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Overview

A One Health Perspective for Defining and Deciphering *Escherichia coli* Pathogenic Potential in Multiple Hosts

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E. coli **is one of the most common species of bacteria colonizing humans and animals. The singularity of *E. coli*'s genus and species underestimates its multifaceted nature, which is represented by different strains, each with different combinations of distinct virulence factors. In fact, several *E. coli* pathotypes, or hybrid strains, may be associated with both subclinical infection and a range of clinical conditions, including enteric, urinary, and systemic infections. *E. coli* may also express DNA-damaging toxins that could impact cancer development. This review summarizes the different *E. coli* pathotypes in the context of their history, hosts, clinical signs, epidemiology, and control. The pathotypic characterization of *E. coli* in the context of disease in different animals, including humans, provides comparative and One Health perspectives that will guide future clinical and research investigations of *E. coli* infections.**

Abbreviations: AA, aggregative adherence; A/E, attaching and effacing; aEPEC, Atypical EPEC; Afa, afimbrial adhesin; AIDA-I, adhesin involved in diffuse adherence; AIEC, Adherent invasive *E. coli*; APEC, avian pathogenic *E. coli*; ATCC, American Type Culture Collection; BFP, bundle-forming pilus; CD, Crohn disease; *cdt*, cytolethal distending toxin gene; Clb, colibactin; CNF, cytotoxic necrotizing factor; CS, coli surface (antigens); DAEC, diffusely adhering *E. coli*; DB, Dutch Belted; *eae*, *E. coli* attaching and effacing gene; EAEC, Enteroaggregative *E. coli*; EAF, EPEC adherence factor (plasmid); EAHEC, entero-aggregative-hemorrhagic *E. coli*; EAST-1, enteroaggregative *E. coli* heat-stable enterotoxin; *E. coli*, *Escherichia coli*; ED, edema disease; EHEC, enterohemorrhagic *E. coli*; EIEC, enteroinvasive *E. coli*; EPEC, enteropathogenic *E. coli*; ESBL, extended-spectrum β-lactamase; Esp, *E. coli* secreted protein; ETEC, enterotoxigenic *E. coli*; ExPEC, extraintestinal pathogenic *E. coli*; *fyuA*, yersiniabactin receptor gene; GI, gastrointestinal; Hly, hemolysin; HUS, hemolytic uremic syndrome; IBD, inflammatory bowel disease; LA, localized adherence; LEE, locus of enterocyte effacement; LPF, long polar fimbriae; LT, heat-labile (enterotoxin); MLST, multilocus sequence typing; NDM, New Delhi Metallo-β-lactamase; NZW, New Zealand White; *pap*, pyelonephritis-associated pilus; *pks*, polyketide synthase; *sfa*, S fimbrial adhesin; SLT, Shiga-like toxin; ST, heat-stable (enterotoxin); STEC, Stx-producing *E. coli*; Stx, Shiga toxin; tEPEC, typical EPEC; UPEC, uropathogenic *E. coli*; UTI, urinary tract infection

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Escherichia coli (*E. coli*) is the most common bacterial model used in research and biotechnology. It is an important cause of morbidity and mortality in humans and animals worldwide, and animal hosts can be involved in the epidemiology of infections.[240,367,373,452,727] The adaptive and versatile nature of *E. coli* argues that ongoing studies should receive a high priority in the context of One Health involving humans, animals, and the environment.[240,315,343,727] Two of the 3 *E. coli* pathogens associated with death in children with moderate-to-severe diarrhea in Asia and Africa are classified into 2 *E. coli* pathogenic groups (also known as pathotypes or pathovars): enterotoxigenic *E. coli* (ETEC) and enteropathogenic *E. coli* (EPEC).[367] In global epidemiologic studies, ETEC and EPEC rank among the deadliest causes of foodborne diarrheal illness and are important pathogens for increasing disability adjusted life years.[355,382,570] Furthermore, in humans, *E. coli* is one of the top-ten organisms involved in coinfections, which generally have deleterious effects on health.[270]

ETEC is also an important etiologic agent of diarrhea in the agricultural setting.[183] *E. coli*-associated extraintestinal infections, some of which may be antibiotic-resistant, have a tremendous impact on human and animal health. These infections have a major economic impact on the poultry, swine, and dairy industries.[70,151,168,681,694,781,797] The pervasive nature of *E. coli*, and its capacity to induce disease have driven global research efforts to understand, prevent, and treat these devastating diseases. Animal models for the study of *E. coli* infections have been useful for pathogenesis elucidation and development of intervention strategies; these include zebrafish, rats, mice, Syrian hamsters, guinea pigs, rabbits, pigs, and nonhuman primates.[27,72,101,232,238,347,476,489,493,566,693,713,744,754] Experiments involving human volunteers have also been important for the study of infectious doses associated with *E. coli*-induced disease and of the role of virulence determinants in disease causation.[129,176,365,400,497,702,703] *E. coli* strains (or their lipopolysaccharide) have also been used for experimental induction of sepsis in animals; the strains used

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for these studies, considered EPEC, are not typically involved in systemic disease.[140,205,216,274,575,782]

This article provides an overview of selected topics related to *E. coli*, a common aerobic/facultative anaerobic gastrointestinal organism of humans and animals.[14,277,432,477,716] In addition, we briefly review: history, definition, pathogenesis, prototype (archetype or reference) strains, and features of the epidemiology and control of specific pathotypes. Furthermore, we describe cases attributed to different *E. coli* pathotypes in a range of animal hosts. The review of scientific and historical events regarding the discovery and characterization of the different *E. coli* pathotypes will increase clinical awareness of *E. coli*, which is too often regarded merely as a commensal organism, as a possible primary or co- etiologic agent during clinical investigations. As Will and Ariel Durant write in *The Lessons of History*: "The present is the past rolled up for action, and the past is the present unrolled for understanding".

Beneficial *E. coli* strains

E. coli, originally called *Bacterium coli commune*, was isolated from a human infant and reported in 1885.[185,193] This isolate, currently identified as National Collection of Type Cultures 86, was sequenced and found to be genetically similar to *E. coli* K-12, a laboratory strain that has played a significant role in research and biotechnology.[185,350,374,429] *E. coli* K-12 was isolated from a convalescent diphtheria patient without diarrhea or urinary tract infection (UTI).[268,374] The K-12 genetic sequence provides evidence of genetic changes (genomic plasticity) that allows the bacteria to adapt.[68,222,391] The phylogenetic and genomic characteristics of K-12 and National Collection of Type Cultures 86 support their roles as commensal bacteria.[185] Another *E. coli,* genetically similar to K-12, is B, which probably originated from Institute Pasteur's *Bacillus coli* and was used by Delbrück and Luria for bacteriophage studies.[150,322,695] In 1969, Delbrück, Luria, and Hershey became Nobel Laureates "for their discoveries concerning the replication mechanisms and genetic structure of viruses".[720] *E. coli* B includes strains BL21 and REL606, which have been used for studies of evolution and recombinant protein production, respectively.[322] BL21 and others strains used for recombinant DNA experiments [such as DH5α, EQ1, and BLR (of K-12 background)] have been investigated in animal models and found to be nonpathogenic.[13,115,259] Shedding of BL21 and EQ1 was still present at week 6 after inoculation in a 1-d old specific-pathogen-free chick.[115] Other laboratory strains of *E. coli* include C [American Type Culture Collection (ATCC) 700078], W (ATCC 9637), and Crooks (ATCC 8739; GenBank: CP000946.1) or Crookes.[16,197,279,373,473] *E. coli* C, which was originally isolated at the Lister Institute, exhibits robust biofilm formation and was recently sequenced.[373] The W strain was isolated from cemetery soil, and its "W" designation alludes to its discoverer, Selman A. Waksman, who also discovered streptomycin and was awarded the Nobel Prize in 1952.[16]

A First World War soldier who was resistant to dysentery was colonized with an *E. coli* strain that was isolated by Alfred Nissle and is currently known as the probiotic Nissle 1917 (*E. coli* O6:K5:H1).[34,598,760] *E. coli* Nissle 1917 (EcN) is commercially available and has been used to treat intestinal disorders including inflammatory bowel disease (IBD), constipation, and diarrhea.[33,34,598,760]

E. coli O9:H4 (HS), isolated from the feces of a healthy human, is another strain considered to be commensal, and it has been useful for studies of colonization and genetics.[398,476,594] Genetic studies comparing commensal and pathogenic *E. coli* have been useful for the determination of the *E. coli* pan-genome, which consists of core (genes present in all strains), dispensable [genes absent in greater than or equal to 1 strain(s)], and unique (present in a particular strain) genes.[594,718,765] Because *E. coli* is characterized by having a mosaic structure (sharing gene clusters with other isolates), commensals are thought to behave as gene "donors" and/or "recipients" and in doing so, become pathogenic.[594,765] In fact, over 90% of the pan-genome is constituted by variable/'accessory' genes.[407]

Mobile genetic elements, such as bacteriophages and plasmids, and homologous recombination contribute to the evolution of *E. coli* virulence.[282,597,730,776] Furthermore, an experiment using mice demonstrated in vivo transduction of a recipient K-12 *E. coli* (MC4100) with a Shiga toxin (Stx) 1-encoding bacteriophage and thereby documented the importance of horizontal gene transfer on *E. coli* evolution and virulence potential.[2,384,562,647]

E. coli the commensal and *E. coli* the pathogen

The pathogenicity of *E. coli* has been investigated in vivo since the 1920s.[621,678] However, *E. coli* is commonly referred to as a commensal and its importance as a pathogen may be underappreciated.[118,388,391,625] The potentially beneficial attributes displayed by some *E. coli* strains, including K-12, Nissle 1917, and HS, do not provide a rationale to exclude the pathogenic potential of other *E. coli* strains isolated from clinically unaffected hosts. Clinicians should not assume that *E. coli* identified/isolated from a clinically unaffected patient is a commensal. A commensal relationship implies that during a host-bacterium interaction, the commensal *E. coli* benefits, while the host is neither benefited nor affected.[716] However, because *E. coli* promotes colonization resistance (or the ability to outcompete pathogens trying to colonize), which benefits the host, this host-bacterium interaction is arguably mutualistic, providing benefits for both bacteria and host.[14,389,415,491,716] In addition, some *E. coli* strains are facultative pathogens, meaning that they can live as commensals in the gastrointestinal (GI) tract and also become associated with disease.[388,391] Furthermore, host factors must also be considered.[566] Even Nissle 1917 can induce systemic disease in susceptible animal hosts if their immune system and microflora are perturbed.[272] Therefore, understanding these relationships provides the basis for pursuing and performing a comprehensive characterization of an *E. coli* pathotype upon isolation and aids in deciphering its clinical relevance.

Identifying serotype and phylogenetic group

Hosts may be infected with more than one *E. coli* pathotype (*E. coli* coinfection).[4,137,669] Therefore, several *E. coli* isolates from a particular host tissue or targeted biologic sample should be selected for characterization. Once *E. coli* has been isolated on selective culture media (that is MacConkey agar, CHROMID CPS) and identified biochemically (that is API 20E), a basic approach is to "name" the *E. coli* by serotype determination. The gold-standard for serotyping *E. coli* consists of identification of the O (O-specific polysaccharide of the lipopolysaccharide) and H (flagellar protein) antigens.[118,162,540] Historically, O serotyping has been performed using sera (antibodies), although current techniques take advantage of molecular methods including polymerase chain reaction (PCR).[162,228,406,540] The *E. coli* Reference Center at Penn State University performed serotyping and select molecular characterization of virulence genes in *E. coli* isolates. Some serotypes are more common within particular pathogenic *E. coli* groups.[500] For example, O157:H7 is a characteristic enterohemorrhagic *E. coli* (EHEC) serotype.[500]

The creation of an *E. coli* reference (ECOR) collection, composed of both human and animal isolates, facilitated the study of *E. coli* diversity.[118,530] Phylogenetic group determination using a multiplex PCR method allowed further classification of the *E. coli* isolate.[48,123,299] During a clinical investigation, classification of *E. coli* into the major phylogenetic groups, including A, B1, B2, and D, provided information about epidemiology and virulence.[241,328] Another study determined that groups A and B2 were prevalent in humans, whereas A and B1 and D and B1 were prevalent in nonhuman mammals and birds, respectively.[195] In general, groups A and B1 represent commensal strains, whereas B2 and D represent pathogenic/virulent strains.[82,123,333,566] B1 isolates are usually not host-adapted, whereas B2 isolates are host-adapted.[770]

Sequence type determination is performed using multilocus sequence typing (MLST), a molecular technique involving the sequencing of 7 to 8 house-keeping genes (loci), and using the genetic data to classify the *E. coli* strains and identify potentially pathogenic clones.[124,412,587,776] By calculating homologous recombination frequency, investigators can determine if the *E. coli* population is clonal.[677,696,776] Currently, *E. coli* MLST databases at The Institut Pasteur and Enterobase can be accessed online.[124,313,515,721] For example, clonal group ST131 is predominant among extraintestinal pathogenic *E. coli* (ExPEC).[515]

In summary, when detecting or describing a particular *E. coli* strain, the investigator may use a combination of phylogenetic group, sequence type, and serotype, respectively, as illustrated with a pandemic antibiotic resistant clonal group known as B2-ST131-O25b (ST131, the sequence type; O25b, a molecular subtype of O25).[125,448,611] High-throughput genome sequencing is useful for rapid molecular characterization of bacteria, including their virulence determinants and comparative analysis.[11,118,458,462] Long-read sequencing methods such as PacBio are useful for deciphering plasmids that may be involved in antibiotic resistance.[257,550] Finally, these sequencing technologies are revealing the heterogeneous nature of *E. coli* in terms of combination of virulence factors, thus expanding their classic pathotypic designation.[92,169,458]

E. coli pathotypes, acronyms, and prototypes

In general, classification of *E. coli* into specific pathotypes depends on which virulence determinants are encoded and expressed by the *E. coli* isolates.[500] For example, molecular methods, including PCR assays with specific primers, can be performed to detect particular virulence determinants that are characteristic of particular *E. coli* pathotypes. Protein expression and phenotypic characteristics such as in vitro cell adherence or cytotoxicity should be confirmed.[151,359,361] In general, *E. coli* pathotypes are categorized into those that induce disease within (diarrheagenic) or outside of (extraintestinal) the GI tract. However, some strains may be considered hybrids because they have virulence determinants/characteristics of more than one pathotype.[187,425,437,524]

Diarrheagenic *E. coli*

Enteropathogenic *E. coli* (EPEC). ***Definition.*** EPEC strains do not produce Shiga toxin, but induce pathognomonic lesions known as attaching and effacing (A/E) lesions that can be observed microscopically.[476,500] EPEC adheres to the intestinal epithelium, the microvilli become effaced, actin is polymerized, and pedestals are formed (Figure 1).[476,500] The A/E phenotype, enterocyte membrane cupping surrounding bacteria adhering to the mucosa, and pedestal formation have been observed in human tissues.[620,640,712,742]

History and pathogenesis. *Bacterium coli* strains including an “O55 B5 H7” (strain 3801) have been reported in human infants with vomiting and diarrhea.[780] Prior to the description of EPEC associated diarrhea, the 2 known mechanisms of *E. coli*-induced diarrhea consisted of enterotoxin production and intestinal mucosa invasion.[186,620] These 2 mechanisms of *E. coli*-induced diarrhea were not involved in the diarrheal disease observed during an EPEC trial in human volunteers.[398,400] However, by experimentally infecting neonatal pigs with *E. coli* “055B5H7”, a human isolate from a diarrheic patient, investigators demonstrated attaching and intracellular *E. coli*, increased density under the attachment area which was thought to be “a cellular response to the bacterium”, and microvillus exfoliation in ileal sections.[476,686] The increased density under the attached bacteria was found to be due to site-specific concentrations of cytoskeletal actin, which characterized the A/E lesion; this was demonstrated using EPEC strains including *E. coli* O55:H7 (strain 660-79) associated with infant diarrhea.[359,360] O55:H7 infant diarrhea strains are evolutionarily relevant because they gave rise to EHEC O157:H7.[212,770]

Investigations of spontaneous cases of diarrhea in rabbits led to the discovery of *E. coli* O15 (strain RDEC-1), the prototype rabbit EPEC which is used experimentally to elucidate EPEC pathogenesis.[101] Infecting New Zealand White (NZW) rabbits with RDEC-1 demonstrated that coincidental bacterial adherence to intestinal epithelial cells occurred only when there was a lack of brush border.[707] Other experimental studies demonstrated RDEC-1-induced A/E lesions and adherence pedestals in both pigs and rabbits.[476] Another NZW rabbit study, using *E. coli* 015:H- (strain U83/39), demonstrated bacterial attachment to goblet cells and absorptive epithelial cells as well as microvillus border effacement.[554]

The locus of enterocyte effacement (LEE) is a genetic region known as a pathogenicity island, which has virulence determinants that are necessary for A/E lesions to develop. It encodes effector proteins and a type III secretion system that operates as an injector apparatus, translocating effectors into human or animal cells.[192,285,325,690,711] LEE effectors include translocated intimin receptor, *E. coli* secreted proteins (Esps), and Map, among others.[690] The chromosomal *eaeA* (*E. coli* attaching and effacing) gene is necessary for the formation of A/E lesions, and the 94-kDa immunogenic protein it encodes is known as intimin.[178,323-325] The characteristic A/E phenotype is the result of EPEC inserting intimin (an outer membrane protein) and translocated intimin receptor (LEE effector) into the host cell.[349,690] Other organisms that induce A/E lesions include EHEC and *Citrobacter rodentium*.[564,690] *C. rodentium* causes transmissible murine colonic hyperplasia and has been used experimentally in mice to study EPEC pathogenesis.[409,564,643]

Prototype. *E. coli* O127:H6 (E2348/69), originally isolated from a diarrheal outbreak in children, is the prototype human EPEC strain. It was used experimentally in humans to elucidate virulence and pathogenic potential.[176,311,400,500,714] For example, in a randomized double-blind human volunteer study, E2348/69 caused diarrhea in 100% of the subjects, whereas the *eaeA* mutant caused diarrhea in only 36% of the subjects, demonstrating *eaeA* was a virulence determinant.[176] In another randomized double-blind human volunteer study, E2348/69 caused diarrhea in 90% of the subjects, whereas the *ΔespB* mutant caused diarrhea in 10% of the subjects, indicating that EspB was another important virulence determinant with immunogenic properties.[703]

Epidemiology and control. Epidemiologically, typical EPEC (tEPEC) strains can be isolated from humans and carry the EPEC adherence factor (EAF) plasmid, which includes genes

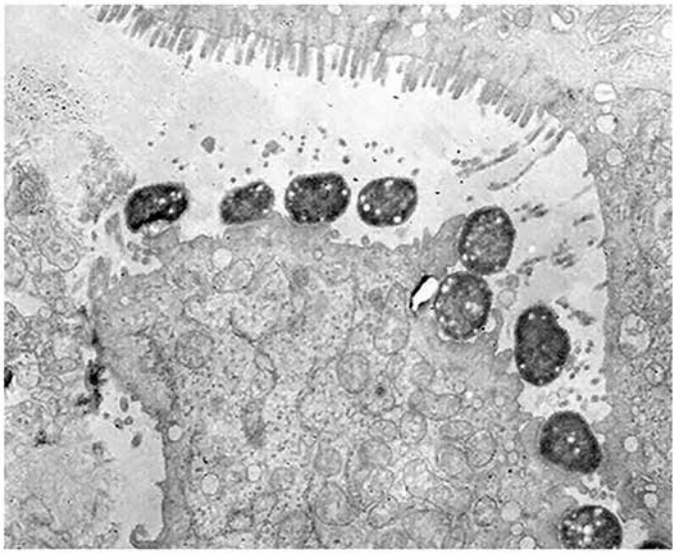

Figure 1. Transmission electron micrograph showing organisms consistent with *E. coli* and associated attaching and effacing lesions and pedestals on the cecal mucosal surface of an experimentally infected Dutch Belted rabbit.

encoding bundle-forming pilus (BFP).[500,732] Having the plasmid gives EPEC the ability to adhere to HeLa and HEp-2 cells with the characteristic localized adherence (LA) pattern/phenotype in which cells attach to the cell surface on one or a few sites.[25,358,502,642] Atypical EPEC (aEPEC) strains isolated from humans and animals do not carry the EAF plasmid.[500,732] This EAF-negative EPEC can exhibit the localized adherence-like pattern ("poor LA") in which less-compact bacterial microcolonies/clusters are found on a few cells when the assay is performed, but a long incubation period (6 h) is necessary.[361,641] tEPEC strains are associated with infantile diarrhea in developing countries, whereas aEPEC strains are not necessarily associated with clinical disease,[306] although prolonged/persistent diarrhea in children has been linked to aEPEC infection.[513,531] tEPEC and 2 other pathogens, including heat-stable toxin (ST)-producing ETEC and *Cryptosporidium* spp., are associated with death in children with moderate-to-severe diarrhea.[367] Both tEPEC and aEPEC can be identified using the fluorescent-actin staining test, which is used to determine if the bacteria can induce A/E lesions. In this test, the A/E lesions are detected as an accumulation of cytoskeletal actin under the attached bacteria.[359,361] Definitive demonstration of protective immunity against EPEC is lacking and an effective vaccine for humans is not currently available.[175,613] An overview of natural EPEC infections in different hosts reveals comparative aspects of etiopathogenesis (Figure 2).

Enterohemorrhagic *E. coli* (EHEC). ***Definition.*** EHEC are Stx-producing *E. coli* (STEC) that encode intimin and induce A/E lesions. Stxs are also known as Shiga-like toxins or Vero toxins.[459,526] The STEC or VTEC designation indicates that a strain is a Stx producer; however, intimin may not be expressed. In addition to the infamous serotype, O157:H7, other STEC with a variety of serotypes are known collectively as non-O157 strains. Some of these strains, including O26 and O111, may originate from aEPEC after transduction with a Stx-encoding bacteriophage.[42,190] EHEC strains can produce Stx 1 and/or 2 (and subtypes/variants); Stx2 production, especially Stx2d, is associated with severe disease.[49,179,459]

History and pathogenesis. Outbreak investigations involving 47 human cases of GI disease, including watery and hemorrhagic diarrhea without pyrexia, in patients that consumed hamburger meat at fast food establishments led to the isolation of *E. coli* O157:H7.[603,767] Previous reports of cases of hemorrhagic colitis in the US and Canada were also associated with *E. coli* O157:H7.[112,338] Two patients with hemorrhagic colitis and O157:H7 infection also developed hemolytic uremic syndrome (HUS), a clinical triad of microangiopathic hemolytic anemia, thrombocytopenia, and acute renal failure.[509,645] An important association was discovered while investigating idiopathic HUS in 40 children, as 75% of them exhibited evidence of Verotoxin-producing *E. coli* infection.[344] The production of this toxin by *E. coli*, and its cytopathic effect on Vero cells (*Cercopithecus aethiops* kidney cells) had been reported in 1977.[364]

Initially, an experiment using infant NZW rabbits reproduced O157:H7-associated diarrheal disease in humans, and histopathologic lesions were observed in the colon of these animals.[542] Weanling NZW rabbits infected with Verotoxin-producing *E. coli* demonstrated A/E lesions and revealed that epithelial cell adherence of organisms was most common in cecum (87%), followed by proximal colon (39%), and distal ilea (26%).[662] Oral inoculation of NZW rabbits with a Stx1-transduced RDEC-1 induced enteric lesions, confirming Stx1 as a virulence determinant in EHEC colitis.[673] A study using infant NZW rabbits experimentally infected with isogenic mutants of an O157:H7 HUS-associated human strain demonstrated that *stx2* is associated with diarrhea and intestinal inflammation, whereas *eae* and translocated intimin receptor gene (*tir*) are important for colonization and induction of diarrhea.[604] Following a report of natural infection of EHEC O153 in Dutch Belted (DB) rabbits with HUS-like disease, our laboratory reproduced enteric and glomerular lesions in experimentally inoculated DB rabbits.[238,243,664] Other experiments developing a rabbit model of HUS or HUS-associated central nervous system disease included IV inoculation of Stxs.[28,29,234,242,470,601,784] Using DB rabbits, our laboratory demonstrated that IV Stx2 promoted enteritis and renal injury.[242] Another HUS model consisting of IV inoculation of baboons with Stx, suggested that HUS was more likely to develop after infection with Stx2-producing *E. coli* than with *E. coli* strains that only produced Stx1.[665]

An experimental strategy using streptomycin, with the objective of promoting EHEC colonization by reducing facultative intestinal flora, has been used to model EHEC infection in mice.[492,754] Disease development in streptomycin-treated

Hosts	Manifestations/Disease conditions	Virulence determinants*	References
Humans (typical EPEC)	Developing country infantile diarrhea and death	Intimin (*eae*), bundle-forming pilus (*bfpA*); Production of BFP may be the best way to differentiate typical versus atypical EPEC	500,732
Humans (atypical EPEC)	Subclinical, mild persistent diarrhea without dehydration (children), or acute diarrhea (children)	*eae*, *bfpA* negative	6,198,300,306,513
Children (typical and atypical EPEC)	Acute diarrhea	*eaeA*, *bfpA* (+ or negative); and supplementary virulence genes (including *cdt*).	552
Cotton-top tamarins (typical EPEC)	Acute diarrhea (profuse) associated with ulcerative colitis	*eae*, *bfpA* +	423
New World Nonhuman primates (NHPs): mainly marmosets (typical and atypical EPEC)	"Healthy" or diarrhea	*eae*, *bfpA* (+ or negative), EAF negative	63,106
Simian immunodeficiency virus-inoculated macaques (EPEC†)	Diarrhea and wasting	*eaeA*	422
Common marmosets (EPEC†)	Hemorrhagic diarrhea, watery diarrhea, acute death	*eaeA*	723
Pot belly pig (EPEC†)	Diarrhea	*eaeA*	304
Pig (atypical EPEC)	"Healthy"	*eae*, *bfpA* negative	233
Pig (typical and atypical EPEC)	"Healthy"	*eae*, *bfpA* (+ or negative)	346
Dog (typical EPEC)	Diarrhea	*eae*, *bfpA* +	32,180,258,371,495,609
Dog (atypical EPEC)	Subclinical or diarrhea	*eae*, *bfpA* negative	32,180,258,371,495,584
Puppy (atypical EPEC)	Chronic diarrhea; coinfection with canine distemper virus	*eae*, EAF negative	753
Cat (typical EPEC)	Diarrhea	*eae*, *bfpA* +	258,371
Cat (atypical EPEC)	Subclinical or diarrhea	*eae*, *bfpA* negative	258,371,481
Birds (atypical EPEC)	"Apparently healthy" (chickens and ducks) or not mentioned (pigeons) "Healthy" (gulls and pigeons) or not mentioned (broilers)	*eae*, *bfpA* negative	210,362
Birds (typical EPEC)	Not mentioned (pigeons and psittacines)	*eae*, *bfp* +	631
Finches	Death	*eae*, *cdt*	225
Cows (typical and atypical EPEC)	"Healthy"	*eae*, *bfpA* (+ or negative)	67
Goats (atypical EPEC)	"Healthy"	*eae*, *bfpA* negative	133
Goat kid (atypical EPEC)	Diarrhea, dehydration, death	*eae*, *bfp* negative	181
Sheep (atypical EPEC)	"Healthy"	*eae*, *bfp* negative	416
Goat kids and lambs	Diarrhea	*eae*, *bfpA* (not determined)	120
Rabbits	Diarrhea	*eae*	101,324
Belgian and Dutch rabbits	"Healthy"	*eae* (negative), EAF negative	572
Belgian and Dutch rabbits	Diarrhea	*eae*, EAF negative	572
Rabbits (Spain)	"Healthy" or diarrhea	*eae* (+ or negative)	59
Dutch Belted (DB) rabbits	Subclinical or diarrhea	*eae*, *bfpA* (not determined)	239,243
DB rabbits (atypical EPEC)	Clinically normal or diarrheic	*eae*, *bfpA* negative	700
Rats	Unknown	*eae*	217
Amargosa voles (with "attaching and effacing *E. coli*")	Colitis, sepsis	*(No molecular characterization, but histologic evidence of attaching and effacing lesions)*	221

Figure 2. Natural EPEC infections: Hosts, manifestations, and virulence determinants.*, This column includes selected virulence determinants investigated in the cited references such as *E. coli* attaching and effacing (*eae* or *eaeA*) gene, bundle-forming pilus (*bfp* or *bfpA*) gene, and cytolethal distending toxin (*cdt*) gene. Typical *E. coli* usually encodes the *bfpA* gene whereas atypical does not. EAF refers to EPEC adherence factor plasmid. †, not characterized as typical or atypical.

MyD88$^{-/-}$ mice infected with *E. coli* O157:H7 provided evidence for the role of innate immunity in pathogenesis.[97] Another mouse model to study EHEC pathogenesis involved feeding C57BL/6 mice a low protein diet (5% protein) that caused intestinal epithelial lesions, and upon infection, resulted in neurologic disease and death.[376] Oro-gastric inoculation of weaned (17 to 21 d old) BALB/c mice with EHEC has also been used as a model for renal lesions.[84] Colonic lesions and acute tubular necrosis are observed in germ-free Swiss Webster mice orally inoculated with EHEC.[188,189] Intraperitoneal inoculation of C57BL/6 mice with Stx2 and lipopolysacharide has been used as a model of HUS that includes glomerular lesions.[347]

The Stx receptor is known as globotriaosylceramide (Gb3) (also known as CD77) and its anatomic location is thought to direct the Stx effect by mediating protein synthesis inhibition and endothelial lesions to the intestine, kidneys, and brain.[81,528,529,651] HUS may result from the inhibition of fibrinolysis and fibrin accumulation after Stx-mediated endothelial injury.[709] Microscopically, edema and hemorrhages are present in the colon, and the kidney shows characteristic lesions consisting of glomerular thrombotic microangiopathy.[348,600] The central nervous system, pancreas, and heart may also be affected.[271,345,370,463,608,719] Brainstem changes have been identified in rabbits and humans (Figure 3).[242,769,784]

Prototype. *E. coli* O157:H7 [strain CDC EDL 933 (ATCC43895)] is the prototype EHEC strain.[602,767]

Clinical aspects. Clinically, performing fecal cultures in human patients within a 6-d window of time that diarrhea begins is important for increasing chances of obtaining an O157:H7 positive culture.[710] STEC may or may not ferment sorbitol;

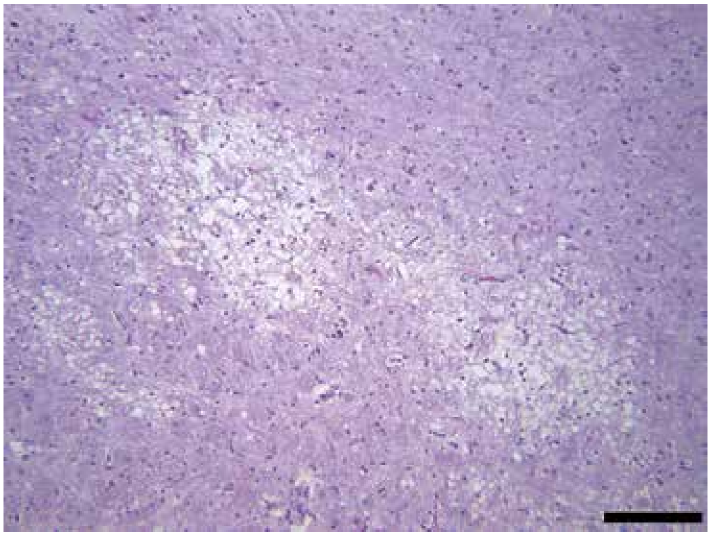

Figure 3. Multifocal brainstem degeneration in a Dutch Belted rabbit after experimental intravenous Shiga toxin 2 infusion (hematoxylin and eosin stain, scale bar: 200 µm). Reprinted from García A, Marini RP, Catalfamo JL, Knox KA, Schauer DB, Rogers AB, Fox JG**.** 2008. Intravenous Shiga toxin 2 promotes enteritis and renal injury characterized by polymorphonuclear leukocyte infiltration and thrombosis in Dutch Belted rabbits. Microbes Infect 10**:**650–656, with permission from Elsevier. Reference 242.

therefore, if selective media based on sorbitol fermentation is used (that is sorbitol-MacConkey agar) to isolate STEC, additional testing may be required.[51,342,424] Physicians treating these cases may encounter the clinical dilemma of whether to use antibiotics. Stxs are encoded in bacteriophages, and the use of some antibiotics to treat STEC infection results in bacterial damage, bacteriophage induction, toxin production and disease.[353,794] A meta-analysis designed to exclude studies with high risk of bias and lacking an acceptable HUS definition, found a significant association between antibiotic administration and HUS risk, supporting the recommendation of avoiding antibiotic use in STEC-infected human patients.[229] A recent literature review however, concluded that although some antibiotics, such as β-lactams, may be harmful, others such as fosfomycin can have positive clinical outcomes.[340]

Epidemiology and control. The epidemiology of STEC/EHEC has been well described and includes both zoonotic and foodborne transmission.[354] A STEC/EHEC review, emphasizing One Health, underscores the interconnections of humans, environment, and animals in epidemiology, prevention and control.[240] Food and vegetables may be contaminated before harvest due to the use of manure fertilizer, feces from wild or farm animals, or contaminated water.[131] Transmission can occur in public settings such as petting zoos, and prevention guidelines have been published.[127,504] Targeting the type III secretion system by vaccination decreases colonization in animals.[453,577,690] The goal of decreasing STEC transmission to humans by cattle vaccination may be more feasible than human vaccination, since vaccine efficacy determination is difficult in humans due to the low disease incidence.[341] An overview of natural STEC/EHEC infections in different hosts reveals comparative aspects of etiopathogenesis (Figure 4).

Enterotoxigenic *E. coli* (ETEC). *Definition.* ETEC strains can produce heat-labile (LT) and/or ST and are an important cause of diarrhea in humans (traveler's and infant diarrhea) and piglets.[263,397,500,606,736] The 2 serologically distinct LTs are LT-I and LT-II.[305,500,567] LT-I is similar to cholera toxin and consists of LTp (p, pig) and LTh (h, human) variants because these toxins were identified in pig and human strains, respectively.[500,672,684,763] LT-II was originally identified in *E. coli* SA53, a water buffalo rectal isolate that is also positive for Stx2.[269,486,567,653] In one study, cow (75%), buffalo (64%), beef from markets (31%) and human (2%) LT-producing isolates encode LT-II genes.[653]

The 2 classes of STs are STa (STI) and STb (STII).[500,532,763] STp and STh are the 2 STa variants that may be found in human ETEC isolates.[326] Human, pig, and cattle isolates may produce STp.[326] STa and STb may be found in porcine ETEC strains.[475] In one study, isolates with genes encoding adhesin involved in diffuse adherence (AIDA-I) and STb were associated with diarrhea in piglets.[512] ETEC may also encode the enteroaggregative *E. coli* heat-stable enterotoxin (EAST-1).[264,606,638,747,788]

History and pathogenesis. The ligated rabbit gut assay, originally used for *Vibrio cholera* research, was used to screen *E. coli* isolates from human babies, calves, pigs and water.[161,715] Many *E. coli* isolates from cases of infantile diarrhea induced dilation in the ligated rabbit gut assay (positive test result).[715] Cattle strains were less effective than human isolates.[715] Isolates from swine enteritis and edema disease (ED) and well water were negative using this assay.[715] A pig gut loop assay revealed a heat-labile enterotoxin in *E. coli* isolates associated with diarrheal outbreaks in pigs.[283] These *E. coli* strains were not invasive and did not damage the villi, but induced fluid secretion and diarrhea.[283] LT and ST enterotoxins were also reported from isolates cultured from diarrheic human patients.[199] The secretory diarrhea caused by ETEC was similar to cholera illness.[186,628]

ETEC can adhere to enterocytes by using multiple surface fimbriae (pili), which in human strains are known as coli surface (CS) antigens.[236,500,606] One group[586] has provided a comprehensive list of CS antigens. These host-specific fimbriae are important for colonization; common ones in strains associated with human diarrhea include colonization factor antigen 1 (CFA/1), CS1, CS2, CS3, CS4, CS5, CS6, CS7, CS14, CS17, and CS21.[236,396,500,586,622,722,778] K88 (F4), K99 (F5), 987P (F6), F41 (F7), and F18 are important for colonization in swine.[109,235,396,456,757,775] In swine, neonatal diarrhea is associated with F5, F6, and F41, whereas postweaning diarrhea is associated with F4 and F18.[456] Newborn and suckling pig diarrhea and mortality are also associated with F4.[456] Coinfections of ETEC and other pathogens

Hosts	Manifestations/Disease conditions	Virulence determinants*	References
Humans	Asymptomatic, diarrhea, bloody diarrhea, and hemolytic uremic syndrome (HUS)	Intimin (*eae*) (+ or negative), Shiga toxin 1 (*stx1*) and/or Shiga toxin 2 (*stx2*) (or variants)	230,231,459,709
Humans	Asymptomatic or mild diarrhea	$stx2_e$ +	682
Humans	Cystitis, hemorrhagic cystitis	*stx2a*, *stx2b* and *stx1c*, *eae* (+ or negative)	731
Rhesus macaques	Clinically healthy or chronic diarrhea	*eaeA*, *stx2c* (Stx2c)	656
Cynomolgus macaques	Diarrhea	*stx1*, *stx2*	363
Pigs	"Healthy"	*eae* negative, $stx2_e$ *eae* positive, *stx1*	346
Pigs	Diarrhea and edema disease (ED) (neurologic signs, vascular lesions, edema)	$stx2_e$, and others [F18, heat-labile toxin (LT) and/or heat-stable toxins (STs)]	108,148,682
Dogs	Not mentioned	Stx1 and Stx2	733
Cats	"Healthy" or diarrhea	*stx1* (Stx1)	1,44,54
Birds	Cellulitis (chickens and turkeys), swollen head syndrome (chickens); septicemia (chickens and turkeys)	*stx1* and/or *stx2*; *eae* (negative)	547
Birds (pigeons)	Not mentioned	*stx1*, *stx1* and *stx2*	667
Cattle	"Healthy"	SLTI and/or SLTII	436,768
Calves	Diarrhea; diarrhea with blood (dysentery)	Verotoxin	320
Goat kid	Severe diarrhea, coma	SLT1 gene and toxin production	184
Goat kid	Diarrhea	*eaeA and stx*	304
Rabbit	Clinical condition not reported. *E. coli* isolated from the mesenteric lymph node of a carcass	*slt-IIera* (SLT-IIera)	352
Belgian and Dutch rabbits; Rabbits (Spain); DB and NZW rabbits	Subclinical or diarrhea	*eae*, *stx1*	59,239,572
DB rabbits	Bloody diarrhea, death, renal lesions, HUS-like disease	*eae*, *stx1*	243
Norway rats	Not mentioned	*eaeA*, *stx1*, *stx2*, pO157	121
Norway rats	Not mentioned	*stx1*	516

Figure 4. Natural STEC/EHEC infections: Hosts, manifestations, and virulence determinants. *, This column includes selected virulence determinants investigated in the cited references such as *stx* genes and Stx production; slt (SLT) refers to Shiga-like toxin (Shiga toxin).

including rotavirus, *Salmonella* Newport, *Crystosporidium parvum*, and *Cystoisospora suis* have been reported in young pigs.[154,447] ETEC can also induce diarrhea in calves; F5 is commonly associated with these infections, which may be concomitant with *Crystosporidium* infections.[155,224,629] Infections with rotavirus may increase susceptibility to ETEC infection and disease in calves.[680,739]

Prototypes. *E. coli* O78:K80:H11/LT1-STh-STp/CFA/I (H10407), originally isolated from the stool of a *Vibrio*-negative patient with diarrheal disease in Bangladesh, is the prototype ETEC strain; its genome sequence indicates that it is related to the nonpathogenic *E. coli* strains K-12, C, and HS.[141,200,201,606] The classification of ETEC into different phylogenetic lineages (polyphyletic) by MLST suggests that the acquisition of colonization factor and toxin genes by nonpathogenic *E. coli* results in ETEC.[736] Regarding ETEC in ruminants (lambs and calves), *E. coli* O101:K99:NM (B41) is the prototype K99 ETEC.[314,485,541] In China, *E. coli* O8:K87:H19 (C83902) is the prototype F4 ETEC of swine.[795,796]

Epidemiology and control. ETEC and cholera have similar clinical presentations of acute watery diarrhea.[626,627] ST-ETEC (positive for ST gene *estA* and LT gene *eltB* or for only *estA*) is one of the 3 pathogens associated with death in children with moderate-to-severe diarrhea.[367] ETEC is a primary cause of traveler's diarrhea.[688,736] In vitro studies suggest that during a coinfection, ETEC and EPEC may interact and increase disease severity.[137] Preclinical studies for ETEC vaccine development used an infection model involving owl monkeys (*Aotus nancymaae*).[615] A phase 1 trial in humans demonstrated protection from ETEC diarrhea using hyperimmune bovine colostral anti-adhesin (anti-CFA/I minor pilin subunit) antibodies, providing supporting evidence for the development of future vaccines against fimbriae of *E. coli* or other organisms.[219,636] More recently, subjects who received hyperimmune bovine colostral anti-CS17 orally did not develop diarrhea after challenge with CS17-expressing ETEC.[637] The use of the antibiotic colistin (polymyxin E) for *E. coli* infections, including postweaning diarrhea prophylaxis in pigs, is discouraged, as this antibiotic is a useful therapeutic alternative in humans for Gram-negative infections that are multidrug-resistant.[599] Vaccines administered during pregnancy impart protection to calves and piglets through ingestion of colostrum.[183,456,474,494,626] However, control of postweaning diarrhea in swine by vaccination has been challenging.[183] A live nonpathogenic *E. coli* strain positive for F4 (Coliprotec F4) used for oral vaccination of pigs was reported to confer protection against diarrhea after weaning.[209] Furthermore, a study using 2 live nonpathogenic *E. coli* strains expressing specific antigenic variants of F4 (Coliprotec F4) and F18 as an oral vaccine found that this vaccination strategy was clinically efficacious for swine diarrhea after weaning.[493] An overview of natural ETEC infections in different hosts reveals comparative aspects of etiopathogenesis (Figure 5).

Enteroinvasive *E. coli* (EIEC). *Definition.* EIEC strains invade the colonic epithelium and cause bacillary dysentery similar to *Shigella dysenteriae*, *S. boydii*, *S. flexneri*, and *S. sonnei*.[12,464,549,559,740] MLST and genome sequencing can be used to differentiate *Shigella* spp. and EIEC.[142,381] Analyses of the *E. coli* O124:H30 (strain M4163 from a cheese-related outbreak in 1971) and *E. coli* O143:H26 (strain 4608-58) genome determined that these were larger than the *Shigella* genomes, consistent with gene loss/decay in *Shigella*.[213,393] Regarding lactose utilization, which is used for identification on MacConkey agar, strain M4163, strain 4608-58, and *Shigella* were lactose negative, positive, and negative,

Hosts	Manifestations/Disease conditions	Virulence determinants*	References
Humans	Acute diarrhea; Traveler's diarrhea Developing country infantile diarrhea and death	Heat-labile toxins (LTs; *eltAB*) and/or heat-stable toxins (STs; *estB*, *estA*); surface fimbriae (various)	199,326,460,606,682,736
Pigs	Subclinical (nondiarrheic)	LT and ST genes	482
Pigs	Edema disease, postweaning diarrhea	Adhesins/fimbriae, LTI, STs, Stx2e	64,108,148,284,456,517,682,752
Dog	Soft feces (coinfection with canine distemper virus)	STap and STb genes	180
Birds (pigeons)	Not mentioned	*elt*, *est*	667
Calves	Diarrhea	K99 (F5), ST	5,224,629
Black-footed ferrets	Sudden death, dehydration, diarrhea, anorexia	*sta*, *stb*	83
Rodents (*Rattus rattus*, *Mus musculus*)	Not mentioned	LT gene	93

Figure 5. Natural ETEC infections: Hosts, manifestations, and virulence determinants. *, This column includes selected virulence determinants investigated in the cited references.

respectively. This demonstrated that EIEC lactose utilization is variable.[393] *Shigella* is so similar genetically to EIEC that investigators have proposed its inclusion into the EIEC group, or alternatively, *Shigella* to be an *E. coli* sister species.[117,563,800]

History and pathogenesis. Investigators of an outbreak affecting people with dysentery/gastroenteritis in 1971 determined that the source of the infection was imported cheese, which was contaminated with an invasive *E. coli* O124:B17 that was not enterotoxigenic.[426,735] One study reported that invasive *E. coli* strains contained a plasmid (~140 megadalton) and that invasiveness was established when a plasmid from *Shigella flexneri* was transferred into avirulent *E. coli*.[632] When *E. coli* O124 strains were inoculated into the eyes of guinea pigs (Sereny test), 6 of 17 strains (35%), including one strain from a primate and 5 from humans, were positive (caused clouding and/or ulceration of cornea).[294,652] All 6 Sereny test positive O124 strains carried the 140 megadalton plasmid known as invasion plasmid (pINV) which was later found to share a basic replicon with pINV from *Shigella* spp.[294,336,666]

In general, pathogenesis involves gaining access to the epithelial cell's basolateral pole through invasion of the M cells found on lymphoid follicles.[549] Macrophages with phagocytized bacteria become apoptotic, expressing IL18 and IL1, followed by the bacteria invading epithelial cells.[549] Once inside the epithelial cells, bacteria spread to adjacent cells and induce IL8.[549] The cytokine stimulation induces polymorphonuclear cell transmigration that increases the susceptibility of the epithelial cell barrier to the influx of bacteria from the lumen.[549] The *ipaH* genes encode proteins considered type III secretion system (delivery apparatus) effectors that have roles in bacterial survival, induction of host cell apoptosis, and NF-κB inhibition.[19,549]

Prototype. *E. coli* O124:NM (NM, nonmotile) (EDL 1284; 929-78) (ATCC 43893), originally isolated from the stool of a human in Texas, is the prototype EIEC.[15,211,294,585,741]

Epidemiology and control. EIEC O96:H19 has been associated with foodborne human outbreaks in Europe.[464,510] Because the genetic composition and pathogenic mechanism of EIEC and *Shigella* are very similar and EIEC are difficult to identify, familiarity with *Shigella* epidemiology and control is useful.[117,297] *Shigella* spp. also constitute one of the 4 common causes of moderate-to-severe diarrhea in pediatric cases from Asia and Africa and can acquire antibiotic resistance plasmids from *E. coli*.[12,367] *E. coli* can also acquire antibiotic resistance plasmids from *Shigella* spp. such as $bla_{\text{CTX-M-55}}$.[588,593] Animal *E. coli* isolates may carry $bla_{\text{CTX-M-55}}$ and related plasmids.[410] Our laboratory reported that macaques can be infected with quinolone-resistant *Shigella flexneri* strains that may transfer antibiotic resistance to *E. coli*.[420]

Several *Shigella* strains have been sequenced, and to date, no vaccines against human shigellosis are available.[619] The development of immunity against *Shigella* is specific to the serotype to which the host is exposed; this feature is one of the challenges of *Shigella* vaccine development.[12,223,399,565] However, cross-protection may be possible because guinea pigs orally immunized with a mutant *S. flexneri* 2a that overexpresses the type III secretion system were protected against *S. dysenteriae* and *S. sonnei;* these animals also developed antibodies against EIEC.[469] An overview of natural EIEC infections in different hosts reveals comparative aspects of etiopathogenesis (Figure 6).

Enteroaggregative *E. coli* (EAEC). ***Definition.*** EAEC are formally defined as those *E. coli* that exhibit an aggregative adherence (AA) pattern on Hep-2 cells and are not enterotoxin (ST or LT) secreting strains.[503] However, because the AA pattern has been observed with aEPEC O125ac:H6, testing for EPEC and EAEC genes is important if an isolate exhibits the AA phenotype in vitro.[30,404] DNA probes can also be used for EAEC identification.[533]

History and pathogenesis. Originally referred to as enteroadherent *E. coli* or enteroadherent-aggregative *E. coli*, these strains exhibit a Hep-2 cell adherence pattern characterized by D-mannose-resistance, as seen with EPEC.[139,397,444-446,501,750,786] Evaluation of the Hep-2 cell adherence patterns of *E. coli* isolates from stools of children from Chile revealed an aggregative phenotype, characterized by bacteria autoagglutination or stacked-brick configuration (aggregative adherence or AA). This phenotype was observed in 84 of 253 (33%) and in 20 of 134 (15%) of strains negative by EPEC adherence factor probe isolated from diarrhea cases and controls, respectively.[500,501] The same aggregative phenotype was observed in ETEC (3/27; 11%) and in EPEC (2/86; 2%).[501] Furthermore, an *E. coli* strain (#221) isolated from a person who traveled from the US to Mexico was later recognized to exhibit the AA pattern and to induce diarrhea in human volunteers.[401,445,446,749,750]

The 3 main pathogenesis steps consist of adherence, the production of mucus and then production of toxin.[301,336,738] AA fimbriae I (AAF/I) and AAF/II contribute to bacterial adherence and AA phenotype.[146,498,500] AAF variants, including AAF/III, AAF/IV, and AAF/V, have also been described.[40,71,334] The AA phenotype can be affected by the composition of the surface protein layer/outer membrane protein.[163,755]

EAEC strains induce the intestinal mucosa to produce more mucus, creating a biofilm in which the bacteria become trapped.[500] However, biofilm production varies with regard to the strain.[659,660] EAST-1 may be encoded/produced by some EAEC and other *E. coli* pathotypes including ETEC (for example, in prototype strain H10407), EPEC, and EHEC.[454,634,635,638,785]

Hosts	Manifestations/Disease conditions	Virulence determinants*	References
Humans	Diarrhea/gastroenteritis/bacillary dysentery	Invasion plasmid (pINV), *ipaH*	267,426,464,549,657,728,735
Rhesus macaques	Diarrhea	*virA*	363
NHP (several species; rhesus apparently more susceptible)	Enzootic outbreak: Severe weakness, bloody diarrhea, hemorrhagic diathesis, lethargy, dehydration, wasting, dystrophic lesions, and mortality	*ipaH*	383
Birds (pigeons)	Not mentioned	*ipaH*	667
Chickens	Yolk sac infection	*ipaH*	616
Lambs	Diarrhea	*ipaH*	248
Rodents (*Rattus rattus*, *Mus musculus*)	Not mentioned	*ipaH*	93
Hamsters	Enteritis (ileitis)	*No molecular characterization but histologic evidence of intra epithelial organisms*	232

Figure 6. Natural EIEC infections: Hosts, manifestations, and virulence determinants. *, This column includes selected virulence determinants investigated in the cited references such as genes for type III secretion system effectors including *ipaH* and *virA*.[464,549]

A large plasmid encodes a serine protein autotransporter toxin known as Pet (plasmid encoded toxin) that is secreted by EAEC and potentially is involved in its pathogenesis.[147,336,505,506] The AA plasmid (pAA) can encode AAF/I, AAF/II, AAF/III, EAST-1, and Pet.[40,147,196,750] EAEC are genetically heterogeneous; horizontal and vertical transmission are involved in AA plasmid inheritance.[147] "Typical" strains carry pAA whereas "atypical" strains do not.[751]

Prototypes. *E. coli* O3:H2 (17-2), originally isolated from the stools of a diarrheic Chilean infant, is a prototype EAEC strain that expresses AAF/I, whereas *E. coli* O44:H18 (042), originally isolated from the diarrheic stool of an infant in Peru, expresses AAF/II and is another prototype that can be used as reference.[146,147,498,499,502,634] Both 17-2 and 042 encode EAST-1, and 042 also encodes Pet.[196,497] EAEC 55989 encodes AAF/III, was isolated from the stool of a person from the Central African Republic who had HIV and persistent diarrhea, is phylogenetically related to entero-aggregative-hemorrhagic *E. coli* (EAHEC) German hybrid outbreak strains, and is considered a prototype strain.[40,92,336,487,730]

Epidemiology and control. EAEC is another common cause of travelers' diarrhea and has also been associated with persistent diarrhea in children and HIV patients.[46,47,336,366,445,759] Clinically, EAEC causes a persistent diarrhea that can be mucoid.[497,500,738] EAEC was also associated with extraintestinal disease, as EAEC O78:H10 ST10 was isolated from urine of humans with UTI during an outbreak in Denmark.[73,534,535] Some experimental vaccine strategies against EAEC have incorporated AAF as a component of the vaccine.[80,536] An overview of natural EAEC infections in different hosts reveals comparative aspects of etiopathogenesis (Figure 7).

Adherent invasive *E. coli* (AIEC). ***Definition.*** The specific virulence determinant(s) that define AIEC have not been elucidated.[118,439] However, the presence of the *pic* gene and resistance to ampicillin can be used to identify AIEC strains.[100] AIEC strains have been sequenced.[122,466,496] Comparative analyses of AIEC genomes from Crohn disease (CD) patients, mice with ileitis, dogs with granulomatous colitis, one non-AIEC genome, and other genomes revealed an overrepresentation of genes for propanediol utilization and iron acquisition in AIEC.[174] Also, long polar fimbriae (LPF; *lpf* operon) are involved in the interaction of AIEC with Peyer patches and M cell translocation.[116]

E. coli designated as AIEC by phylogenetic analysis, clustered by phylogenetic group and not by pathotype and some clustered with ExPEC in phylogenetic groups B and D.[174] Genetically, AIEC strains share virulence determinants with ExPEC; however, phenotypically, distinguishing features of AIEC include adherence and invasiveness of the epithelium and survival with replication inside macrophages.[255,440]

History and pathogenesis. *E. coli* O83:H1 was originally isolated from the affected ileum of a human patient with CD.[79,152] Another study reported intracellular *E. coli* in colorectal carcinoma and adenoma mucosae of humans.[701] *E. coli* can be found adhering to and invading the intestinal mucosa of patients with CD and colon cancer.[434] A relative increase in *E. coli* and a decrease in a Clostridiales subset in the mucosa is also associated with some cases of CD ileitis.[31]

In one study, the percentage of ExPEC strains exhibiting AIEC phenotype was 6%.[440] In another study, human *E. coli* isolates from colon cancer mucosa were found to encode virulence genes associated with uropathogenic *E. coli* (UPEC).[89] Furthermore, isolates from human cases of CD and colorectal cancer were characterized by afimbrial adhesin (*afaC*) and *lpfA* expression whereas isolates from ulcerative colitis and colorectal cancer encoded *afaC* and polyketide synthase (*pks*) pathogenicity island.[439,582] AIEC strains can also create biofilms efficiently and induce inflammation that may be modified by an AIEC's cellulose production.[105,191,441] Adding to the complexity of the role of *E. coli* in the etiopathogenesis of IBD, an invasive, LPF-encoding *E. coli* O126:H27 (strain D92/09) exhibiting AA pattern and also encoding intimin and Shiga toxin 1 was isolated from the ileal lesions and stools of a CD patient.[149] This D92/09 hybrid strain was 97% similar to EAHEC O104:H4/2011C-3493 strain from the HUS outbreak that occurred in Germany in 2011.[149]

Prototype. *E. coli* O83:H1 (LF82), which was originally isolated from the affected ileum of a human patient with CD, is the prototype AIEC strain.[79,152]

Epidemiology and control. AIEC are associated with intestinal disease, and AIEC epidemiology has not been completely elucidated.[439] However, a survey of the ECOR collection identified AIEC in apparently healthy humans and animals including pig, elephant, goat, cougar, and Celebes macaque.[590] A possible strategy to protect individuals against AIEC and development of CD incorporates type 1 fimbriae adhesin protein (FimH) antagonists.[589,671] An overview of natural AIEC infections in different hosts reveals comparative aspects of etiopathogenesis (Figure 8).

Diffusely adhering *E. coli* (DAEC). ***Definition.*** Plasmid or chromosomal encoded genes give DAEC the ability to adhere to HeLa and HEp-2 cells with the characteristic diffuse adherence pattern in which the whole cell surface is covered by bacteria.[25,38,52,502,641,642]

Hosts	Manifestations/Disease conditions	Virulence determinants*	References
Humans	Traveler's diarrhea; Persistent diarrhea (infants/children); HIV patients with and without diarrhea	Aggregative adherence fimbriae (AAF) in plasmid (pAA); In vitro aggregative adherence (AA) phenotype	47,336,445,460,759
Humans (0–5 y old)	Infants with diarrhea	With (typical) or without (atypical) plasmid-borne genes	751
Pigs (0–6 mo old)	Diarrhea	Without (atypical) plasmid-borne genes	751
Dogs	Subclinical or diarrhea	*agg*R; AA phenotype	584
Dogs (0–6 mo old)	Diarrhea	With (typical) or without (atypical) plasmid-borne genes	751
Cat	Subclinical	*agg*R; AA phenotype	584
White-eyed conure	"In a good health condition"	Atypical with AA phenotype	427
Cows (0–6 mo old)	Diarrhea	Without (atypical) plasmid-borne genes	751
Goats (0–6 mo old)	Diarrhea	Without (atypical) plasmid-borne genes	751

Figure 7. Natural EAEC infections: Hosts, manifestations, and virulence determinants. *, This column includes selected virulence determinants such as the plasmid-borne transcriptional activator gene (*aggR*) and also the adherence phenotype investigated in the cited references.

Hosts	Manifestations/Disease conditions	Virulence determinants*	References
Humans	Crohn disease; colorectal cancer	Epithelial adherence and invasion and macrophage survival (phenotype); *dsbA*, *htrA*, *lpfA*.	31,79,87,88,116,152,255,440
Humans	"Healthy"	Epithelial adherence and invasion and macrophage survival (phenotype). Also, lack of genes associated with diarrheagenic and uropathogenic *E. coli*.	590
Celebes macaque	"Healthy"	Epithelial adherence and invasion and macrophage survival (phenotype). Also, lack of genes associated with diarrheagenic and uropathogenic *E. coli*.	590
Pig	"Healthy"	Epithelial adherence and invasion and macrophage survival (phenotype). Also, lack of genes associated with diarrheagenic and uropathogenic *E. coli*.	590
Dogs	Granulomatous colitis, hematochezia	Epithelial adherence, invasion, and replication (phenotype).	418,668
Cats	Enteritis	Adhesion, invasion, and survival/replication indices	438
Cougar	"Healthy"	Epithelial adherence and invasion and macrophage survival (phenotype). Also, lack of genes associated with diarrheagenic and uropathogenic *E. coli*.	590
Goat	"Healthy"	Epithelial adherence and invasion and macrophage survival (phenotype). Also, lack of genes associated with diarrheagenic and uropathogenic *E. coli*.	590
Mice	*Toxoplasma gondii*-induced ileitis	Propanediol dehydratase (*pduC*), iron acquisition (*chuA*), long polar fimbriae (*lpfA*)	138,174

Figure 8. Natural AIEC infections: Hosts, manifestations, and virulence determinants. *, This column includes selected virulence determinants and phenotypic characteristics investigated in the cited references.

DAEC and EAEC share phylogenetic and adherence characteristics. For example, a phylogenetic tree based on multilocus enzyme electrophoresis of 20 enzymes revealed 5 overlapping clusters constituted by DAEC and EAEC strains that were akin to the clusters seen with EPEC and EHEC.[147,177] Another common feature is that EAEC and DAEC adhesins belong to the same Dr superfamily.[71] Broadly, DAEC can be differentiated by whether they express Afa/Dr or Afa/Dr-related adhesins including F1845 (from C1845) and AIDA-I.[35,52,654,655] AIDA-I was originally cloned from plasmid DNA of EPEC O126:H27 (strain 2787) from an infant diarrhea case.[38,39]

History and pathogenesis. Human volunteers did not develop diarrhea after ingestion of either of 2 DAEC strains.[702]

E. coli with Afa/Dr adhesins have been isolated in cases of urinary tract disease or diarrhea.[52,62,316,379,386,522,655] The association of DAEC with urinary or intestinal disease may be related in part to the capacity of some DAEC to induce tight-junction

Hosts	Manifestations/Disease conditions	Virulence determinants*	References
Humans	Subclinical; Diarrhea; Traveler's diarrhea; Persistent bloody diarrhea without fever; Bloody diarrhea with fever; Urinary tract infection including gestational pyelonephritis	Afa/Dr or Afa/Dr-related adhesins; *afa/dr*	4,62,317,460,523,551,552,655,746
Humans	Inflammatory bowel disease, colon cancer	*afaC*, *lpfA*, *pks*	582
Pigs	Postweaning diarrhea or edema disease	Adhesin involved in diffuse adherence (AIDA); *orfA*, *orfB*	517
Pigs	Not mentioned	*afaB*	757

Figure 9. Natural DAEC infections: Hosts, manifestations, and virulence determinants. *, This column includes selected virulence determinants investigated in the cited references.

lesions through secreted autotransporter toxin, one of serine protease autotransporters of *Enterobacteriaceae*.[278,421,655,704,705]

The genes for *afa*/*dra*/*daa* can be found in various *E. coli* pathotypes including STEC and ExPEC.[194,387] Furthermore, some strains positive for *daaC* (F1845 accessory gene) and one encoding AIDA-I that exhibit DA pattern may also encode *eae*, be fluorescent-actin staining test positive, and can be considered aEPEC strains.[35,38,655] In addition, AIEC strains from the mucosa of CD and colorectal cancer patients may be positive for *afa*.[152,437,582]

Prototypes. *E. coli* O75:NM (C1845) is the prototype DAEC and was isolated from a child with a 3-wk duration (protracted) diarrheal illness that lacked evidence of other pathogens.[52,99] Prototypic UPEC strains include O2 (KS52), a urine isolate from a pyelonephritis patient, and O75:K5:H- (IH11128), isolated from a person with UTI.[380,521,655,743] *E. coli* O75:K5:H- (IH11128) expresses Afa/Dr adhesins and is genetically related to *E. coli* O75:NM (C1845).[53] C1845, KS52, and IH11128 express F1845, AfaE-I, and Dr adhesins, respectively.[278]

Epidemiology and control. In France, DAEC was commonly isolated from hospitalized diarrheic human patients.[317] In developing countries, DAEC is the third most important cause of traveler's diarrhea after ETEC and EAEC.[688] DAEC was one of 3 prevalent pathotypes, including EAEC and EPEC, detected in asymptomatic Peruvian children and was the most prevalent in coinfections.[4] In Mexico, DAEC was identified in 35% of hospitalized diarrheic children.[552] An association of DAEC infection and bloody diarrhea with fever has been reported.[551,552] Vaccines against DAEC have not been reported. However, traveler's diarrhea chemoprophylaxis and chemotherapy have been reported.[688] An overview of natural DAEC infections in different hosts reveals comparative aspects of etiopathogenesis (Figure 9).

Extraintestinal pathogenic *E. coli* (ExPEC). ***Definition.*** The acronym ExPEC has been proposed for use in referring to strains associated with diseases outside the GI tract including (but not limited to) meningitis, urinary tract, and systemic (septicemia) infections.[624] These *E. coli* strains can also be recognized by the names neonatal meningitis *E. coli*, UPEC, and sepsis-causing *E. coli*.[151] Prostatitis is another manifestation of ExPEC infection.[372,625] Strains expressing cytotoxic necrotizing factor (CNF)1 or CNF2 are referred to as necrotoxigenic *E. coli* 1 or 2, respectively, and CNF3 has also been described.[159,335,538] Necrotoxigenic *E. coli* can cause disease in animals and humans.[159,332]

History and pathogenesis. Initially, hemolysin was proposed as a virulence determinant associated with *E. coli* involved in extraintestinal infections; a later report found that some hemolytic isolates also produced a toxin known as CNF.[103,111] *E. coli* encoding CNF1 was associated with enteritis/diarrhea of neonates and children.[56,102]

UTIs are ascending infections, meaning that intestinal bacteria (such as UPEC) enter through the urethral orifice before reaching the bladder and inducing inflammation.[465] More extensive colonization of UPEC may allow it to reach the kidneys and blood, causing life-threatening disease.[465] Experimental mouse models of lethality involving *E. coli* injection showed that clinical ExPEC isolates classified as phylogenetic group B2 induced lethality and encoded relatively more virulence determinants including *pap* (pyelonephritis-associated pilus; P fimbriae) and *hly* (α hemolysin) operons.[566] Another study using mice found that *fyuA* (yersiniabactin receptor), *usp* (uropathogenic-specific protein), *malX* (pathogenicity island marker), *pap*, and phylogenetic group B2 significantly predicted the "killer" status of ExPEC isolates.[309,328] ExPEC may also encode other genes associated with virulence and express α or β hemolysin.[151,333,596] However, comparative sequence analysis suggested that no single virulence mechanism is used by ExPEC isolates and that extraintestinal infection in a particular organ is not dependent on expression of a single virulence determinant.[91,151] A phylogenetic group B2 *E. coli* isolated from a human with fatal hemorrhagic pancreatitis has been classified as a translocating *E. coli* based on its ability to translocate across epithelial cells into the mesenteric lymph nodes and blood.[22]

E. coli can produce toxins that affect the cell cycle (cyclomodulins), including CNF's, cytolethal distending toxins (CDTI, CDTII, CDTIII, CDTIV, CDTV), cycle inhibiting factor, and colibactin (Clb; encoded by *pks*).[182] Analyses of urosepsis *E. coli* strains determined that encoding CNF-1 and Clb was associated with the B2 phylogenetic group.[182] B2 isolates from prostatitis cases also encoded at least one cyclomodulin including *Clb*, *Cnf*, or *Cdt*.[372] In addition, many *E. coli* K1 isolates that are associated with systemic infections in neonates encode *Clb*, which is important for virulence.[241,450] Secreted proteases including serine protease autotransporters of *Enterobacteriaceae* can also impact ExPEC pathogenesis.[708]

The role of *E. coli* pathotypes in IBD has been recently reviewed.[467] Previously, hemolytic and necrotoxic *E. coli* were isolated from humans with ulcerative colitis; these strains seemed to colonize after relapses.[128] A microarray study found genetic similarities between *E. coli* isolates from humans with IBD and ExPEC.[748] B2 phylogenetic group cyclomodulin-expressing *E. coli* strains have been detected in colonic biopsies of patients with colorectal cancer.[94] A study of human fecal samples using a quick PCR assay for direct quantification of bacterial genes in stools detected *Clb* genes in 20% of the samples.[261] In several different experimental mouse models, *Clb* is associated with cancer promotion consistent with its in vitro phenotype, which includes megalocytosis and DNA breaks.[17,74,136,143,520,592] Paradoxically, the Nissle 1917 strain used as probiotic also encodes Clb; its probiotic activity depends on ClbP, a Clb-activating peptidase.[442,520]

CDT is considered genotoxic and carcinogenic in other experimental infections.[245-247,706] For example, chronic inflammation and dysplastic nodules were observed in an A/JCr mouse model of liver cancer involving oral inoculation of *Helicobacter hepaticus*, which naturally encodes CDT.[247] The tumor promoting effect of CDT-encoding *H. hepaticus* was reproducible in a different model and organ system; 129/SvEv Rag2 deficient mice developed intestinal cancer 20 wk after inoculation.[245] Also, after 21 wk, intestinal pathology was significantly exacerbated in *H. hepaticus*-infected 129/SvEv $Rag2^{-/-}$ $Il10^{-/-}$ gpt δ male and female mice.[246] The fecal and mucosal (cecal and colonic) levels of *pks+ E. coli* significantly increased in *H. hepaticus*-infected 129/SvEv $Rag2^{-/-}$ $Il10^{-/-}$ gpt δ mice.[246] CDT may also be encoded by *pks+ E. coli* colonizing laboratory rats.[377]

Prototypes. *E. coli* O4:K6:H5 (J96), isolated from a human patient with pyelonephritis, is a prototype ExPEC strain expressing *papG* alleles and *cnf1*.[309,330] J96-like strains (O4 serotype) have been isolated from urosepsis, acute cystitis, and bacteremia.[330] *E. coli* O6:K15:H31 (536) is another pyelonephritis human archetypal strain that encodes S fimbrial adhesin (*sfa*) comparable to some human isolates from newborn cases of meningitis, including RS218 and IHE3034.[69,285,286,333] *E. coli* O18ac:K1:H7 (RS218 and IHE3034) ("K1 strains"), isolated in California and Finland, respectively, are prototype meningitis-associated ExPEC with known genetic sequences.[3,153,764,774] *E. coli* O6:K2:H1 (CFT073) is the prototype acute pyelonephritis-associated (uropathogenic) *E. coli* that has been sequenced.[331,408,472,765] Pathogenicity island differences exist between CFT073, 536, and J96.[285,765] *E. coli* CFT073 (O6:K2:H1) is genetically related to the probiotic Nissle 1917 (O6:K5:H1).[598]

Avian pathogenic *E. coli* (APEC) is considered ExPEC and *E. coli* O2:K1:H5 (IMT5155) is the prototype strain isolated from the internal organs of a chicken during an outbreak of colisepticemia.[202,203,402] *E. coli* ONT:H21 (SCI-07) is another strain classified as APEC due to its molecular characteristics. It was isolated from a laying hen with "swollen head syndrome" signs and has been genetically sequenced.[204,614] *E. coli* OR:H10 (SEPT362), a hepatic isolate from a septicemic chicken, is another sequenced APEC strain of interest, given it encodes EAST-1, serine protease autotransporters of *Enterobacteriaceae* Tsh, and has an enterotoxigenic-like phenotype.[417,613]

E. coli O2:K53,93:H1 (BM2-1) is a prototype bovine CNF-1-expressing hemolytic *E. coli* strain isolated from the feces of a calf with enteritis.[157,158,160] *E. coli* O15:K+:H21 (S5) is a prototype CNF-2-producing strain isolated from blood of a bacteremic lamb.[561,675]

Disease in ferrets may be caused by strains positive for *cnf1*, *hlyA*, and *pap1* including: O4:H-, O4:H5, O6:H-, and O2:H4.[428] Rat *E. coli* strains with potential to cause disease have been recently characterized and include O7:H7 (*pks+*, *cdt-*, *cnf-* and *pks+*, *cdt+*, *cnf-*), O166:H6 (*pks+*, *cdt+*, *cnf-*), OM:H6 (*pks+*, *cdt+*, *cnf-*), and O4:H5 (*pks+*, *cdt-*, *cnf+*).[377] In mice, *E. coli* O2:H6/41 (NC101 strain) is considered a prototypic *pks+* strain that, in monoassociation experiments, induces intestinal inflammation in interleukin-10 knockout ($IL10^{-/-}$) mice and also promotes invasive carcinoma in $IL10^{-/-}$ mice administered azoxymethane.[17,351,405]

Epidemiology and control. In humans, the clinical presentation of ExPEC infections can vary and these diseases including UTIs have significant medical and economic impact.[151,220,465,625] Given their importance, epidemiologic studies should include genotypic and phenotypic (protein expression) information regarding ExPEC associated virulence determinants.[151] Antibiotic therapy for UTI is hampered by the emergence of resistant bacterial strains and mechanisms of resistance.[471] The dissemination of particular clonal groups with antibiotic resistant and hypervirulent characteristics warrants investigations of ExPEC transmission and clonal expansion.[151]

Human UTI vaccines are available in Europe but not in the US.[465] Experimentally, UTI vaccine targets include antigens related to bacterial iron acquisition.[471] The human ExPEC4V vaccine includes 4 different *E. coli* O antigens and has been evaluated in Phase 2 studies.[310,312,679] Also, a multiantigen (including 4 surface proteins) vaccine against APEC reduced lesions due to APEC O2, as well as blood and organ load, after experimental challenge in chickens.[745] An overview of natural ExPEC infections in different hosts reveals comparative aspects of etiopathogenesis (Figure 10).

Mix and Match: Challenges

Hybrids. Hybrid strains are an emerging public health risk with associated medical and epidemiologic challenges that behoove the investigation of isolates for an expanded set of virulence determinants using techniques such as whole-genome sequencing.[298,524,525,579]

In 1998, HUS-outbreak associated *E. coli* O111:H2 strains were reported to exhibit STEC and EAEC characteristics, providing a prelude to entero-aggregative-hemorrhagic *E. coli* (EAHEC).[480] In 2011, an outbreak of EAHEC O104:H4 associated with sprout consumption caused close to 4000 cases of acute gastroenteritis or hemorrhagic colitis (855 HUS cases and 53 deaths).[95,724] EAHEC O104:H4 was antibiotic resistant and phenotypically produced extended-spectrum β-lactamase (ESBL).[50,226,458] Two O104 patient isolates from this outbreak were sequenced and found to be similar to an EAEC African strain (55989); however, these 2 isolates contained a Stx-encoding prophage.[40,92,458] The role of farms as virulent determinant pools for the emergence of EAHEC O104:H4 was suggested by a study performed in Germany and Spain, in which the genes characteristic of this strain, including *stx2*, *aggR*, wzx_{O104}, and fli_{H4}, were identified in samples from one German abattoir that was closer to the outbreak epicenter, and that used animals originating from farms near the epicenter.[96] Furthermore, genome sequence analyses of sporadic (not outbreak related) O104 strains suggested that O104 variants may emerge from other reservoirs and not necessarily from the epidemic strain.[724]

EPEC/ETEC hybrids are *E. coli* strains carrying LEE genes and expressing type III secretion system effector (EspB) and LT that appear to have originated from plasmid-acquiring EPEC.[298] Children/infants were colonized with these EPEC/ETEC strains in Africa and India.[187,298] A study in cattle reported EPEC/ETEC and EHEC/ETEC isolates.[20] STEC and/or EHEC/ETEC hybrids are *E. coli* strains encoding Stx(s) and ST, and some have been recovered from disease cases that include HUS in young human patients in Finland, and animals, including cattle.[339,433,524,525,579] The plasmid of *Escherichia* sp. cryptic lineage 1 O2:H25 (strain 7v) from healthy cattle feces encodes a mix of virulence determinants from STEC and ETEC plasmids, including K88, which is usually found in ETEC plasmids from pig isolates.[394] Pigs can harbor ETEC and STEC/ETEC hybrid strains that are resistant to multiple antibiotics.[86]

In Spain, O153:H10-A-ST10 *eae*-β 1 aEPEC-ExPEC has been isolated from diarrheic humans and canid (fox) feces.[169] In France, infection with *E. coli* O80:H2 (clonal group ST301) was associated with a high percentage of HUS cases (91%), of which 3 cases included bacteremia, peritonitis/septic shock, or pancreatic abscess .[425,683] The genetic characteristics of *E. coli* O80:H2, encoding intimin and Stx2 and positive for genes associated with extraintestinal virulence of plasmid pS88, suggest that this *E. coli* is an EHEC/ExPEC hybrid.[425,557,683] An overview of natural

Hosts	Manifestations/Disease conditions	Virulence determinants*	References
Humans	Diarrhea (infant/children)	Cytotoxic necrotizing factor 1 (CNF1) and hemolysin (Hly) production	56,103
Humans	Colorectal cancer	B2 phylogenetic group; *cnf1* and *pks* (and cytotoxin production)	94
Humans	Urinary tract disease	Various genes or combinations including: *pap*, *sfa*, *afa*, *aer*, and *cnf*; alpha or beta hemolysis	596
Humans	Asymptomatic and symptomatic bacteriuria	Hly production	308
Humans	Urosepsis	Several genes and *fyuA*, *traT*, pathogenicity-associated island marker	331
Humans	Bacteremia	Various genes: *cnf*, bla_{TEM}, *fyuA*	478
Humans	Prostatitis	Various genes including *cdt1*, *clb*, and *cnf1*	372
Humans	Meningitis	Colibactin production (*pks*); K1 capsule	3,256,450,607
Humans	Septic arthritis/pyomyositis, pneumonia, spontaneous meningitis, nonvertebral hematogenous osteomyelitis	≥2 virulence determinants including: *papA* and/or *papC*, *sfa/foc*, and *kpsM* II	327
Humans	Cholangitis and bacteremia	≥1 adhesin; *papG* class II	758
Macaques	Clinically normal	*cnf1* (and cytotoxic), *papG*, *hlyA*, and beta hemolytic	435
Macaques	Clinically normal	*pks*, *cnf1* (and cytotoxicity demonstrated for both)	214
Pigs	Postweaning diarrhea	*cnf1* (5.9% of strains/isolates). These *cnf1+* isolates produced Hly and two were *cdtB+*	729
Pigs	Abortion	*cnf1*, Hly production	571
Pigs	No clinical signs ("healthy")	*cdtB*	303
Dogs	"Healthy"	No virulence determinant genes (most common) or positive for ≥ 1 virulence determinant gene including: *cnf* , *sfa/foc*, *papGIII*, *hlyD*	689
Dogs	Diarrhea	*cnf1*, *pap*, *hlyA*, *fyuA*, and other genes	687
Dogs	Diarrhea, septicemia, and other conditions	*cnf1*	571,687
Dogs	Urinary tract infection	*hly*, *fyuA*, *pap*, *papG* allele III, *sfa/foc*, *sfaS*, *iroN*, and *ompT*	329,333,791
Dogs	Pyometra	*cnf* , *sfa*, *pap*, *hly*, *iuc*, *afa*	126
Dogs	Cystic endometrial hyperplasia	CNF	167
Cats	"Healthy"	Hly, CNF1, CNF2	54
Cats	Diarrhea, septicemia	*cnf*	571
Cats	"Healthy"; urinary tract infection	*pil*, *pap*, *sfa*, *hly*, *cnf1*	791
Cats	Pyometra	Hemolytic	119
Cats	Infertility	*pks*, *cdt*, *cnf*	419
Birds (poultry)	Omphalitis, swollen head syndrome, cellulitis, septicemia, other lesions	*iutA*, *iss*, *hlyF*, *iroN*, *ompT*, *tratT*, other genes, ColV plasmids, production of aerobactin and colicin V	262,337,449,511,546
Cattle	"Healthy"	*cnf2*, *cdtB*, *ehaA*	303
Cattle	"Healthy", diarrhea (calves), septicemia, pneumonia, mastitis, abortion	*cnf1* (CNF1), *cnf2* (CNF2)	57,156,571
Cattle	Metritis	*cnf2*, *fyuA*	55,571,661
Goats	Septicemia	*cnf1*	571
Goats	"Healthy" (kids or lambs)	*cnf1* and/or *cnf3*, *eae*, *ehxA*	538
Goats	Diarrhea (kids)	*cnf3*, *eae*, *ehxA*; CNF2, *eae*	120,538
Sheep	Septicemia (lamb)	CNF2	156,675
Sheep	"Healthy" (adult), diarrhea (lambs)	*cnf3*, *eae*, *ehxA*	538
Ferrets	Subclinical, gangrenous mastitis, systemic disease	Hemolytic *E. coli* (virulence genes not characterized)	403
Black-footed ferret	Sudden death, dehydration, diarrhea, anorexia	*cnf1* (one isolate from a kit's kidney and liver)	83
Ferrets	Diarrhea (and diseased tissues including mammary gland, brain, uterus)	*cnf1*, *hlyA*, *pap1*	428
Rabbits	Diarrhea	CNF1, Hly	60
Rabbits	Diarrhea	*cnf1* (CNF1), *cnf2* (CNF2)	59
Mice	Abscesses (subcutaneous and others affecting seminal vesicles, preputial glands, kidney, uterus), septicemia, pneumonia, or endometritis	Not reported	36
Mice	Subclinical; Cystic endometrial hyperplasia	*clbA*, *clbQ*; Cytotoxicity	241
Mice	Urosepsis, meningitis	*clbA*, *clbQ*; Cytotoxicity	24
Mice	Peritonitis	Not reported (ß-hemolytic *E. coli*)	334
Mice	Intestinal inflammation (cecum, colon)	*sfa/focCD*, *fyuA*, *cnf1/2*, and others	777
Hamsters	Enterocolitis, diarrhea	ß-hemolytic *E. coli*; some co-infected with *Lawsonia intracellularis*	172
Hamsters	Necrosuppurative mastitis	Not reported (*E. coli*)	172
Guinea pigs	Diarrhea	*pks*	208

Figure 10. Natural ExPEC infections: Hosts, manifestations, and virulence determinants. *, This column includes selected virulence determinants investigated in the cited references.

Hybrid type	Hosts	Manifestations/ Disease conditions	Virulence determinants*	References
EAEC/STEC	Humans	HUS outbreak	*stx2* (Stx2), *astA*, AA phenotype	78,480
	Humans	Gastroenteritis, hemorrhagic colitis, HUS, death	stx_{2a}, (Stx2), lpf_{O113}, lpf_{O26}, *iha*, *aggR*, *aatA*, *aap*, *aggA*, *aggC*, *set1*, *pic*, AA phenotype	50,95,227
EPEC/ETEC	Humans	Symptomatic or asymptomatic	LEE (EspB), LT (inactive)	298
	Human	Diarrhea	*eae*, *elt*, (*Campylobacter* co-infection)	187,298
	Humans	Lethal	LEE (EspB), *bfp*, *eatA*	298
	Ruminants (cattle)	Not reported	*eae*, *estA*	20
STEC and/or EHEC/ETEC	Humans	Asymptomatic, diarrhea, HUS	*stx2* (Stx2), *estIa* (STIa), *hly* genes, *eae*, *fyuA*, others	524,525
	Humans	Diarrhea, abdominal pain, fever	Stx (*stx2g*), *stIa* (ST)	579
	Human	Cystitis	stx_{2a}, *estIA*, *eae*	731
	Pig	Not reported	stx_{2k}, *sta*, *stb*	787
	Pigs	Postweaning diarrhea	stx_{2e}, genes for F18, STa, and STb	752
	Pig at slaughter/pork	Not reported	Stx2e (stx_{2e}), STIp and STII (STb) genes, *astA*	45
	Cattle	Not reported	*stx2*, *stx1* (Stx1), *estIa* (STIa), *astA*, *hly* genes, others	20,433,524,525,579
	Goats and sheep	Not reported	*stx1*, *stx2*, *sta*	339
aEPEC/ExPEC	Humans and a fox	Diarrhea (humans)	*eae*, $fimAv_{MT78}$, *traT*, *fimH54*	169
EHEC/ExPEC	Humans	HUS with bacteremic complication	*stx2*, *eae*, pS88 plasmid genes	425,683
	Humans	Diarrhea	*stx*, *hlyA*, *vat*, *clb* island, *cnf1*, *iro* cluster, *ybt* cluster	244
ETEC/DAEC	Gorilla	"Healthy"	*tia*, *afaD*	590
EIEC/EHEC/EAEC	Human	Crohn disease	*aggR* /*eae*/*stx1*/invasive and AA phenotypes	149
tEPEC/STEC	Cockatiel and budgerigar	"Healthy"	*eae*, *bfpA*, *stx2f*	251

Figure 11. Natural hybrid *E. coli* infections: Hosts, manifestations, and virulence determinants. *, This column includes selected virulence determinants investigated in the cited references.

hybrid *E. coli* infections in different hosts reveals comparative aspects of etiopathogenesis (Figure 11).

Mobile drug resistance: Carbapenamase. ESBL-producing bacteria are defined by non-susceptibility to extended-spectrum cephalosporins (including third-generation cephalosporins) and aztreonam and susceptibility to clavulanic acid.[544,595] A proposed ESBL nomenclature seeks to add non-susceptibility to carbapenems to this definition.[253,756] Carbapenems are used to treat infections caused by ESBL-producing *Enterobacteriaceae*.[544] *E. coli* carrying ESBL genes have been found in companion animals.[104,171,307,726] The recent documentation of ESBL transmission leading to bacteremia and death in a human patient treated for *C. difficile* colitis via fecal microbiota transplantation has raised concerns regarding donor screening for this therapy.[164]

Carbapenem resistance can be transferred by plasmids and includes New Delhi Metallo-β-lactamase (NDM), *Klebsiella pneumoniae* carbapenamase (KPC), and oxacillinases (OXA).[518,519,756,766] NDM-1 encoding bacterial strains can be resistant to almost all antibiotics and represent a global health threat.[375,519] NDM-1 gene was detected in a *Klebsiella pneumoniae* isolate from a human UTI patient who visited New Delhi, India.[789] This patient was also colonized with an enteric *E. coli* carrying a plasmid with NDM-1 gene (bla_{NDM-1}) suggesting in vivo conjugation.[789] In the US, *Klebsiella pneumoniae*, *E. coli*, and *Enterobacter cloacae* human isolates with bla_{NDM-1} were reported from patients with a history of medical care in India.[113] A study of multidrug-resistant *Enterobacteriaceae* from India, Pakistan, and UK found that NDM-1 encoding isolates consisted mainly of *Klebsiella pneumoniae* and *E. coli*, and that NDM-1 was mainly found on plasmids.[375] Furthermore, human patient and environmental (vacuum cleaner dust from patient's home) ST131 *E. coli* encoding bla_{NDM-1} have been characterized.[75,378,558,574]

In companion animals, urine (4 canine and one feline), wound (canine), and nose (canine) *E. coli* isolates were positive for NDM-1 genes (bla_{NDM}), suggesting that these animals can be a potential reservoir for these resistant strains to infect humans; however, the travel history of owners of these pets was not reported.[658] Meropenem resistant (NDM-5) *E. coli* belonging to ST167 were isolated from 2 dogs with chronic otitis and a human living in the same household in Finland.[273] Interspecies transmission of small col-like plasmids (likely high copy number and possibly highly mobile) encoding bla_{KPC} may be epidemiologically important.[691] OXA-48 carbapenamase-expressing *E. coli* and *Klebsiella pneumoniae* have been characterized from 6 dogs hospitalized in Germany.[692] Carbapenamase-encoding *E. coli* have also been isolated from pigs in Germany and Korea.[218,290,618]

A bla_{KPC-2}-encoding plasmid was detected in an *E. coli* isolate from a river in Portugal, suggesting that aquatic environments be reservoirs.[573] Surface, drinking, and ground waters can be a source of *E. coli* for animals and humans that could subsequently become vectors.[114,288,461,579,766]

Identification of *E. coli* in animal host

Nonhuman primates (NHPs). Historically, *E. coli* has been isolated along with other bacterial or viral pathogens in nonhuman primates with respiratory or systemic diseases.[206,266,543] EPEC was isolated from a 20-wk-old simian immunodeficiency virus (SIV)-inoculated macaque (*Macaca mulatta*) at the New England Regional Primate Research Center that exhibited profuse diarrhea and wasting.[422] Retrospectively, EPEC was identified as one of the pathogens associated with a similar clinical presentation in macaques dying with AIDS.[422] Other pathotypes that have been isolated from macaques include ExPEC[435] and *pks+ E. coli*[214] from subclinical cases, and EIEC and EHEC from an outbreak of diarrhea in outdoor-housed macaques.[363]

In New World monkeys, a clinical investigation of acute profuse diarrhea in cotton-top tamarins (*Saguinus oedipus*) at New England Regional Primate Research Center led to the isolation of EPEC O26:HNM encoding BFP.[423] Tamarins with intimin-positive *E. coli* fecal isolates exhibited higher incidence of colitis and higher active colitis histologic scores.[423] The incidence of EPEC in cotton-top tamarins, a model of human ulcerative colitis, is reminiscent of the *E. coli* prevalence in humans with IBD including ulcerative colitis.[145,368,423,568,633]

EPEC has also been isolated from common marmosets (*Callithrix jacchus*) with bloody stools/diarrhea and the genetic sequence of an isolate was determined.[296,723] EPEC was mostly detected in stool or rectal swab samples from marmosets with bloody stools (100%), but was also found in samples from diarrheic (20%) and clinically healthy (10%) marmosets.[295] Another NHP study that included marmosets found that 27% and 47% of the *E. coli* isolated from both apparently healthy monkeys and diarrhea/enteritis cases, respectively, were positive for *eae*, suggesting a role of EPEC in diarrheal disease observed in captivity.[106] The expression of BFP, a characteristic of tEPEC strains, suggested zoonotic potential.[63,106] Marmosets were proposed as a human EPEC infection model.[106] Laboratory housed marmosets can be colonized with *E. coli*, including *pks*+ or *cnf*+ strains.[321,451]

Pigs. Pigs can be colonized with EPEC and have shown A/E lesions.[233,304] Forty-three STEC strains, mostly encoding Stx2e (Stx2 variant associated with porcine edema disease) and mostly *eae* negative, were isolated from slaughtered (apparently healthy) finisher pigs.[346,431] One of these strains (O103:H2) could be considered an EHEC, as it was positive for both *stx1* and *eae*.[346] Pigs can be considered reservoir hosts of STEC/EHEC, including O157, and have been used experimentally to study infection and disease.[76,77,132,280,603,737] Swine can also harbor EAEC.[751]

Virulence determinants including Stx2e and F18 adhesin (found in ETEC) are associated with ED and diarrhea in weanling pigs, and AIDA-I (found in DAEC) is proposed to play a role as well.[517] AIDA-positive Stx2e-negative isolates were identified in pigs that did not show signs of postweaning diarrhea, suggesting that they were DAEC strains.[517] Some of the Stx2e-producing *E. coli* in one study encoded STs including STIp (STp), STII (STb), and EAST1, suggesting that they can be considered STEC-ETEC hybrid strains.[45,532] A study of postweaning diarrhea in pigs determined that 6% of the *E. coli* strains encoded CNF-1.[729] Hybrid strains with various characteristics were isolated from diarrheic piglets and could not be classified into particular pathotypes.[581]

Dogs. Dogs are reservoirs of aEPEC, tEPEC, STEC, and EAEC.[44,289,371,488,495,584] A/E lesions have been diagnosed in diarrheic 7 to 9 wk old dogs.[304,319] However, some EPEC-colonized dogs may not exhibit diarrhea.[495,584] Isolation of a tEPEC strain with the same genotype, phenotype, and serotype in a pet dog with diarrhea and a child from the same household provided evidence of zoonotic transmission.[609]

Isolates from dogs with GI disease can also be positive for LT and/or ST and thus be considered ETEC, or positive for Stx and considered STEC.[37,237,537,578,687,761] Isolation of *E. coli* O157 from a clinically unaffected dog during an outbreak investigation suggested that dogs act as vectors.[733] Dog feces collected on dairy farms were positive for *E. coli* O157.[291] Stx, LT, and ST gene and protein expression were detected in fecal samples from Greyhounds with and without acute diarrhea.[685] Greyhounds have been used experimentally to study Stx-induced disease.[591]

AIEC, similar to LF82 from human CD, have been isolated from colonic mucosa of boxer dogs with granulomatous colitis.[668] French Bulldog granulomatous colitis may be associated with *E. coli* infection and has been described in young (≤ 1 y old) dogs with hematochezia.[418] Sequence analysis of a 904 bp 16S rRNA PCR amplification product from DNA of formalin-fixed paraffin embedded colonic tissue identified *E. coli* LF82 in the colon of a laboratory Beagle dog with histiocytic typhlocolitis.[107] According to an American College of Veterinary Internal Medicine consensus statement article, if dogs are exhibiting systemic signs of illness, the use of antibiotics is warranted for treating granulomatous colitis.[418,430] Metagenomic analyses determined that the microflora of dogs with IBD (lymphocytic-plasmacytic duodenitis and mixed lymphocytic-plasmacytic duodenitis and neutrophilic duodenitis) is characterized by an abundance of members of the family *Enterobacteriaceae*, to which *E. coli* belongs.[783]

Dogs are also reservoirs of ExPEC strains (some *papG*+) that can be transmitted to humans.[215,329,332] Genotypic analysis revealed common electrophoretic types of clinical isolates from dogs, cats, and humans in different geographic locations, including Florida, Tennessee, and Michigan, suggesting virulent clones.[772] ExPEC strains isolated from dog feces and urine (UTI) were molecularly similar to strains from human clinical cases.[332,333] The virulence determinants of CNF-1-encoding strains from dogs with diarrhea also suggests involvement in UTI.[687] ESBL genes have been detected in canine and feline UTI isolates and in fecal isolates from healthy animals.[134,527] Other potential clinical presentations of dogs with ExPEC infection include hemorrhagic pneumonia and fatal pneumonia with concomitant canine adenovirus type 2 infection.[10,85,293]

E. coli is commonly isolated from the uterus of dogs with pyometra; in cases with concurrent UTI, the same *E. coli* strain may be the causative agent of both infections.[287] Isolates from dogs with pyometra or healthy controls encoded virulence determinants associated with ExPEC involved in UTIs.[7,167,670] Genotypically, some isolates from purulent uterine fluid of affected dogs were similar to those isolated from their saliva, suggesting that dogs can transmit these virulent isolates to humans.[7] Within households, the prevalence of *E. coli* sharing between healthy dogs and owners was determined to be 4%, 8%, and 8% using 3 different fingerprinting (genotyping) methods.[508] *E. coli* with similar genotypes or plasmid pattern have been identified in family members and pets, including dogs and a cat.[110,761]

Cats. A/E bacteria have been identified by histopathology and electron microscopy in 2 clinically affected cats with catarrhal enteritis; *E. coli* was isolated from one of them, suggesting the possibility of EPEC infection.[576] EPEC O-:NM was isolated from the feces of a kitten with diarrhea that later resolved.[304] Clinically affected and unaffected cats may be colonized with tEPEC.[258,371] aEPEC also colonizes kittens, is associated with terminal illness, and has higher colonization levels in animals with diarrhea than in those without diarrhea.[249,514,762] However, in another study, aEPEC were mostly isolated from nondiarrheic cats.[481] Furthermore, *E. coli* isolates from diarrheic or healthy cats can be cytotoxic to Vero cells, and *stx2* has been detected in *E. coli* strains isolated from cats.[1,37,43,44] Cats without diarrhea may also harbor EAEC.[584]

According to genetic analyses, Firmicutes (Clostridiales) were abundant in the GI tract of a healthy specific-pathogen-free cat, whereas *Enterobacteriaceae*, *Clostridium* spp., and *E. coli/Shigella* numbers correlated with clinical signs, duodenal mucosal changes and cytokine upregulation in cats with IBD.[318,605] The virulence determinants of feline IBD-associated *E. coli* have not been reported.[318]

Healthy cats can also harbor CNF-1 positive *E. coli* strains in the feces.[54] Diarrhea and septicemia in dogs and cats were associated with CNF-positive *E. coli*.[571] An isolate encoding CNF-1 and CNF-2 was cultured from one kitten with necrotizing enterocolitis.[514] UTI-associated *E. coli* isolates from dogs and cats may be characterized by a common set of virulence determinants including *hly*, *pap*, *sfa*, and *cnf1*.[215,791] ExPEC infection in cats may be associated with severe respiratory disease including

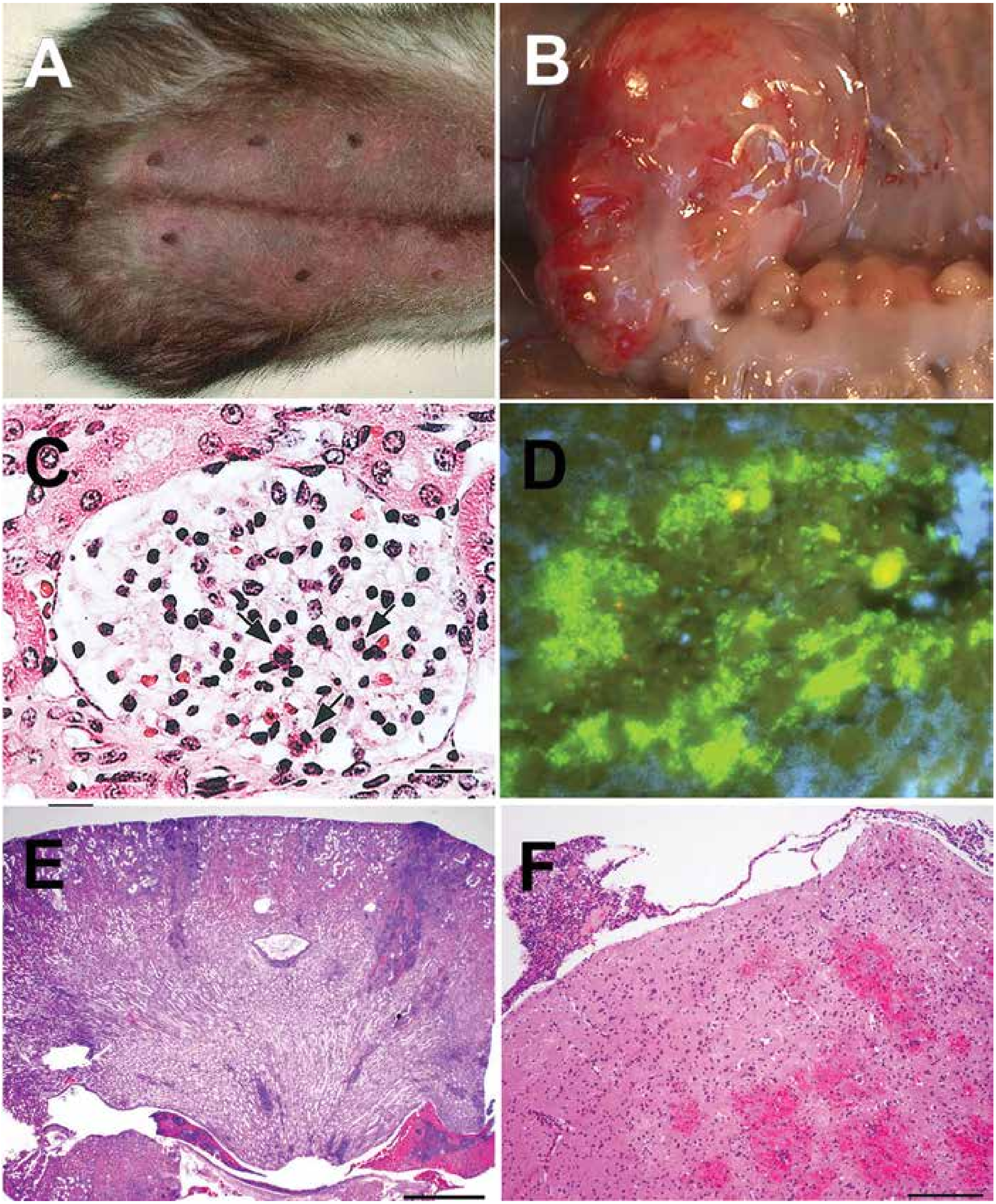

Figure 12. (A) Ferret naturally infected with *E. coli* exhibiting signs of mastitis including swollen and erythematous mammary tissue. (B) Hyperemic and hemorrhagic serosa at the level of the distal cecum adjacent to the junction with the proximal colon in a Dutch Belted rabbit experimentally infected with enterohemorrhagic *E. coli* O157:H7; Copyright © American Society for Microbiology, [Infection and Immunity 80, pages 369-380, 2012]. (C) Global intracellular edematous swelling, increased numbers of heterophils (arrows), and decreased number of erythrocytes ("bloodless glomerulus") in a glomerulus of a Dutch Belted rabbit experimentally infected with enterohemorrhagic *E. coli* O153 (scale bar: 60 µm); García and colleagues, Renal Injury Is a Consistent Finding in Dutch Belted Rabbits Experimentally Infected with Enterohemorrhagic *Escherichia coli*, The Journal of Infectious Diseases, 2006, volume 193, issue 8, pages 1125-1134, by permission of the Infectious Diseases Society of America. (D) *E. coli*-associated necrotizing suppurative metritis (pyometra) in a naturally infected "alpha V integrin$^{+/-}$; alpha v fl$^{/+}$; Tie 2, Cre$^{+/-}$"

fatal pneumonia.[90,302,698] *E. coli* encoding cyclomodulins such as *cnf*, *pks*, and *cdt* have been isolated from feces and vaginal swabs of specific-pathogen-free inbred laboratory cats with a history of infertility, including pyometra, stillbirths, and resorptions.[419]

Birds. Chickens can be carriers of EPEC and STEC O157, and chicks less than or equal to 1 d-old can be experimentally colonized with *eae*-encoding *E. coli* including O157:H7[362,569,649,697] One study found that EPEC colonized the intestine of chickens, pigeons and ducks; pigeons also harbored EHEC[210] and are carriers of STEC/EHEC strains that may encode Stx2f and have zoonotic potential.[165,210,275,362,479,648,682] "Swollen head syndrome" is a poultry disease caused by *E. coli* strains that produce another Stx variant known as VT2y.[483,548,630] Chickens with or without diarrhea may be infected with ETEC (STII/STb).[8] Yolk sac infection in chickens may be associated with *ipaH*-positive bacteria, suggestive of EIEC.[616,617] Pigeons and conures can also be vectors of EIEC and EAEC, respectively.[427,667] In addition, avian organic fertilizer may be contaminated with EAEC and/or EAEC/EPEC hybrid strains.[583]

APEC are ExPEC strains associated with local or systemic colibacillosis; these infections are an important disease category that economically affects the poultry industry.[250,276,449,694] These strains may be classified into subpathotypes, defined by their associated clinical presentation, including omphalitis, "swollen head syndrome", and septicemia.[449] APEC can encode several virulence determinants, and some strains have been proposed to represent human UPEC (ExPEC) or influence human disease by transferring virulence determinants to other strains.[144,202,457,468,610,650,694] Using MLST, APEC and human UPEC isolates were found to belong to 4 sequence types including ST10, ST48, ST117, and ST2016, suggesting zoonotic potential.[173] ExPEC strains involved in UTIs and APEC strains may belong to the same serogroups and may also be genotypically and phylogenetically similar.[610]

Ruminants. Ruminants including goats, sheep, and cows are well-recognized and thoroughly researched reservoir hosts of STEC/EHEC.[41,44,61,65,66,292,799] Some cows are known as super shedders that can excrete O157 at estimated levels of greater than 10^4 CFU/g of feces, a characteristic that could be epidemiologically relevant.[18,135,507] The recto-anal junction has been identified as a lymphoid follicle rich area of the intestine that is colonized by O157:H7 with aggregative adherent phenotype.[135,507] Vaccination strategies have been developed for cattle to reduce the level of intestinal colonization with EHEC.[674] Cattle, sheep, and goats can all carry EPEC that may be zoonotic.[67,96,133,233,416]

Ruminants can also be reservoirs of ETEC, which is shed by diarrheic newborn calves.[61,385,717,773] Virulence determinants of bovine ETEC isolates include STaP, F41 and K99.[413] The K99 plasmid was associated with diarrhea in calves and lambs.[314,484,541,676] K99 and/or F41 detection in goat kid and lamb *E. coli* isolates that were not STI or LTI producers suggested that these strains were virulence determinant reservoirs.[490] In Bangladesh, 34% of the ruminant *E. coli* isolates were STEC-ETEC hybrids and 50% of these were antibiotic resistant.[339] Also, *ipaH*-positive *E. coli* suggestive of EIEC infection were isolated from lambs with diarrhea.[248] *ipaH*-positive *E. coli* and other pathotypes, including hybrid-like strains, were isolated in cultures from bulk tank milk and raw milk filters.[166]

Septicemia and enteric disease in calves can be associated with *E. coli* strains encoding *afa-8*, *east1*, *clpG*, and also virulence determinants of ExPEC (*cnf1*, *hly*, *pap*), suggesting gene exchange between intestinal and extraintestinal isolates.[252] The bovine *E. coli* isolates had some features in common with those from human cancer patients with sepsis.[252] Cnf-2-encoding *E. coli* strains have also been isolated from calves with septicemia and enteric disease.[252,414,539] *E. coli* isolated from goat and sheep feces may express CNF-3 and also encode plasmid-encoded hemolysin/enterohemolysin (*ehxA*) and *eae*.[538,646] Two EPEC O115:H- isolates from the colon and rectum of an O157:H7-inoculated lamb encoded CNF-1, CNF-2, and EAST-1, and another O115 strain encoding these same virulence determinants was isolated from a sheep.[9,130] An outbreak of lamb septicemia was associated with neonatal *E. coli* O78 (K46) infection.[356,357]

Mammary pathogenic *E. coli* was proposed as a "pathotype" for *E. coli* strains isolated from cases of mastitis in cows; however, mastitis-associated *E. coli* and commensal *E. coli* could not be distinguished phylogenetically.[392,663] More recently, in vivo experiments indicated that the ferric dicitrate uptake locus (*fec* locus) is associated with the ability of mammary pathogenic *E. coli* to induce mastitis.[70] Cows develop pelvic inflammatory disease/metritis, which has been associated with *E. coli* strains that encode *fyuA*.[661] These *fyuA*-encoding *E. coli* strains, currently known as endometrial pathogenic *E. coli*, did not encode adhesion and invasion genes of enteric or ExPEC strains.[661] However, comparative genome analysis of the prototype endometrial pathogenic *E. coli* strain MS499 indicated that this strain encodes ExPEC factors.[260]

Ferrets. An investigation of gangrenous mastitis in ferrets implicated hemolytic *E. coli* as the causative agent (Figure 12 A).[403] This disease had an acute septicemic or peracute presentation.[403] The same organism was also isolated from rectal swab samples of ferrets both with and without mastitis.[403] An investigation of *E. coli* isolates from diarrheic feces, uterus, brain, or mammary gland of clinically affected ferrets characterized the isolates as β-hemolytic and positive for *cnf1*, *hlyA*, and *pap1*.[428] These isolates were negative for *cnf2*, *eae*, *stx1*, *stx2*, *sta*, and *stb*.[428] In another study, clinical disease, including sudden death or anorexia and loose mucoid feces (for 12 to 24 h), was observed in captive black-footed ferrets.[83] ETEC (positive for *sta* and *stb*) was isolated from clinically affected adults and kits.[83] The only isolate not characterized as ETEC was isolated from kit tissues and was positive for *cnf1*.[83] To date, Stx-encoding *E. coli* have not been reported in ferrets; however, an experimental model involving Stx-encoding *E. coli* infection of streptomycin treated ferrets has been reported.[779]

Rabbits. Historically, *E. coli* has been recognized as an agent that can commonly colonize clinically unaffected rabbits, including Cottontail rabbits (*Sylvilagus floridanus*), but can also

mouse. *E. coli* is fluorescently labeled with a green peptic nucleic acid in situ hybridization probe that detected bacteria in the affected and luminal areas of the uterus. The nuclei of the cells are stained blue with 4′,6′-diamidino-2-phenylindole (DAPI) (no scale bar: x100); Reprinted from Microbes and Infection18(12), García A, Mannion A, Feng Y, Madden CM, Bakthavatchalu V, Shen Z, Ge Z, Fox JG, Cytotoxic *Escherichia coli* strains encoding colibactin colonize laboratory mice, 777-786, Copyright (2016) with permission from Elsevier. (E) Renal section of a mouse naturally infected with cytotoxic *E. coli* (pks+) and exhibiting multifocal subacute suppurative pyelonephritis, intraluminal bacteria, and tubular necrosis (scale bar: 1 mm). (F) Brain section of a mouse naturally infected with cytotoxic *E. coli* (pks+) and exhibiting focally extensive subacute necrohemorrhagic meningoencephalitis (scale bar: 200 µm). Figures 12(E) and 12(F) have been reprinted from Bakthavatchalu and colleagues (2018) Cytotoxic *Escherichia coli* strains encoding colibactin isolated from immunocompromised mice with urosepsis and meningitis. PLoS One 13(3): e0194443. doi: 10.1371/journal.pone.0194443, with permission through an open access Creative Commons Attribution (CC BY) license. (C, E, F are hematoxylin and eosin stained sections).

	Human	NHP	Pigs	Dogs	Cats	Birds	Ruminants	Ferrets	Rabbits	Rodents
EPEC	X	X	X	X	X	X	X		X	X
STEC and/or EHEC	X	X	X	X	X	X	X		X	X
ETEC	X		X	X		X	X	X		X
EIEC	X	X				X	X			X
EAEC	X		X	X	X	X	X			
AIEC	X	X	X	X	X		X			X
DAEC	X		X							
ExPEC	X	X	X	X	X	X	X	X	X	X
EAHEC	X									
EPEC/ETEC	X						X			
STEC and/or EHEC/ETEC	X		X				X			
aEPEC/ExPEC	X									
EHEC/ExPEC	X									
ETEC/DAEC		X								
EIEC/EHEC/EAEC	X									
tEPEC/STEC						X				

Figure 13. Reported *E. coli* pathotypes or hybrids and the animals in which they have been identified. EPEC, enteropathogenic *E. coli*; STEC, Shiga toxin-producing *E. coli*; EHEC, enterohemorrhagic *E. coli*; ETEC, enterotoxigenic *E. coli*; EIEC, Enteroinvasive *E. coli*; DAEC, Diffusely adhering *E. coli*; ExPEC, Extraintestinal pathogenic *E. col*i; EAHEC, Entero-aggregative-hemorrhagic *E. coli*; aEPEC, atypical EPEC; tEPEC, typical EPEC; EPEC/ETEC, STEC and/or EHEC/ETEC, aEPEC/ExPEC, EHEC/ExPEC, ETEC/DAEC, EIEC/EHEC/EAEC, tEPEC/STEC are hybrids; X, reported; Empty box, not reported.

induce fatal disease.[254,369,790] Similarly, EPEC and STEC/EHEC have been detected or isolated in rabbits with or without clinical signs.[59,239,395,572,699] In addition to RDEC-1, EPEC O103 strains exhibited high pathogenicity along with an inability to ferment rhamnose.[58,98] Coinfection with other pathogens may influence the severity of EPEC infection.[555,644] Particular serotypes may be associated with disease in weaned as compared with suckling rabbits.[553,556]

Rabbits have been reported as vectors of O157:H7 or non-O157 STEC strains.[23,390,580,639] EHEC O153 infection was associated with an outbreak of diarrhea and HUS-like disease in DB rabbits; characterization of the natural cases lead to the development of an experimental model involving oral inoculation (Figure 12 B and C).[238,243,545,664,790,793] Rabbits experimentally infected with other EHEC strains by the intraperitoneal route also develop disease.[281] Other toxigenic *E. coli* strains that can be found in rabbits include those encoding CNF1 or CNF2.[59,60]

Rodents. *E. coli* has been isolated from mice and rats, particularly the murine oral cavity, which may harbor *E. coli* due to coprophagia.[21,265,411,455,734] In a study of Norway rats in New York City, aEPEC was detected in the feces along with other potentially zoonotic pathogens.[217] In farm environments, rats can be EHEC/STEC carriers, and experimentally,[516] intraperitoneal inoculation of recombinant Stx2-expressing *E. coli* culture supernatant has been used to develop a rodent model of HUS.[516,798]

Lesions of *E. coli*-infected clinically affected mice include abscesses (subcutaneous and others affecting seminal vesicles, preputial glands, kidney, uterus), septicemia, pneumonia, or endometritis (Figure 12 D).[24,36,241] Development of spontaneous β-hemolytic *E. coli* peritonitis in homozygous mutant *Myd88*^{tm1Aki} female and male mice suggested susceptibility due to impaired innate immunity.[334] Mice developed hyperplasia and hypertrophy of mesothelial cells.[334] The intestine of interleukin 10-deficient mice with intestinal inflammation contained a higher number of *E. coli* O7:K1:H7 than did that of control mice without disease.[777] A study using laboratory mice, including sentinels, found that animals were colonized by Clb-encoding (*pks*+) *E. coli*, which may confound experimental studies.[241] Cases of urosepsis, including meningitis, were diagnosed in immunocompromised mice infected with Clb-encoding *E. coli* (Figure 12 E and F).[24] *E. coli* was identified in a mouse diagnosed with cystic endometrial hyperplasia; Clb-encoding *E. coli* was isolated from the uterine fluid/wall.[241] In another study, laboratory rats from various commercial suppliers were colonized by Clb-encoding *E. coli*, and some of these isolates also encoded CDT or CNF.[377] Currently, *E. coli* pathotypes are not included in conventional health surveillance protocols for mice or rats.

"E. coli O:105" (strain 1056), an invasive *E. coli* isolated from the ileum of a hamster with proliferative ileitis was shown experimentally to induce acute enteritis in 32% of Syrian hamsters.[232] In addition, spontaneous enterocolitis of Syrian hamsters was associated with coinfection of β-hemolytic *E. coli* and *Campylobacter*-like organisms (now known to be *Lawsonia intracellularis*).[172] Furthermore, *E. coli* infection is one of the potential etiologies associated with urinary tract disease including cystitis, cystic calculi, and urolithiasis in guinea pigs,[560] apparently with a disease predisposition in aged females.[560] These clinical conditions of guinea pigs were observed at mean ages of 35 mo (cystitis) and 30 mo (cystic calculi and urolithiasis).[560] Unfortunately, molecular characterization of hamster and guinea pig *E. coli* isolates was not reported.[172,232,560] Recently, a study characterizing *E. coli* isolates from small mammals identified Clb-encoding *E. coli* in 2 diarrheic pet guinea pigs.[207]

In a fatal case of septicemia in a chinchilla, Gram-negative rods were found adhering to intestinal epithelial cells and EPEC O13:H30 (negative for genes encoding LT, STa, Stb, CNF-1, CNF-2, Stx1, Stx2) was isolated from the kidney and spleen.[170] *E. coli* including ETEC and possibly EIEC (*ipaH* gene amplification) were detected in fecal samples from peridomestic rodents (*Rattus rattus* and *Mus musculus*) samples from rural Madagascar.[93]

Figure 13 illustrates the apparent distribution of *E. coli* pathotypes or hybrids in a variety of animals based on published studies. These data reveal that some pathotypes/hybrids have not been reported in animals and thus represent opportunities for discovery of new hosts. Also, from an epidemiologic perspective, these data underscore the potential for *E. coli* transmission between animals, including zoonotic risks. The combination of *E. coli* diversity and host range generate conditions that could result in the emergence of new virulent strains.

Solutions. The mobility of virulence determinants and antibiotic resistant traits, combined with the range of *E. coli* hosts and reservoirs, represent an underappreciated, dangerous, and puzzling public health threat.[141,336,725] Developing One Health models that help explain the roles of humans, animals, and the environment in current and emerging infections, as well as antibiotic resistance, will help devise intervention or control strategies.[240,315] For example, 4 stages have been defined[26] to represent genetic reactors impacting antibiotic resistance in which water has a critical role: 1) Human and animal microbiota (at stage 1, bacteria become exposed to antibiotics); 2) Locations such as farms, aquaculture operations, hospitals, and long-term care facilities (at this stage 2, bacterial exchange occurs between hosts); 3) Waste and residues from stage 2, including lagoons, wastewater, sewage, or compost (at stage 3, interactions occur between bacteria from different hosts); and 4) Soil and water (surface or ground) (at stage 4, bacteria from stages 1 to 3 interact with organisms in the environment). This model tries to simplify the complexity of emerging antibiotic resistance in a way that could also be applied to understand the emergence of new or hypervirulent *E. coli* strains. The *ESBL E. coli Tricycle Antimicrobial Resistance Surveillance Project* seeks to develop an integrated, trans-sectoral (human, food-chain, and environment) surveillance system of antibiotic resistance using ESBL *E. coli* as the single key indicator organism.[443] Genomic studies in the context of One Health can reveal opportunities for timely intervention and prevent the spread of antibiotic resistance.[623] Other important One Health strategies to prevent *E. coli*-associated infection and disease include organizing groups of scientists such as the *Latin American Coalition for Escherichia coli Research* (LACER) to engage in coordinated scientific and public health efforts, ensuring effective surveillance, research, public education, communication, and the creation of new policies.[343,727]

Conclusion

Our synthesis of historic scientific reports and clinical cases in humans and animals will enlighten future investigations and serve as a comparative medicine reference compendium for the elucidation of spontaneous cases of disease, as well as a reference for the selection and design of experimental models of *E. coli* infection. These models will help us confront the challenges of the newly emerging *E. coli* strains and will play important roles in understanding the pathogenesis of *E. coli*-induced disease, treatment, and control strategies. Furthermore, tabulating *E. coli* cases by pathotype and host animal species heightens the possibility of exposing those strains that have yet to be discovered and the animal species that may be affected. Finally, this article serves as a tribute to those investigators, who through their steadfastness and discoveries, have paved the way for a continuing understanding of *E. coli*, a truly versatile and ubiquitous bacteria with seemingly unlimited pathogenic potential.

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