheal disease that results from a characteristic intestinal pathology induced by this organism. They cause histopathologic changes in the intestinal mucosa called "attaching and effacing" (A/E) lesion (69), involving destruction of the mucosal microvilli, which can be observed in intestinal biopsy specimens from infants with EPEC diarrhea (70). Effacement of the microvilli structures will lead to decreased fluid absorptive surface, which, of course, would result in net fluid loss–or malabsorption diarrhea. Recovery from this type of diarrhea would require regeneration of the microvilli, and thus EPEC infection can be associated with persistent diarrhea—diarrhea that lasts more than two weeks.

The ability of EPEC to produce the A/E histopathology involves a complex series of steps mediated by a variety of virulence factors, reviewed elsewhere (37, 71). The production of the A/E lesion is linked to genes located on a 35-kb chromosomal segment called the locus of enterocyte effacement (LEE), which is EPEC's pathogenicity island (72, 73). One important protein encoded by a gene (*eae* gene) on the LEE is intimin, which facilitates tight attachment of EPEC to mammalian intestinal mucosal surface (74). Intimin binds to another EPEC protein called Tir (translocated intimin receptor), which is secreted through EPEC's type III secretion apparatus and injected into the plasma membrane of target mammalian cells (75). EPEC, thus, injects its own receptor into intestinal mucosal cells to facilitate intimate attachment. Genes that encode intimin, Tir, and type III secretion system proteins are all located in EPEC's pathogenicity island LEE (37).

Typical strains of EPEC carry a plasmid called EPEC adherence factor (EAF) plasmid that carries a gene encoding a fimbrial protein called bundle-forming pili (BFP) (76). BFP is responsible for the characteristic pattern of attachment called LA described above (68, 76, 77). A subgroup of EPEC called "atypical" EPEC do not possess EAF but have the LEE (78).

This way of assessing patterns of attachment to cultured cells led to the identification of additional pathogenic groups of *E. coli*, including enteroaggregative *E. coli* (EAEC) and diffusely-adherent *E. coli* (DAEC), reviewed in detail elsewhere (37, 77, 79, 80). While genetic markers that define EAEC an DAEC have been identified (Table 2), not all strains that exhibit the characteristic pattern of attachment to cultured cells carry these markers (37, 71, 81). Thus, *E. coli* strains collectively called EAEC and DAEC may represent a mixture of commensal *E. coli* as well as true pathotypes.

EAEC is associated with persistent diarrhea among malnourished children and immunosuppressed adults (82–87). Its association with traveler's diarrhea among visitors to regions where this organism is prevalent has been reported (79, 88), but the absence of genetic markers that clearly define EAEC has recently suggested this association to be perhaps overestimated (80).

In 2011, an outbreak of gastroenteritis, hemorrhagic colitis, and hemolytic-uremic syndrome (HUS) involving more than 3800 people and 54 deaths occurred in Germany (89–91). The outbreak was traced to contaminated bean sprouts grown in the Saxony region of Germany. The sprouts were contaminated with a shigatoxin-producing *E. coli* strain belonging to serotype O104:H4. This strain contained virulence genes *attA, aggR, aap, aggA*, and *aggC* on a plasmid seen in classical EAEC, but also expressed shigatoxin and caused hemorrhagic colitis/HUS. As such, it was classified into a new group of IPEC and labeled EHEC-EAEC. It appears to have descended from an EAEC strain that gained a phage that expressed a variant Stx2 (Stx2a) (92).

The above bioassays (tissue culture cytotoxicity, attachment, invasion, animal models) and the characterization of virulence factors (heat labile toxin, heat stable

toxin, shigatoxin) led to the identification of IPEC group-specific genes associated with these virulence phenotypes. These genes, thus, came to be used as markers to differentiate subgroups of IPEC. Table 2 lists some of the major virulence genes and their regulatory genes that are unique to each of the major groups of IPEC. Today, the different subgroups of IPEC can be rapidly identified by PCR designed to amplify these group-specific virulence genes by procedures that came to be called virulence typing or pathotyping (37, 56, 71, 93–99). Thus, these pathogenic strains of *E. coli*, particularly ETEC, EIEC, EPEC, and STEC, can now be readily identified, which has greatly expanded our knowledge of the epidemiology of enteric diseases caused by them.

As can be seen from the above discussion on IPEC, the demonstration that subsets of what are called *E. coli* are pathogenic relied on the following sequence of events and conditions: 1) occurrence of point-source (e.g, contaminated food, water, environment) outbreaks in which *E. coli* strains were implicated as the causative agent, 2) evidence of person-to-person (e.g., institutional, family) transmission of *E. coli* strains associated with diarrheal illness, 3) recognition of distinct clinical manifestations of a gastrointestinal illness (e.g., watery diarrhea, inflammatory diarrhea, hemorrhagic colitis, persistent diarrhea) attributable to a specific IPEC subgroup and IPEC virulence genes, 4) application of bioassays and animal models, and 5) human volunteers studies, when possible and safe, and 6) availability of strain subtyping tests (serogrouping and serotyping; multilocus sequence types, etc.).

The differentiation of ExPEC from commensal *E. coli*, however, has been more complicated and a different set of approaches needed to be taken, as discussed below.

Extraintestinal Pathogenic *E. coli* (ExPEC)

Two important questions relevant to public health need to be addressed regarding ExPEC: 1) are ExPECs a member of the human intestinal commensal microbiota that breach a sterile barrier to cause disease, or 2) are they true pathogens that first enter the human gut via a contaminated ingested product, transiently colonize the gut, and from there, enter sterile sites to cause disease? If they are a subgroup of human intestinal commensal microflora, then the primary reservoir of ExPEC is the human gut. If the latter, the primary reservoir of ExPEC is somewhere outside of the human intestine. These questions have been previously addressed in other reports as well (23, 100–103). Public health control of ExPEC infections will depend on answers to these questions. Addressing these questions, therefore, is one important scope of work of molecular epidemiology (see *Advances in Molecular Epidemiology of Infectious Diseases*. Molecular epidemiology: definitions, approaches, and scope of the field. *Microbiology Spectrum*. 2018 (104).).

The main challenge in separating IPEC from commensal *E. coli* was the task to attribute a particular subgroup of *E. coli* strains to a disease (diarrhea) that affected the same organ where the commensal *E. coli* reside. This was ultimately achieved by the identification of a distinct set of genes in IPEC that can be targeted for detection by PCR (Table 2). Commensal *E. coli* strains do not carry these genes, and hence we know that IPEC's reservoirs are outside of the human intestine. Indeed, IPEC outbreaks of diarrhea attributed to contaminated meat, vegetables, fruits, and water are well documented, as described above. For example, it is well established that the primary reservoir of EHEC/STEC O157:H7 (as well as most other serotypes of STEC) is cattle. That is, IPECs transiently colonize the human intestine to cause gastrointestinal illnesses but their natural reservoirs exist in nonhuman warm-blooded animal intestine.

On the other hand, unlike IPEC infections, ExPEC infections are actually easy to diagnose. ExPEC infections occur at "sterile" sites, outside of the natural habitat of commensal *E. coli*. Therefore, in most situations, the isolation of *E. coli* from such sites is sufficient to claim that the *E. coli* caused the disease. The challenge with ExPEC, however, is in addressing the epidemiologic question—what is the origin or primary reservoir of *E. coli* that cause extraintestinal infections? Is it the intestine of the person who developed the disease, intestine of someone else, or intestine of a non-human animal?

E. coli-associated extraintestinal infections such as community-associated urinary tract infections (CA-UTI), bloodstream infections (BSI), wound infections, or neonatal meningitis are not usually recognized to occur as part of epidemics or outbreaks. As such, until recently, outbreaks could not be used as a reference to identify commonly shared *E. coli* phenotypic or genotypic markers, as was done with IPEC. Thus, with ExPEC, the typical approach used to identify such defining markers has had to rely on phylogenetic and virulence comparisons of isolates from patients with disease vs isolates from feces of healthy, asymptomatic persons.

One early attempt to study *E. coli* variation and genetic structure in natural populations was based on multilocus enzyme analysis (MLEE) of 72 *E. coli* isolates from a variety of hosts and geographic locations (105). This collection (*E. coli* reference collection, or ECOR)

became the basis for phylogenetic classification of *E. coli* used to distinguish commensal vs pathogenic *E. coli* strains (106–113). Interestingly, the original 72-member ECOR collection did not include any IPEC strains and hence, this may be one of the reasons the separation of IPEC from commensal *E. coli* took a different path, as described above.

The ECOR classification includes four major phylogenetic groups A, B1, B2, and D (107, 113). Studies have found that genes encoding so-called *E. coli* virulence factors (VF) were most frequently carried by strains belonging to group B2 followed by strains in group D (109, 114–116). These factors include adhesins, siderophores, hemolysins, toxins, polysaccharide antigen biosynthetic machinery, invasins, colicins, outer membrane proteins, and pathogenicity island-encoded products. They are regularly updated and reviewed in detail elsewhere (23, 109, 116–119). In general, strains isolated from extraintestinal infections are disproportionately represented among phylogenetic groups B2 and D; some of the commonly reported lineages of ExPEC, such as ST10, belong to phylogenetic group A (108, 109, 120–123). Interestingly, later MLEE analyses of IPEC strains have shown many of them to distribute among all four major ECOR phylogenetic groups, but also in groups C and E (124).

Picard et al. used a mouse model of infection to compare virulence potential of *E. coli* isolates from normal feces and extraintestinal infections and found that, in general, commensal strains belonging to ECOR phylogenetic groups A and B1 carrying virulence determinants but not those that lacked these determinants were lethal to mice (114). A later study compared phylogenetic group B2 commensal *E. coli* isolates with B2 *E. coli* isolates from extraintestinal and intestinal infections in a mouse model and found that, while extraintestinal virulence was associated with a common set of VF, these factors were also likely to facilitate intestinal colonization needed for commensalism within the normal gut environment (125).

A study from Denmark compared genome sequences of urine and fecal *E. coli* isolates from women with UTI to fecal isolates from a different group of healthy women with no previous history of UTI residing in the same city (126). They found that clonal complexes CC73 and CC12, as well as some accessory genes were significantly more frequent among the UTI strains, but overall, the genomic sequences of fecal strains from healthy women were closely related to those of urine and fecal isolates from women with UTI. Single nucleotide polymorphism (SNP) analysis did not show UTI isolates to cluster separately from fecal isolates (126). This study suggested that ExPEC isolates do not comprise a distinct subgroup of commensal *E. coli*, and that there is overlap of genes among ExPEC and fecal strains that are needed for strain adaptation to extraintestinal as well as intestinal ecosystems (126).

Thus, it is not straightforward to distinguish microbial factors responsible for pathogenesis vs niche adaptation based on comparison of genes in pathogenic vs commensal *E. coli* or by their association with some phylogenetic groups. Clearly, many of what have been described as *E. coli* virulence factors are essential for *E. coli* to survive or establish colonization in a particular ecologic niche (125, 127, 128) and thus it is not surprising that there is overlap of these VF genes in ExPEC and commensal fecal *E. coli* isolates (109). None of these genes, thus, can serve as definitive markers of ExPEC in the way virulence genes of IPEC (shown in Table 2) are used to define IPEC subgroups.

Thus, *E. coli* considered ExPEC need to satisfy other sets of criteria than were used to define *E. coli* as IPEC. These criteria include providing epidemiologic evidence that 1) the disease occurs in clusters in time and place suggestive of an outbreak or point-source (common-source) exposures (transmission from food, water, companion animals, other persons, environment); 2) genotypes of *E. coli* isolated from extraintestinal infections and what we eat overlap; 3) genotypes of *E. coli* isolated from extraintestinal infections and sources other than food (other persons, companion animals, environment) overlap.

Do ExPEC strains cause outbreaks?

It was the outbreaks of diarrhea linked to *E. coli* subtypes that first led to the identification of subsets of *E. coli* as IPEC. Since the incubation period of most diarrheal diseases is limited, these outbreaks could then be used to approximate the time of exposure and implicate vehicles of the outbreaks. Unfortunately, determining incubation time for extraintestinal infections to assess potential exposures, especially community-onset or community-acquired infections, is difficult. A person once colonized with ExPEC may develop UTI or BSI at any time during the period of colonization and it would be difficult to determine point-source exposures or if such exposures even exist. A point-source outbreak occurrence could be suggested, however, if all the *E. coli* isolates from cases of extraintestinal infections that cluster in time and place are found to belong to a same genotype and that this genotype differs from those not associated with the cluster.

Such occurrences of community-acquired UTI and BSI were first observed in southeast London in the mid-1980s (129–131). Multidrug-resistant *E. coli* serotype O15:K52:H1 was isolated from several cases of community acquired UTI, bacteremia, and endocarditis from 1986-1987 (129). This serotype was rare in London prior to this period. During the same time period, an increased prevalence of BSI caused by serogroup O15 was reported from several London hospitals (130, 131). O15:K52:H1 *E. coli* strains were later isolated from patients with community-acquired UTI and BSI in Spain, Denmark, other countries in Europe, Australia, Asia and in the US (132–137). Thus, in these settings, the same serotype of *E. coli* was identified to cluster in time and place, indicating outbreaks. This serotype has subsequently been shown to belong to ST393 by MLST (135).

In 2001, Manges et al.described cases of community-acquired UTI caused by *E. coli* resistant to trimethoprim-sulfamethoxazole (TMP-SMZ) at a California college campus (138). The cases were identified from October 1999 to January 2000 in a population-based study, in which urine samples from suspected cases of UTI were consecutively collected and analyzed. Of 255 *E. coli* isolates, 55 (22%) were resistant to TMP-SMZ. Agarose gel electrophoretic band patterns generated by ERIC-PCR amplicons of these TMP-SMZ-resistant strains revealed that 51% of them had a similar band pattern; these strains were initially labeled "clonal group A" or CgA based on their distinct electrophoretic banding pattern (138). Comparison isolates obtained from cases of UTI in college campuses in Minnesota and Michigan found that 39% and 38% of TMP-SMZ-resistant isolates, respectively, had the CgA band pattern (138). These CgA strains also had closely-related PFGE patterns, and were subsequently typed as ST69 by the Achtman 7-gene MLST scheme (139). ST69 includes strains belonging to serogroups 011, 015, 017, 073, 077 (101).

In the California college community, the proportion of UTIs caused by CgA declined by 38% one year after the above study, but the prevalence of TMP-SMZ resistant UTI remained unchanged, while six new clonal groups of *E. coli* were identified (140). These new clonal strains accounted for 32% of the TMP-SMZ-resistant UTIs, which explained the unchanged prevalence of TMP-SMZ resistance (140). Another follow-up study conducted at the same California college campus over the same three-month period (October-January) in 2003-2004 and 2004-2005 showed CgA prevalence to fluctuate, accounting for 13% and 9% of all cases of UTI, respectively (141). The fluctuation of these genotypes over time and appearance of new genotypes in one community suggested multiple common-source outbreaks.

The clustering of CgA by time and distinct locations led to a hypothesis that it may be spread by contaminated food distributed nationally (138, 140, 141). After all, *E. coli* O157:H7, an IPEC, is regularly implicated in multistate diarrhea outbreaks due to a variety of contaminated food products (https://www.cdc.gov/ecoli/outbreaks.html).

ST69 is a member of so-called pandemic or intercontinental lineages of ExPEC that are responsible for large proportions of community-acquired UTI and BSI identified in population-based studies from different regions of the world (101). In addition to ST69, they include ST10, ST73, ST95, ST131, and ST393 (101). Other genotypes such as ST12, ST117, ST127, ST405, ST648 and ST1193 are emerging in multiple regions of the world (101, 142–145). ST131 is perhaps the most widely studied ExPEC, due to its rapid emergence and spread worldwide over the last 20 years, its (in particular, fimbrial subtype *H*30) association with a wide spectrum of antimicrobial drug resistance, and its occurrence in food animals and environment (146–150). When *E. coli* isolates are selected from clinical sources for fluoroquinolone resistance and production of extended-spectrum beta-lactamase (ESBL), ST131 is the most common ExPEC genotype reported in most regions of the world (149, 150). Interestingly, however, strains of ST131 that did not express ESBL but were sensitive or resistant to fluoroquinolone were identified in 7% of fecal *E. coli* isolates from 332 independent healthy subjects in Paris (151).

Surprisingly, one-third to more than half of all CA-UTI and BSI cases examined in different regions of the world are caused by strains belonging to just five to six lineage (ST) of ExPEC (101, 123, 152–162). In a recent report, Yamaji et al.compared by MLST, genotypes of *E. coli* isolates from suspected cases of CA-UTI in a California college community 17 years apart (138, 160). Both studies were population-based in which urine samples were prospectively and consecutively collected from patients with UTI attending the campus health service clinic. They found ST10, ST69, ST73, ST95, ST127, and ST131 to account for 125 (56%) of 255 *E. coli* isolates from 1999-2000, and 148 (64%) of 233 isolates from 2016-2017 (160). More than 60 distinct STs were found in both periods. Thus, only 10% of all the ExPEC genotypes caused more than half of all UTIs that occurred in one community 17 years apart.

A study based on WGS comparisons supports the studies that show dominance of a restricted set of ST

lineages causing extraintestinal infections. Salipante et al.found that one subclone of ST131 (ST131-H30) caused 28% of all ExPEC BSIs identified in one hospital over a 3-year period (159). They found patient-to-patient transmission of ExPEC to be infrequent in the hospital, suggesting common-source exposures to account for the clusters of ExPEC infections. Why certain genotypes dominate in causing extraintestinal infections is not known, but attempts to address this question may provide evidence that ExPECs are true pathogens distinct from commensal *E. coli*.

It should be noted that what is called a pandemic or intercontinental ExPEC lineage could change over time. For example, in Fuzhou, China, ST1193, a member of clonal complex ST14, was the most common ST among 73 non-ST131 fluoroquinolone-resistant phylogenetic group B2 clinical isolates consecutively collected at a hospital during 2014-2015 (163). This genotype was first described in Australia among clinical isolates from human and canine sources in 2012 (164). Fimbrial type *H*64 of ST1193 was seen to emerge in Minneapolis Veterans Administration Medical Center (VAMC) patients beginning in 2013, continued to increase into early 2017, and declined afterwards (165). What makes some genotypes expand and persist in the human population in a defined geographic site, while others decline is unknown, but, again, these types of observation suggest human exposures to contaminated point sources.

In the Enterobase MLST database, the first MLST entries of human strains belonging to ST10, ST69, ST73, ST95, ST127, ST131, and ST393 include strains first isolated in 1800 (ATCC strain 35328, from a collection of Wellcome Sanger Institute), 1982 (FDA, USA), 1917 (Nissle strain, Germany), 1941 (Denmark), 1974 (Brazil), 1967 (BioProject, U.S.), and 1985 (U.S.), respectively (http://enterobase.warwick.ac.uk/). While sampling design and data collection differences could contribute to these differences in the year of isolation recorded in the database, it is curious that among 403 *E. coli* samples collected before 1980, not a single human isolate of ST69 or ST393 (101) and only one human isolate of ST131 is included in the MLST database. This type of observation suggests that these pandemic ExPEC genotypes (especially ST69, ST131, and ST393) were introduced into the human population from sources outside of human intestine relatively recently.

With IPEC, it was not until the 1980s that *E. coli* O157:H7 was recognized to cause outbreaks of gastrointestinal illness, and it was not until 2011 that *E. coli* O104:H4 was observed to cause a large German epidemic. The appearance of these *E. coli* strains in the human communities corresponds to the period of intensification and centralization of food animal feeding operations and expansion of antibiotic use for growth promotion and infectious disease prevention. These practices may have contributed to gradual alteration of the bacterial microbiota of these animal intestines and the environment, which may then have led to the introduction of new *E. coli* genotypes into the human population, including new IPEC and ExPEC genotypes. Thus, the human intestinal microbiota may evolve with changes in what we eat to reflect the microflora found in food, water or environment. In fact, there may be no such entity as human-specific gut commensal flora, at least at the sub-species level. The human intestinal microflora may just be a continuum or an extension of the microbiota of what we ingest. If so, extraintestinal sources of ExPEC clearly need to be considered.

Are ExPECs disseminated by contaminated food?

Diseases that cluster and fluctuate in time and place may represent an outbreak or an epidemic. Even before MLST came to be used to subtype *E. coli*, studies comparing *E. coli* serogroups or ECOR phylogenetic groups have shown these *E. coli* subtypes to overlap among strains isolated from extraintestinal infections and food animals/products (166–173). Modern genotyping tests such as MLST and WGS support these early observations. Indeed, nearly all of the above pandemic ST lineages, as well as less common STs have been isolated from a wide variety of food products or food animal sources all over the world (100, 142–144, 162, 174–195).

Since *E. coli* is an organism that resides in the intestine of warm-blooded vertebrate hosts, livestock animals were first suspected as a potential source of CgA that was described earlier (138). From 495 animal and environmental *E. coli* isolates belonging to serogroups 011, 015, 017, 073, 077, collected by Gastroenteric Disease Center at Pennsylvania State University between 1965 and 2002, Ramchandani et al.found 128 (26%) CgA isolates (175). They were detected from cow, pig, chicken, turkey, dog, horse, sea gull, and environmental water. Fourteen of these CgA strains were TMP-SMZ-resistant. One of them from a cow showed a PFGE pattern 94% similar to that of an isolate from a case of UTI from the California college campus (175). CgA was not seen in this collection until the mid-1970's and TMP-SMZ-resistant CgA did not appear until the mid-1980's (175). A retail food survey conducted in the Minneapolis-St. Paul area in 1999-2000 found CgA in meat, particularly in turkey products (166). CgA was

also identified among *E. coli* isolates from broiler chicken and chicken meat collected between 2005 and 2006 in one region in Denmark (196).

CgA or ST69 strains have subsequently been identified from all over the world from livestock animals and food products, including meat and produce (101, 166, 196–202). Interestingly, according to the Enterobase MLST database, among ST69 strains with known year of isolation, the first curated data are from those isolated in 1982 and 1983 in the U.S. from a cow and human, respectively (http://enterobase.warwick.ac.uk/).

Of all food animal products, poultry appears to be most frequently reported to contain these dominant lineages, especially ST10, ST69, ST95, ST117, and ST131 (142, 171, 176, 177, 180, 182, 185–187, 203, 204). Of 258 poultry samples (chicken parts, ground turkey) collected from retail stores over an 11-month period in Northern California between 2016-2017, 16 (6%) contained these genotypes (177). In a 12-month study conducted in Flagstaff, Arizona in 2012, Liu et al. found 76 distinct STs shared by 2,452 meat and 1,188 clinical *E. coli* isolates (171). Of the meat isolates, they found 27 strains belonging to ST131; all but 2 of them were isolated from poultry and carried fimbrial adhesin *H*22 (sublineage ST131-*H*22) (171). Of the clinical isolates, ST131 was the most common ST, accounting for 182 (15%) of them; 24 expressed *H*22. Twenty-one (84%) of the meat isolates and 6 (25%) of 24 human clinical isolates of ST131-*H*22 carried a plasmid pColV (171), which is associated with virulence in avian pathogenic *E. coli* (APEC) strains (205–207). The above studies point to poultry as an increasingly important potential zoonotic source of human ExPEC strains (205, 208–210).

Indeed, the poultry-related zoonotic potential and public health implications of ExPEC infections are highlighted by the progressive increase in global consumption and production of poultry food. According to the USDA, in the U.S., the annual per capita consumption of chicken increased from 28 pounds in 1960 to 93.5 pounds in 2018 (https://www.nationalchickencouncil.org/about-the-industry/statistics/#). In 2017, Netherlands, Poland, Belgium, the U.S., and Germany were the top 5 countries that exported the highest dollar value worth of fresh or chilled chicken, while Brazil, the U.S., Netherlands, Hong Kong, and Poland were the top 5 exporters of frozen chicken (http://www.worldstopexports.com/chicken-exports-by-country/). Only 15 countries accounted for more than 90% of all the chicken exports in the world. Thus, globalization of food trade may be one factor in the global dissemination of key ExPEC lineages.

Other potential exposure sources of ExPEC

Other potential exposures to point sources of ExPEC have been identified, including the environment (wastewater, river, soil, sewage), companion and domestic animals (cats, dogs, horses, donkey), and wild animals. Several studies have identified pandemic lineages of ExPEC in the environment (211–216), companion animals (133, 164, 217–231), and wild birds and animals (208, 209, 232–237). A recent comparative WGS analysis of 323 avian pathogenic *E. coli* (APEC) and human ST95 ExPEC strains revealed no distinct phylogenetic branch for the human ExPEC genomes (236). In fact, there was genetic overlap between APEC and human ST95 ExPEC genome sequences, and some sequences were found to be nearly identical, suggesting that APEC can cause disease in humans and ExPEC can cause disease in birds.

In another study, investigators found that the genome sequences of ST95 isolates from a river in Japan showed no significant differences from those of clinical ST95 isolates from people residing in the same environment (216). In these two studies above, the direction of transmission of ST95 strains could not be determined with certainty. Birds or river could serve as sources of ExPEC, but human feces could also contaminate river, and birds could be exposed to untreated wastewater.

E. coli strain genotypes annotated in the MLST database include source, time, and place of their isolation (Table 3). The database includes pandemic lineages identified in a variety of companion animals, wild mammals and birds, domesticated non-food animals (horse, donkey), as well as the environment (sewage water, untreated water, tap water, river, soil, farms) (Table 3). Of note, environmental, companion, or wild animal isolates but not poultry isolates of ST73, ST393 and ST405 are recorded in this MLST database (as of November 2020).

As mentioned above, the direction of transmission involving companion or wild animals and environment is difficult to demonstrate. Companion and wild animals could get infected by humans, and the environment could get contaminated by human feces. In fact, person-to-person transmission of uropathogenic strains of *E. coli* has been documented (238–243), which suggests that humans could serve as a source for extraintestinal infections that occur in their close contacts. Such person-to-person transmissions are well documented with enteric organisms such as Salmonella and Campylobacter that cause foodborne outbreaks. However, person-to-person transmissions in general would result in more geographically confined clusters of genotypes. In a

TABLE 3 Non-human sources of intercontinental extraintestinal pathogenic *E. coli* (ExPEC) sequence types (ST) based on multilocus sequence typing (MLST) archived in the Enterobase database (http://enterobase.warwick.ac.uk/species/index/ecoli) as of November 2020. The total number of each ST in the database as of November 8, 2020 is shown in the right column.

Sequence type	Food and livestock sources	Companion and wild animal sources	Environmental sources	Total number deposited
ST10	Bovine, poultry, swine, fish, cheese, fresh coriander	Camel, dog, rabbit, horse, sea lion, pigeon, reptile, seagull, Tasmanian devil, elephant, badger, bat, waterfowl, mouse	River, soil, septic tank, wastewater, fish farm	9575
ST69	Bovine, swine, poultry, sheep, raw milk cheese, oyster	Seagull, dolphin, dog, mink, baboon, white stork	River, septic tank, sewage, soil, wastewater	2254
ST73	Bovine, swine	Dog, cat, wild turkey, duck, gorilla, orangutan, giraffe, elephant, parrot, ferret, colobus, marmoset	River, wastewater, soil	2238
ST95	Poultry, bovine, honeydew melon, poultry feed, lettuce, cow milk	Wild turkey, dog, ostrich, rat, gecko, penguin, pheasant, dove, seal	River, septic tank, wastewater, tap water, sewage, pasture soil	2100
ST127	Poultry, bovine, celery, oyster	Dog, cat, horse, seal, hedgehog, skunk, waterfowl, badger, panda, marmoset, fish	River, wastewater, sewage, deciduous forest soil	778
ST131	Poultry, swine, bovine	Dog, cat, horse, crow, rook, seagull, urban rat, dolphin, flying fox	River, sewage, soil, wastewater	9615
ST393	Swine	Dog	Sewage, hospital sewage tank	215
ST405	Swine	Dog, marmoset, whale, seagull	River, sewage, wastewater, hospital washroom sink	938
ST648	Poultry, bovine swine, sheep, cabbage	Dog, cat, horse, pigeon, duck, stork, seagull, ferret	Soil, sewage, river, wastewater	1083

recent population-based modeling study of *E. coli* strains carrying β-lactam resistance genes in the Netherlands, most (~60%) community-acquired carriage of these organisms was attributed to human-to-human transmission within or between households, while food accounted for about 19% (244). Nevertheless, the basic question remains—where do strains transmitted within households come from?

The identification of strains belonging to the same ST in food animals and humans is not necessarily evidence that food is a vehicle of ExPEC (245–247). The Enterobase MLST database for *E. coli* contains more than 8000 unique STs and 56 clonal complex members (http://enterobase.warwick.ac.uk/). As such, chances of meaningfully identifying identical STs in two or more distinct sources (clinical vs food) will require analysis of many samples. In addition, comparison of isolates from different sources at different time periods or from different geographic sites, or pre-selected (e.g., drug-resistant strains) or convenience samples instead of population-based samples, could all underestimate the frequency of ExPEC lineages that are shared between clinical and food sources. Large-sample size and population-based studies of *E. coli* isolates collected from food and clinical sources contemporaneously from the same geographic site, provide ecological evidence in support of the idea that food contaminated with ExPEC contributes to human extraintestinal infections. Surveillance of extraintestinal infections caused by *E. coli* could be included as part of bacterial enteric disease surveillance systems to monitor potential outbreaks and point-source exposures, which can be investigated epidemiologically. While there is accumulating evidence that some genotypes of ExPEC have their sources in contaminated food, especially poultry, the magnitude or importance of food as a source of ExPEC remains to be explored further with large studies based on detailed genotypic characterizations and comparison of clinical isolates of ExPEC, prospectively analyzed *E. coli* isolates from feces of healthy individuals, and *E. coli* isolates from food sources.

Regardless of where the reservoir of ExPEC occurs, one well-established but unexplained observation is the global distribution of a small set of lineages that are responsible for a large proportion of extraintestinal infections. If such strains are indeed disseminated via globally traded food products, why just these genotypes? How do these pandemic STs differ biologically from other *E. coli* STs that rarely or never cause disease? How much of their pangenome genes differ? These questions need to be addressed in order to classify a group of what is called *E. coli* as true pathovars.

Biological factors that contribute to ExPEC pandemicity

Molecular epidemiologic studies of ExPEC have unmasked the existence of key lineages of *E. coli* responsible

for a large proportion of extraintestinal infections diagnosed in all parts of the world. This observation of clonal distribution and restricted lineages causing large proportions of infectious diseases is not limited to diseases caused by ExPEC. In fact, it may be a fundamental feature of many infectious agents. A large proportion of tuberculosis (TB) cases, especially multidrug-resistant TB in the northern hemisphere, is caused by *Mycobacterium tuberculosis* belonging to Beijing clade (248, 249). In hospitals, particularly in the East Coast of the United States, the largest proportion of carbapenemase-producing *Klebsiella pneumoniae* infections is caused by clonal complex ST258, which is now globally distributed (250–256). The two major intercontinental lineages of multidrug-resistant *Acinetobacter baumannii* that cause healthcare-associated infections are called global clone 1 and 2 (GC1 and GC2) (257–259). The dominant methicillin-resistant *Staphylococcus aureus* (MRSA) strain in the U.S. in the early 2000s was ST8 (or USA300 by the PFGE designation) (260), while MRSA ST80 is common in Europe and other regions of the world (261–264), and ST59 and ST30 dominate in Asia (265–267). A large proportion of invasive disease caused by penicillin non-susceptible *Streptococcus pneumoniae* is due to a limited set of pandemic clonal lineages, including ST156 (Spain^{9V}-3), ST81 (Spain^{23F}), and ST236 (Taiwan^{19F}) (268–270). Factors that contribute to the global and local predominance of these clonal infectious agents may vary. Dissemination by food, human travel, and environmental contamination could explain global spread of some of these clonal lineages, but these explanations do not fully explain why the same genotypes are consistently represented in different regions of the world for several-year intervals. Possible epidemiological factors that contribute to ExPEC clonal dissemination were discussed above. Below we discuss possible biological mechanisms that may contribute to the global dominance of these highly successful ExPEC lineages.

Bacterial virulence

As discussed earlier, a variety of so-called virulence factors (VFs) have been identified in ExPEC strains, which have been shown to be over-represented among ExPEC than in commensal *E. coli* strains. However, no sets of VFs that uniquely and specifically distinguish ExPEC from commensal *E. coli* are known. Even more important, no sets of genes that clearly distinguish pandemic lineages of ExPEC from other ExPEC lineages have been discovered.

Another way to assess virulence of ExPEC includes animal infection models. Early studies compared ECOR phylogenetic group affiliation of commensal and clinical *E. coli* isolates in mouse infection models to identify VFs associated with mouse virulence. Commensal strains belonging to ECOR phylogenetic groups A and B1 lacking the so-called virulence genes did not kill mice but those in groups A, B1 and D that carried these determinants were lethal to mice (114). In particular, B2 had the highest level of VFs and killed mice at high frequency (114). VFs shared by clinical and commensal B2 *E. coli* isolates were later shown to be associated with mouse virulence but also with mouse intestinal commensalism (125).

E. coli strains belonging to B2 phylogenetic group and CgA isolates from both chicken and humans have been shown to cause bladder as well as kidney infections in mouse infection models (196, 271). *E. coli* strains with similar PFGE patterns isolated from human UTI patients and meat sources (broiler chicken and pork) were similarly virulent in a mouse model of UTI (182). Mellata et al.showed that human clinical *E. coli* isolates and chicken and egg *E. coli* isolates caused sepsis, meningitis, and UTI in rodent models, but these virulent isolates genetically defined as ExPEC or non-ExPEC did not necessarily share any genotypic or phenotypic virulence traits (272). APEC strains from birds with colibacillosis and ExPEC strains from cases of neonatal meningitis belonging to ST95 were shown to cause meningitis in a rat infection model (233).

These animal studies show that food *E. coli* isolates genetically related to human ExPEC isolates are pathogenic in the mouse model, and thus the potential for zoonotic transmission of such *E. coli* strains to humans to cause extraintestinal infection is plausible. However, the question here is why only a few clonal lineages of ExPEC cause most of the human extraintestinal infections. Using a mouse sepsis model, Johnson et al. found no difference in disease severity in mice infected with ST131, the most commonly-studied ExPEC strain, vs other ExPEC genotypes (273). Manges et al.observed that the prevalence of pyelonephritis cases among women infected with a pandemic ExPEC lineage ST69 was not significantly different from that caused by other strains of ExPEC, suggesting that ST69 did not necessarily cause a more severe form of UTI (274). Thus, virulence per se does not appear to explain enhanced transmissibility and thus clonal distribution of key ExPEC lineages.

Drug resistance

Many of the intercontinental lineages of ExPEC are characteristically resistant to multiple antimicrobial

agents. Among them, ST131 is the most frequently described genotype, which became prominent in the early 2000s and is now globally recognized (146, 147, 150). One reason for its wide recognition may be due to a selection bias related to the large number of studies based on genotyping pre-selected clinical isolates of *E. coli*, such as those resistant to fluoroquinolones or those that express extended-spectrum β-lactamase (ESBL). A large proportion of fluoroquinolone-resistant or ESBL-producing ExPEC strains belong to ST131, especially to fimbrial subtype *H30* (149, 150, 153, 275, 276). The frequency of ST131 among non-selected, prospectively collected *E. coli* isolates from extraintestinal infections varies depending on the type of extraintestinal infection source, age of patients, and geographic location; the frequency has been reported to range from 6% among children with UTI in Australia (277) to 26% among patients with BSI in San Francisco, U.S (278). Thus, while ST131 remains a dominant ExPEC, especially among fluoroquinolone resistant or ESBL-producing ExPECs, its successful clonal spread is not necessarily related to its drug resistance (150).

Pandemic ExPEC lineage ST95 has been the most common uropathogenic *E. coli* genotype causing CA-UTI at a college community in Northern California, and the second most common genotype after ST131 isolated from patients with BSI in a general hospital in San Francisco (152, 160). One characteristic feature of this genotype is its low frequency of drug resistance. Among ST10, ST69, ST73, ST95, ST127, and ST131 strains isolated from patients with UTI in 2016-17 at the college community, ST95 had the lowest frequency of resistance to ampicillin (20.5%), TMP-SMZ (2.6%), and ciprofloxacin (0%); in 1999-2000 in the same community, the resistance frequency to ampicillin (2.9%), TMP-SMZ (2.9%), and ciprofloxacin (0%) was also lowest for ST95 (279). Among BSI isolates from the general hospital in San Francisco, only 8 (20%) of 40 ST95 strains and 92% of 51 ST131 strains were multidrug resistant (280). Among 16 isolates of *fimH6* subtype of ST95, 14 (88%) were susceptible to all drugs tested (280). Susceptibility to all tested drugs (pan-susceptibility) was later shown to be associated with the presence of a 114-kb IncFIB/IncFII plasmid in ST95 strains (281). Others have also observed the relative low frequency of drug resistance among ST95 strains. Between 2007 and 2009 in England, ST95 isolates showed the lowest resistance score among the nine commonest ST clonal groups (154). Thus, antimicrobial drug resistance does not explain the global distribution of these pandemic ExPEC strains.

Niche adaptation

The global dissemination and their over-representation in human extraintestinal infections suggest that pandemic ExPEC lineages must have evolved to adapt to a wide variety of ecologic niches, including the intestinal microbiota of human and non-human animals, human extraintestinal organs, and the environment. Le Gall et al.showed using a mouse sepsis model that sepsis caused by some strains of *E. coli* B2 phylogenetic group was associated with a common set of genes involved in transcriptional regulation, iron metabolism, adhesion, LPS biosynthesis, and peptide polyketide hybrid synthesis system (125). They proposed that these "virulence genes" may also be viewed as genes encoding factors to facilitate intestinal colonization and survival for commensalism to provide fitness advantage to these strains in the intestinal environment, and that "virulence" is a coincidental by-product of commensalism (125). However, for the pandemic lineages to cause extraintestinal infections, they must also be able to out-compete other bacterial populations in the intestine to then enter extraintestinal sites and replicate efficiently in such sites. Currently, pandemic ExPEC factors that promote such competition and adaptation to multiple environments are unknown.

CONCLUSION

Our progressive understanding of what constitutes *E. coli* has evolved not only with advancements made in microbiologic methods, experimental animal models, and human clinical studies, but also through opportunities created by new epidemiologic events, such as outbreaks of previously unrecognized syndromes or a recognition of modes of disease transmission that had not been previously considered. However, the advances in molecular microbiology, such as the pangenome analyses of bacterial species, have also raised a new question of whether bacterial organisms identified biochemically or by 16S rDNA sequences as *E. coli* belong to any meaningful taxonomic entity. Epidemiologic and molecular microbiologic studies have clearly shown that IPECs have reservoirs outside of the human intestine, but with ExPEC, it has been more challenging to distinguish them from human commensal *E. coli*. This challenge stems from the fact that ExPEC maintain colonization in the human intestine, from which they breach a sterile barrier to cause extraintestinal infections. Whether ExPEC constitute taxonomically distinct human pathogenic groups of bacteria with reservoirs outside of the human intestine, or variants of human

intestinal commensal *E. coli* is still unclear. In fact, the notion of so-called human intestinal commensal *E. coli* itself is vague. *E. coli* as defined by 16S DNA is always found in the human intestine, but at the subspecies level, the population of what is called *E. coli* constantly fluctuates, most likely affected by what eat. Microbial populations that cause extraintestinal infections will require mechanisms to successfully establish and sustain colonization in a microbial niche, and outcompete other microbes to gain entry into sterile sites to cause disease. Thus, our understanding of what constitutes pathogens and commensals among bacterial populations called *E. coli* will require better understanding of the intestinal microbiome not only based on 16S rDNA sequences but also on the microbiome structure at the subspecies level.

Such an understanding will require molecular epidemiologic approaches that include detailed analysis of the intestinal microbiome linked to human food intake, environmental exposures, and behavior.

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