Chapter

Introductory Chapter: The Versatile *Escherichia coli*

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1. Introduction

There are not so many organisms that are so well studied and researched as the bacterium *Escherichia coli* (*E. coli*). Since its discovery in 1885, it was used in research, and by end of 2018, there are now already 368,071 publications in PubMed about *E. coli* [1]. **Figure 1**, presenting data about number of publications found in PubMed for the search term "*Escherichia coli*" in the time frame from 1932 to 2018, clearly demonstrates the high and still growing research interest in this microbe.

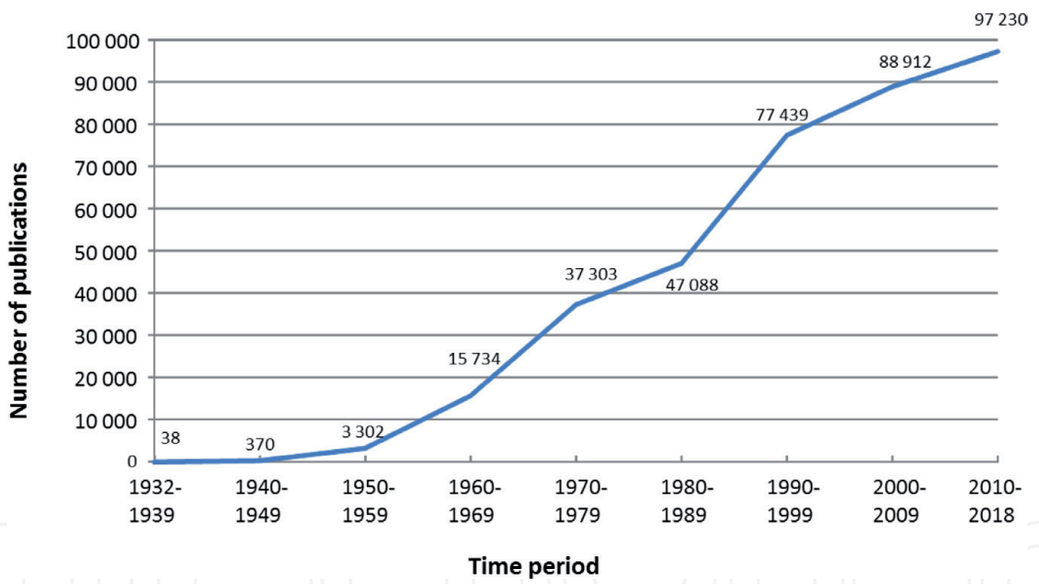

Figure 1.
Number of publications in PubMed for the search term "Escherichia coli" in the time frame from January 01, 1932 to December 31, 2018 [1].

2. The discovery of *Escherichia coli*

The bacterium *E. coli* was discovered by the German-Austrian pediatrician Dr. Theodor Escherich (1857–1911) in 1885 [2]. He conducted examinations of neonate's meconium and feces of breast-fed infants with the aim to gain insight into the development of intestinal "flora." In preparations of meconium and stool samples under the microscope, he observed "slender short rods" of the size of 1–5 μm in length and 0.3–0.4 μm in width, which he named *Bacterium coli commune* (**Figure 2**). Further, he cultured these bacteria on agar and blood serum plates, where these bacteria grew as white, non-liquefying colonies. He also showed that these bacteria slowly cause milk to be clotted, as a result of acid formation, and

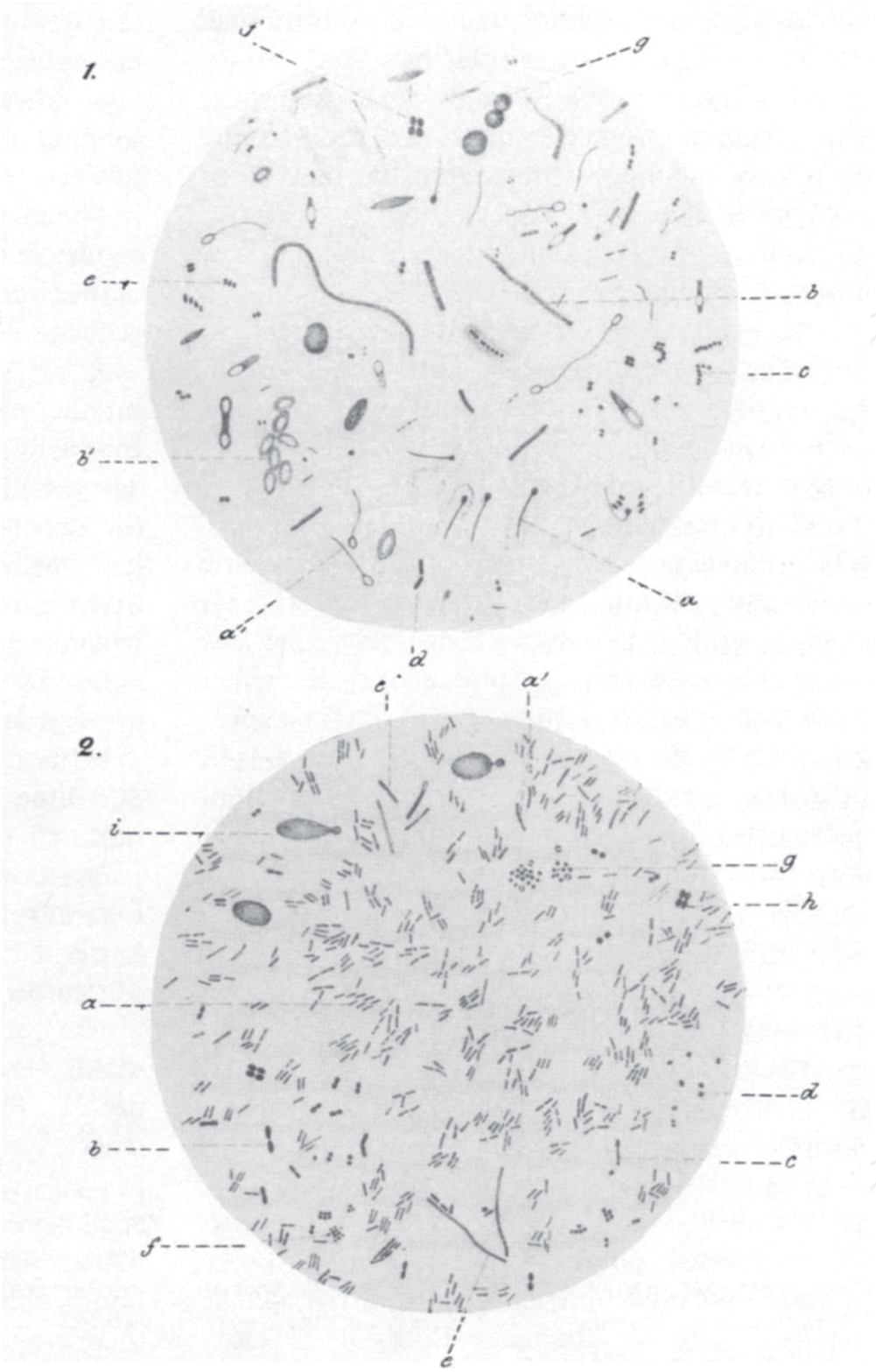

Figure 2.
Escherich's drawing of the stool bacteria, as seen under light microscope [4]. Panel 1: Preparation of a meconium of a 27-hour-old infant. The E. coli as Bacterium coli commune is represented under d. Panel 2: Preparation of a stool of a 2-month-old healthy breast-fed child. The E. coli as Bacterium coli commune is represented under a and a′.

demonstrated that these bacteria have fermentative ability. He also performed the Gram method of staining and revealed that these bacteria rapidly take color with all aniline dyes but lose the color after treatment with potassium iodide and alcohol [2]. Later, in 1919, the bacterium was renamed after its discoverer by Castellani and Chalmers and became *Escherichia coli* [3].

3. Characteristics of *Escherichia coli*

3.1 Basic characteristics

The bacterium *E. coli* (**Figure 3**) belongs into the family of *Enterobacteriaceae*. It is a Gram-negative rod-shaped bacterium, non-sporulating, nonmotile or motile by peritrichous flagella, chemoorganotrophic, facultative anaerobic, producing acid from glucose, catalase positive, oxidase negative, and mesophilic [5].

E. coli is a well-known commensal bacterium that is among the first colonizing bacteria of the gut after birth. It is a highly successful competitor in the human gut and is comprising the most abundant facultative anaerobe of the human intestinal microbiota [7]. As it is a facultative anaerobe, it survives when released to the environment and can be spread to new hosts. *E. coli* is thus an important component of the biosphere [8].

Even though *E. coli* is a well-known commensal bacterium, many pathogenic strains of *E. coli* do exist. Several highly adapted *E. coli* clones have acquired specific virulence factors, which confer an increased ability to adapt to new niches and allow them to cause a broad spectrum of disease, and intestinal and also extraintestinal infections [7].

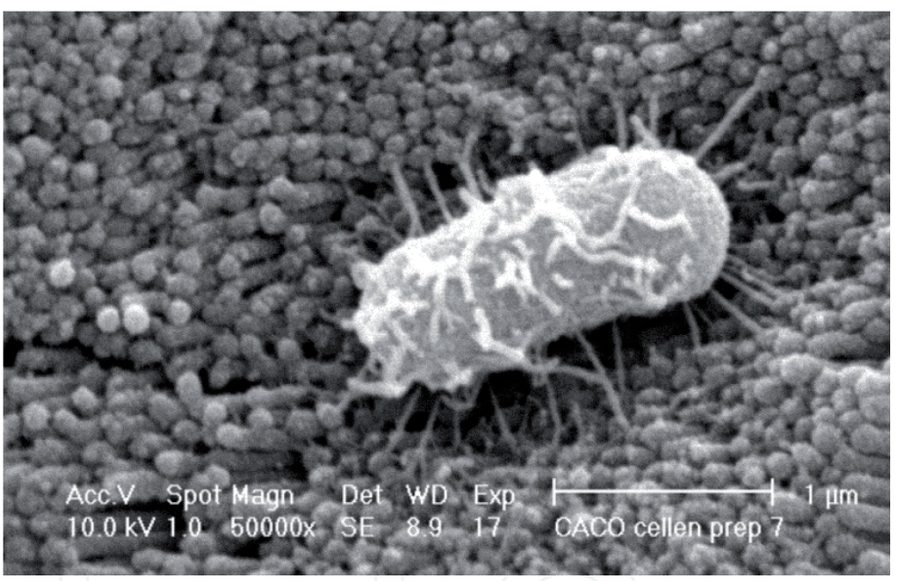

Figure 3.
Scanning electron microscopy of a single bacterial E. coli cell adhering to 19-day-old Caco-2 cells [6].

3.2 The *E. coli* genome

The first complete *E. coli* genome sequence was the sequence of the K-12 MG1655 strain of *E. coli*, published in 1997. The sequenced strain has been maintained as a laboratory strain with minimal genetic manipulation, having only been cured of the temperate bacteriophage lambda and F plasmid. The published genome has 4,639,221 base pairs. Protein-coding genes account for 87.8% of the genome, 0.8% encodes stable RNAs, and 0.7% consists of noncoding repeats. Eleven percent of the genome are involved in regulation of gene expression and also other functions [9]. A circular map of the *E. coli* genome is represented in **Figure 4**.

The map is based on the K-12 MG1655 sequence data as deposited in GenBank (Accession number NC_000913) [10]. The multiplier for the ticks is 1e-6 (1.0 represents 1,000,000). In blue, the forward genes are shown, in purple the reverse genes, tRNA genes in orange, and rRNA genes in red. The map was drawn with

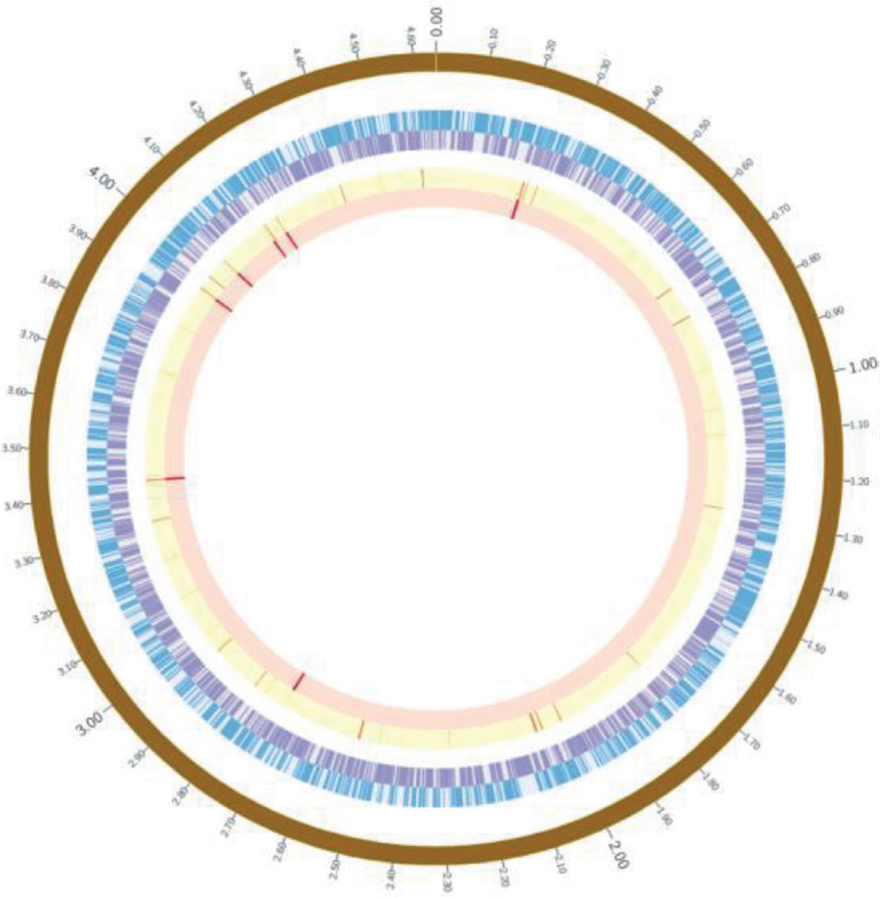

Figure 4.
Circular map of the E. coli K-12 MG1655 strain.

the online tool ClicO FS, available at the Internet site http://www.codoncloud.com:3000/home [11, 12].

Genomes of pathogenic *E. coli* strains are general bigger, as the pathogenic strains need several special properties, so-called virulence factors. These are encoded in the virulence-associated genes (VAGs), which are frequently clustered in DNA regions called pathogenicity islands (PAIs) [13]. Often the pathogenic strains possess also extrachromosomal DNA elements, i.e., plasmids, that can also carry additional VAGs [7]. Some examples of genomes of pathogenic strains in comparison with the K-12 MG1655 strain are given in **Table 1**.

Data in the table are based on data available in the genome database of the National Center for Biotechnology Information (Internet site: www.ncbi.nlm.nih.gov) [14].

The most famous *E. coli* plasmid is the plasmid F (**Figure 5**). It is the paradigm plasmid for plasmid-specified transfer systems, as bacterial conjugation was first identified as a function of the F plasmid. Further, this plasmid was used to develop many of the genetic techniques commonly used to dissect prokaryotic systems, and F product analysis has been central in elucidating the basic mechanisms of plasmid replication and transmission [15].

F plasmid has two functional replication regions, RepFIA and RepFIB. The RepFIA region is believed to be primarily responsible for the typical replication properties of F [16]. The secondary replication region, RepFIB, is independently functional and can perform replication in the absence of RepFIA. F plasmid has also remnants of a third replication region, RepFIC, whose function was abolished by transposition of Tn*1000* into this replication region [17]. Apart from Tn*1000* also insertion sequences IS2 and IS3 are carried on F plasmid [16]. The plasmid-specified transfer system is encoded in the *tra* region, starting with the origin of transfer (*oriT*) [15].

E. coli strain	Associated with infection	Chromosome size (Mbp)	Number of genes in the chromosome	Plasmids	Plasmid size (bp)	Number of genes on the plasmid
K-12 MG1655	/	4.64	4.566	/	/	/
O157:H7 Sakai	Hemorrhagic diarrhea	5.5	5.329	pO157	92.721	85
				pOSAK1	3306	3
O7:K1 IAI39	Urinary tract infection	5.13	5.092	/	/	/
O83:H1 NRG 857C	Crohn's disease	4.75	4.532	pO83_CORR	147.060	154
O104:H4 2011C-3493 ASM29945v1	Hemolytic-uremic syndrome	5.27	5.081	pG-EA11	1549	1
				pAA-EA11	74.217	82
				pESBL-EA11	88.544	94
UMN026	Urinary tract infection	5.2	5.096	p1ESCUM	122.301	156
				p2ESCUM	33.809	49

Table 1.
Genomes of different E. coli strains.

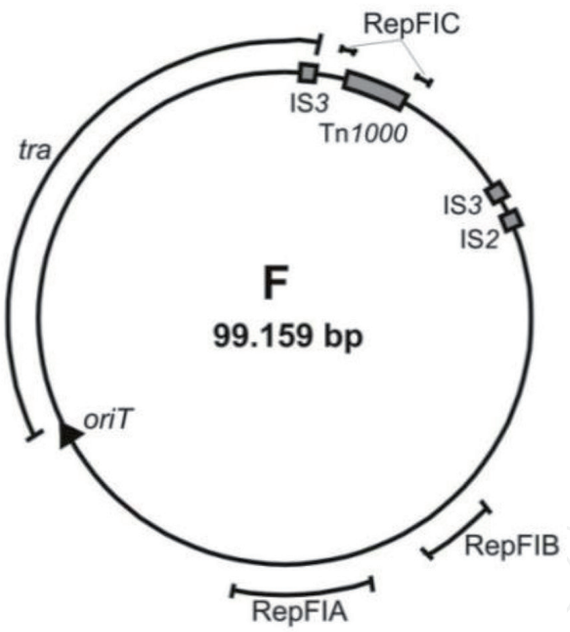

Figure 5.
Map of the E. coli F plasmid. The map was drawn based on the complete nucleotide sequence of the F plasmid as deposited in GenBank [18].

3.3 The phylogenetic groups of *E. coli*

The *E. coli* species has an extensive genetic substructure and the methods to assess the phylogenetic relationship among *E. coli* strains evolved during the time. In the pre-molecular era, the *E. coli* diversity was studied by serotyping. Serotyping studies showed that the somatic (O) antigen, the flagellar (H) antigen, and to a lesser extent the capsular (K) antigen are useful in distinguishing *E. coli* strains [19]. The *E. coli* serotyping is complex—173 O antigens, 80 K antigens, and 56 H antigens are known—and the O, K, and H antigens can be found in nature in many of the possible combinations. The final number of *E. coli* serotypes is therefore very high, 50,000–100,000 or more [20].

The molecular studies of *E. coli* diversity began with the measurement of variations in electrophoretic mobility of enzymes derived from different *E. coli* strains [21]. In 1980s the multi-locus enzyme electrophoresis (MLEE) became the common technique for the study of bacterial diversity. It was found that *E. coli* populations evolve in a clonal manner, with recombination playing a limited role, and it also became clear that genetically distant strains can have the same serotype and that closely related strains may have different serotypes [19]. Based on the MLEE studies of 38 enzyme loci, four major phylogenetic groups among *E. coli* were found: A, B1, B2, and D [22]. Clermont et al. [23] established a method of rapid and simple determination of the *E. coli* phylogenetic groups by a triplex PCR. This genotyping method is based on the amplification of a 279 bp fragment of the *chuA* gene; a 211 bp fragment of the *yjaA* gene; and a 152 bp fragment of TSPE4.C2, a noncoding region of the genome. The presence or absence of combinations of these three amplicons is used to assign the *E. coli* to the phylogenetic groups: A, B1, B2, or D (**Figure 6**).

However, subsequently, on the basis of multi-locus sequence typing and complete genome data, additional *E. coli* phylogenetic groups were recognized [24, 25]. The number of defined phylogenetic groups thus rose to eight (A, B1, B2, C, D, E, F that belongs to *E. coli* sensu stricto, and the eighth—the *Escherichia* cryptic clade I). Clermont et al. [26] thus revised their method to encompass the newly described phylogenetic groups. To enable identification of the F phylogenetic group, the new extended PCR phylotyping method employs an additional gene target, *arpA*, which serves also as an internal control for DNA quality. Thus, the revised PCR method is based on a quadruplex PCR, and if required, additional single PCR reactions are employed to distinguish between E and clade I, A or C, and D or E phylo-group [26] (**Figure 7**).

Two collections of human fecal isolates were screened using the quadruplex phylo-group assignment method demonstrating that 12.8% of *E. coli* isolates belonged to the newly described phylo-groups C, E, F, and clade I and that strains assigned to phylo-groups A and D by the triplex method are worth to be retested by the quadruplex method, as it is likely that they are going to be reclassified [26]. Logue et al. [27] performed a comparative analysis of phylogenetic assignment of human and avian extraintestinal pathogenic (ExPEC) and fecal commensal *E. coli* (FEC) strains and showed that a total 13.05% of studied human *E. coli* strains and 40.49% of avian *E. coli* strains had to be

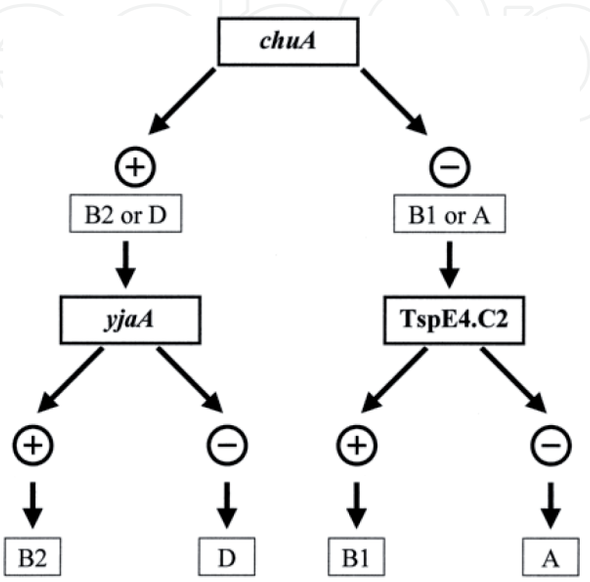

Figure 6.
Dichotomous decision tree to determine the phylogenetic group by the Clermont triplex PCR method [23].

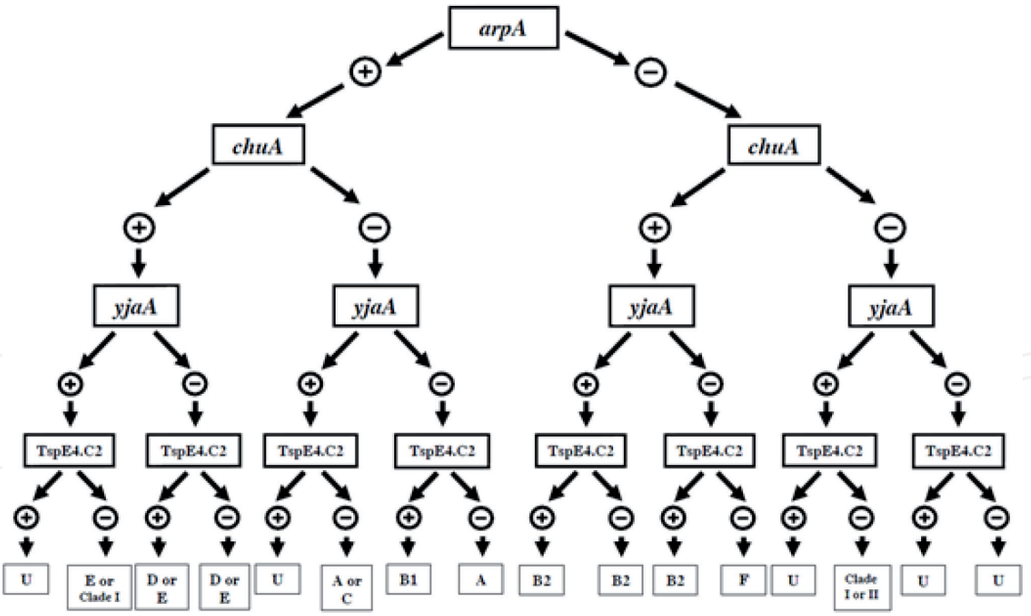

Figure 7.
Dichotomous decision tree to determine the phylogenetic group by the Clermont quadruplex PCR method [26].

reclassified. Another study using human *E. coli* strains isolated from skin and soft-tissue infections and fecal *E. coli* strains from healthy humans and also avian and brown bear fecal strains revealed that 27.60% of human, 23.33% of avian, and 70.93% of brown bear strains had to be reclassified. Moreover, a high number (12.22%) of reclassifications from the previous phylo-groups to the non-typeable (NT) group were observed among the avian fecal strains of this study. Further, a survey performed on other published data by Starčič Erjavec et al. [28] showed that also a number of other studies report occurrence of NT strains by the quadruplex method, for example, a study including 140 uropathogenic *E. coli* strains from Iran reported 27.14% of NT strains [29]. These data emphasizes that there is a need to search for more *E. coli* strains from novel environments (new hosts in not yet explored geographic regions) and to revise the PCR phylotyping method again in order to type these NT strains.

3.4 The commensal *E. coli*

As *E. coli* is a facultative anaerobe, and among the first gut colonizers, these bacteria help to establish the anaerobic environment of the gut that enables the further colonization of the gut by anaerobic bacteria [30]. After the *E. coli* colonization, usually the host and *E. coli* coexist in mutual benefit for decades [7]. *E. coli* gets "food and shelter," and the host benefits due to the *E. coli* vitamin K production and the so-called colonization resistance. Colonization resistance is the phenomenon of protection against colonization by pathogenic bacteria, including pathogenic *E. coli* [31]. The niche of the commensal *E. coli* is the mucous layer of the colon [7]. On average five different commensal *E. coli* strains colonize a human host at any given time [32]. As host and the *E. coli* profits from their association, these *E. coli* could be also designated as mutualistic *E. coli*.

3.5 The pathogenic *E. coli*

E. coli is also a medically important species, as it is involved in many different types of infections. Two major groups of pathogenic *E. coli* exists: the intestinal

pathogenic *E. coli* (IPEC), associated with infections of the gastrointestinal tract, and the extraintestinal pathogenic *E. coli* (ExPEC), associated with infections of extraintestinal anatomic sites [7]. The medical diversity of this species is nicely exhibited by its classification of pathogenic *E. coli* (**Figure 8**), the so-called *E. coli* pathotypes.

The versatility of pathogenic *E. coli* strains depends on their genetic makeup, on the presence of so-called virulence genes, and possession of such genes distinguishes pathogenic from nonpathogenic bacteria [34]. Virulence factors help bacteria to (1) invade the host, (2) cause disease, and (3) evade host defenses [35].

3.5.1 Adhesins and invasins

Once a bacterium reaches the host surface, in order to colonize, it must adhere to host cells. For this purpose bacteria have different fimbrial and afimbrial adhesins. Fimbrial adhesins are rod-shaped protein structures, which consists primarily of an ordered array of single protein subunits, which build a long cylindrical structure. At the top, there are proteins, adhesins, which mediate the adherence to the host's molecules. A fimbrial adhesin is thus a structure that extends outward from the bacterial surface and establishes the contact between the bacterial surface and the surface of the host cells. Afimbrial adhesins are surface proteins important for tighter binding of bacteria to host cells. Some bacteria have evolved mechanisms for entering nonphagocytic host cells. Bacterial surface proteins that provoke actin rearrangements and thereby incite the phagocytic ingestion of the bacterium by host cells are called invasins [36]. The most known *E. coli* adhesins and invasins are presented in **Table 2**.

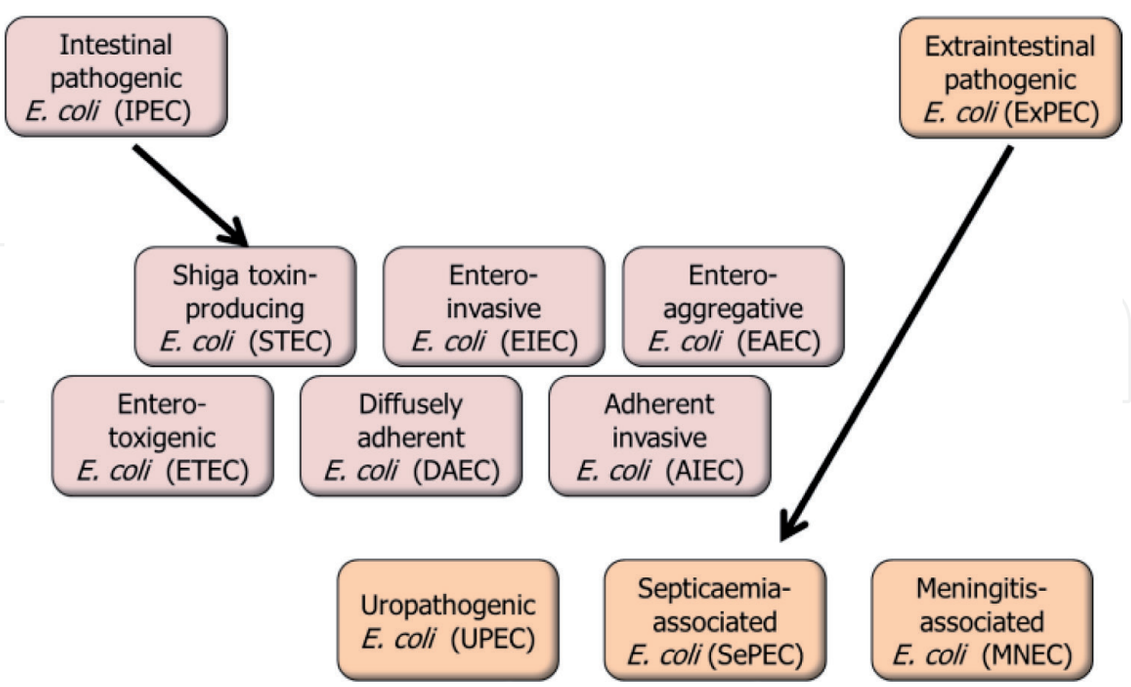

Figure 8.
Classification of pathogenic E. coli, based on Roy et al. [33]. The IPEC are also designated as diarrheagenic E. coli (DEC)—Although not all of the subtypes in this group necessarily cause diarrhea. STEC that cause hemorrhagic colitis and/or the hemolytic uremic syndrome are called EHEC—For enterohemorrhagic E. coli. Among ExPEC also strains associated with pneumonia, skin and soft-tissues, and infections of many other extraintestinal anatomic sites are present, though they are not yet established as separate pathotypes.

Adhesin/invasin	Most commonly tested virulence (associated) genes
Type 1 fimbriae (Fim)	*fimH*
P fimbriae (Pap/Prf)	*papC*, *papG*
S/F1C fimbriae (Sfa/Foc)	*sfa/focDE*
N-Acetyl-D-glucosamine-specific fimbriae (Gaf)	*gafD*
M-Agglutinin (Bma)	*bmaE*
Bifunctional enterobactin receptor/adhesin (Iha)	*iha*
Afimbrial adhesin (Afa)	*afa/draBC*
Invasion of brain endothelium (IbeA)	*ibeA*
Colonization factor antigen I (CFA/I)	*cfaB*
Bundle-forming pili (BFP)	*bfpA*
Intimin	*eaeA*
Aggregative adherence fimbriae (AAF/I)	*aaf/I*

Table 2.
Typical adhesins and invasins of pathogenic E. coli strains.

3.5.2 Iron acquisition mechanisms

Iron is essential for bacterial growth, but iron concentrations in nature are generally quite low, particularly low in host organism. To survive in the host organism, bacteria must have some mechanisms for acquiring iron. The best studied type of bacterial iron acquisition is the siderophores. These are low-molecular-weight compounds that chelate iron with very high affinity [36]. The most known *E. coli* iron uptake systems are presented in **Table 3**.

3.5.3 Systems to evade host immune response

The healthy host usually has multilayered defenses that prevent the establishment of bacterial infection. Among the most effective of these defenses is the immune response. However, bacteria have evolved systems to avoid, subvert, or circumvent innate host defenses and to evade acquired specific immune responses of the host [34]. A capsule is a loose, relatively unstructured network of polymers that covers the surface of a bacterium. The role of capsules in bacterial virulence is to protect bacteria from the host's inflammatory response [36]. Further, increased serum resistance is often found among pathogenic bacteria, especially those associated with systemic infections [36]. Serum resistance is the ability to prevent complement activation on the bacterial cell surface and to inhibit insertion of the membrane attack complex into the bacterial membrane [34]. The feature is often based on the modifications in lipopolysaccharide (LPS), which can be of two types: either attachment of sialic acid to LPS O antigen or changes in the LPS O antigen side chain [36]. However, other proteins can also be implicated in increased serum resistance; for example, the TraT protein of the surface exclusion complex involved in conjugation [37]. Another important protein of pathogenic *E. coli* is the Toll/interleukin-1 receptor domain-containing protein (Tcp) that interferes with the TLR signaling system of the innate immunity [38]. The most known *E. coli* systems to evade host immune response are presented in **Table 4**.

Iron uptake system	Most commonly tested virulence (associated) genes
Aerobactin (Iuc)	*iucD*, *iutA*
Yersiniabactin (Ybt)	*fyuA*, *irp2*
Salmochelin (Iro)	*iroCD*, *iroN*
Siderophore receptor IreA	*ireA*
Temperature sensitive hemagglutinin (Tsh)—in birds, Hemoglobin protease (Hbp)—in humans	*tsh*, *hbp*
Periplasmic iron binding protein (SitA)	*sitA*
Ferrichrome-iron receptor (Fhu)	*fhuA*

Table 3.
Typical iron uptake systems of pathogenic E. coli strains.

Host immunity evading system	Most commonly tested virulence (associated) genes
Group II capsule including K1 and K5 capsules	*kpsMT II*
Conjugal transfer surface exclusion protein (TraT)	*traT*
Outer membrane protease T (OmpT)	*ompT*, *APEC-ompT*
Increased serum survival (Iss)	*iss*
Suppression of innate immunity (Toll/interleukin-1 receptor domain-containing protein Tcp)	*tcpC*

Table 4.
Typical host immunity evading systems of pathogenic E. coli strains.

3.5.4 Toxins

Toxins are the virulence factors that damage the host. Exotoxins are toxic bacterial proteins that are excreted into the medium by growing bacteria or localized in the bacterial cytoplasm or periplasm and released during bacterial lysis. Exotoxins vary considerably in their activities and the target host cell types [36]. The most known *E. coli* toxins (exotoxins) are presented in **Table 5**.

Toxins	Most commonly tested virulence (associated) genes
alpha-Hemolysin (HlyA)	*hlyA*
Cytotoxic necrotizing factor 1 (CNF-1)	*cnf1*
Cytolethal distending toxin IV (CDT 1)	*cdtB*
Uropathogenic specific protein (Usp)	*usp*
Colibactin (Clb)	*clbAQ*
Serine protease autotransporters Sat, Pic	*sat*, *picU*
Heat-stable toxins (STa, STb)	*stIa/stIb*
Heat-labile toxin I (LTI), heat-labile toxin II (LTII)	*eltI*, *eltIIa*
Shiga toxin 1 (Stx1), Shiga toxin 2 (Stx2)	*stxI*, *stxII*
EHEC hemolysin (Ehx)	*ehxA*
Low-MW heat-stable toxin (EAST1)	*astA*

Table 5.
Typical toxins (exotoxins) of pathogenic E. coli strains.

However, *E. coli* possess also an endotoxin, namely, the lipopolysaccharide, which is an integral component of the outer membrane of Gram-negative bacteria. The lipid portion (lipid A) is embedded in the outer membrane, with the core and O antigen portions extending outward from the bacterial surface. Lipid A is the toxic portion of the molecule, and it exerts its effects only when bacteria are lysed. The toxicity of lipid A resides primarily in its ability to activate, complement, and stimulate the release of bioactive host proteins, such as cytokines [36].

3.6 The antibiotic-resistant *E. coli*

Antibiotics are low-molecular-weight compounds that kill or inhibit growth of bacteria [36]. Antibiotic treatment is one of the main approaches of modern medicine to combat bacterial infections, including also *E. coli* infections [39]. However, bacteria evolved different mechanisms that confer resistances to antibiotics. Resistant bacteria are able to either (i) modify/degrade the antibiotic, (ii) actively transport the antibiotic out of the cell or prevent its intake, (iii) sequester the antibiotic by special proteins, or (iv) modify, bypass, or protect the target [40]. The emergence, spread, and persistence of resistant and even multidrug-resistant (MDR) bacteria or "superbugs", also among *E. coli*, are now posing a serious global health threat of growing concern [39]. The antimicrobial resistance surveillance data of European Centre for Disease Prevention and Control (ECDC) also showed the increase in antibiotic resistance among invasive *E. coli* isolates (**Figure 9**).

The mechanisms of resistance to antibiotics are encoded in resistance genes. A list of typical *E. coli* resistance genes is given in **Table 6**.

As many of the resistance genes are encoded on conjugative plasmids or conjugative transposons, they are easily transferred between different bacteria and hence spread in the population [36].

3.7 The bacteriocinogenic *E. coli*

Bacteriocins are ribosomally synthesized, proteinaceous substances that inhibit the growth of closely related species through numerous mechanisms [51].

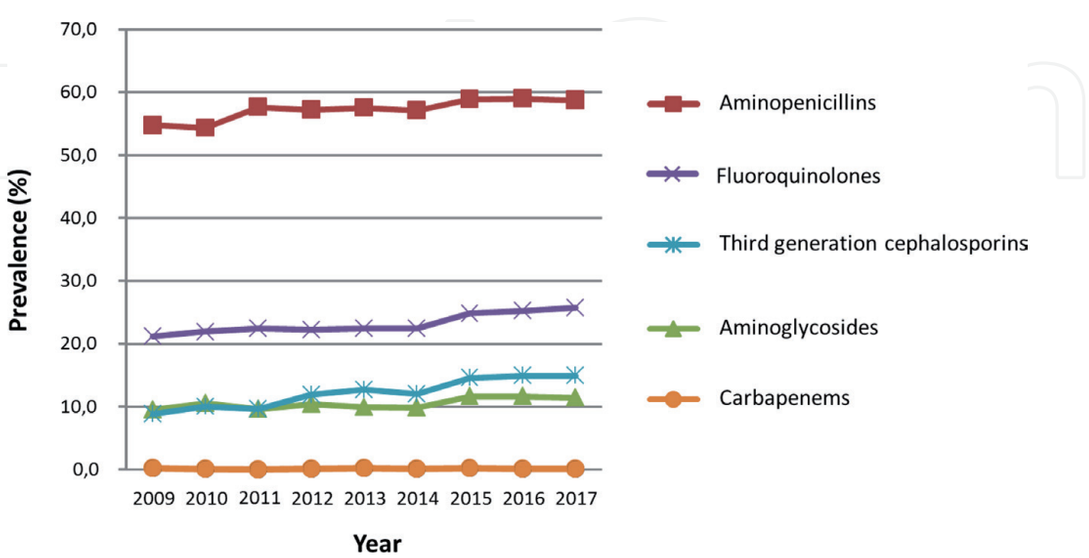

Figure 9.
Prevalence of invasive E. coli isolates with antimicrobial resistance to aminopenicillins, fluoroquinolones, third-generation cephalosporins, aminoglycosides, and carbapenems—the population weighted mean EU/EEA is shown. The prevalence of antimicrobial resistance to carbapenems in 2009 and 2011 was 0%, in 2012 <0.1%, in 2013 and 2015 0.2%, and in 2014, 2016, and 2017 0.1% [41–49].

Resistance gene(s)	Antibiotic class	Resistance to
strA [*aph(3′)-Ib*], *strB* [*aph(6′)-Id*]	Aminoglycosides	STR
aadA1, *aadA2*, *aadA5*, *aadA7*, *aadA24*	Aminoglycosides	STR
aph(3′)-Ia	Aminoglycosides	KAN
aac(3′)-VI, aac(3′)-IId	Aminoglycosides	GEN
$bla_{\text{TEM-1}}$	β-Lactams	AMP
$bla_{\text{OXA-1}}$	β-Lactams	AMP
$bla_{\text{CMY-2}}$	β-Lactams	AMC, AMP, CRO, FOX, TIO
ampC	β-Lactams	AMC, AMP, FOX
sul1, *sul2*, *sul3*	Folate synthesis inhibitors	FIS
dfrA1, *dfrA5*, *dfrA12*, *dfrA17*	Folate synthesis inhibitors	SXT
mphA	Macrolides	AZM
floR	Phenicols	CHL
cmlA	Phenicols	CHL
catA1, *catB3*	Phenicols	CHL
qnrB2, *qnrB6*, *qnrS2*	Quinolones	NAL, CIP
tet(A), *tet*(B), *tet*(C), *tet*(D), *tet*(M)	Tetracyclines	TET

STR, streptomycin; KAN, kanamycin; GEN, gentamicin; AMP, ampicillin; AMC, amoxicillin/clavulanic acid; CRO, ceftriaxone; FOX, cefoxitin; TIO, ceftiofur; FIS, sulfisoxazole; SXT, trimethoprim/sulfamethoxazole; AZM, azithromycin; CHL, chloramphenicol; NAL, nalidixic acid; CIP, ciprofloxacin; TET, tetracycline [50].

Table 6.
Typical E. coli resistance genes.

They are a heterogeneous group of particles with different morphological and biochemical entities. They range from a simple protein to a high molecular weight complex [52]. The bacteriocins with molecular masses below 10 kDa are designated as microcins [53]. Bacteriocins are potent toxins that are usually produced during stressful conditions and result in the rapid elimination of neighboring bacterial cells that are not immune or resistant to their effect. The killing is exhibited after adsorption to specific receptors located on the external surface of sensitive bacteria, by one of the three primary mechanisms: forming channels in the cytoplasmic membrane, degrading cellular DNA/RNA, or inhibiting protein synthesis. Because of their narrow range of activity, it has been proposed that the primary role of bacteriocins is to mediate intraspecific, or population level, interactions [54]. The genetic determinants of most of the bacteriocins are located on the plasmids, apart from few, which are chromosomally encoded [52]. Bacteriocins of *E. coli* are usually called colicins. A relatively high frequency of colicin-encoding plasmids is found in isolates of pathogenic *E. coli* [55], for example, ~80% of O157:H7 enterohemorrhagic *E. coli* strains studied by Bradley and Howard were colicinogenic [56]. Especially microcins have been associated with pathogenic strains [54]. In a collection of *E. coli* strains isolated from skin and soft-tissue infections, 55% of strains possessed microcin M, and 43% possessed microcin H47 [57]. Further, colicin insensitivity among these strains correlated with a higher prevalence of extraintestinal virulence factors [58]. Typical *E. coli* bacteriocins, their receptors, translocation systems, and mode of action are given in **Table 7**.

Bacteriocin	Receptor	Translocation system	Mode of action
ColA	BtuB	Tol	Ion channel
ColB	FepA	Ton	Ion channel
ColD	FepA	Ton	Stops translation
ColE1	BtuB	Tol	Ion channel
ColE2	BtuB	Tol	DNA-endonuclease
ColE3	BtuB	Tol	rRNA-endonuclease
ColE4	BtuB	Tol	rRNA-endonuclease
ColE5	BtuB	Tol	Stops translation
ColE6	BtuB	Tol	rRNA-endonuclease
ColE7	BtuB	Tol	DNA-endonuclease
ColE8-J	BtuB	Tol	DNA-endonuclease
ColIa	Cir	Ton	Ion channel
ColIb	Cir	Ton	Ion channel
ColK	Tsx	Tol	Ion channel
ColM	FhuA	Ton	Inhibition of peptidoglycan synthesis
ColN	OmpF	Tol	Ion channel
ColS4	OmpW	Tol	Ion channel

Table 7.
Typical E. coli bacteriocins, their receptor, translocation system, and mode of action [59, 60].

3.8 The probiotic *E. coli*

Probiotics are live microorganisms that, when administered in adequate amounts, confer a health benefit on the host. Probiotic bacteria act via a variety of means, including modulation of immune function, production of organic acids and antimicrobial compounds, interaction with resident microbiota, interfacing with the host, improving the gut barrier integrity, and enzyme formation [61]. Several *E. coli* strains were recognized as good and effective probiotics and are now used in drugs (see **Table 8**). The probiotic *E. coli* are applied to a variety of human conditions, including intestinal bowel diseases and diarrhea. Further it was shown that colonization of newborns led to reduced disease rates, lower incidence of allergies, and reduced mortality [62].

E. coli Nissle 1917 is nowadays often used as a reference strain or model microorganism in experimental biomedical studies, including recombinant manipulations of the strain in order to construct derivatives with novel properties [64]. One such example is the strain ŽP, which is a genetically modified Nissle 1917 possessing a bacterial conjugation-based "kill"-"anti-kill" antimicrobial system—a conjugative plasmid carrying the "kill" gene (colicin ColE7 activity gene) and a chromosomally encoded "anti-kill" gene (ColE7 immunity gene). Hence, in the process of conjugation, the conjugative plasmid transfers the "kill" gene into a recipient cell, where it is expressed and the recipient killed [65, 66].

Drug name	Mutaflor	Symbioflor 2	Colinfant newborn
E. coli strain	*E. coli* Nissle 1917 strain	Six different *E. coli* strains (G1/2, G3/10, G4/9, G5, G6/7, and G8)	*E. coli* A0 34/86 strain
Product	Capsules	Suspension	Powder for preparation of per oral solution
Produced by	Ardeypharm GmbH, Herdecke, Germany	SymbioPharm GmbH, Herborn, Germany	Dyntec, Terezín, Czech Republic
Contents	2.5–25 × 10^9 CFU/capsule	1.5–4.5 × 10^7 CFU/ml	0.8–1.6 × 10^8 CFU/dosis
Recommended daily dose	1–2 capsules/day (2.5–50 × 10^9 CFU)	2–4 ml (3.0–18 × 10^7 CFU)	0.8–1.6 × 10^8 CFU three times/week
Isolation date of the used strain(s)	1915	1954	Data not available
Serotype	06:K5:H1	Variable including 035,129, 0:169, rough, all H–	083:K24:H31
Plasmid content	2 cryptic plasmids	12 plasmids	No plasmids
Microcin production	Microcin M, H47	Microcin S	Data not available
Motility	Motile (flagella present)	Nonmotile (flagella absent)	Data not available
Closest relatives	CFT073, ABU83972 (UPEC)	K12, ATCC8739 (commensals)	CFT073, 536 (UPEC)
Year of first publication describing the use in humans	1989	1998	1967

Table 8.
Probiotic E. coli drugs [62, 63].

3.9 The "workhorse" *E. coli*

E. coli is known for its fast growing rate in chemically defined media and extensive molecular tools available for different purposes. All these make it an important model organism, which is also called the "workhorse" of molecular biology. Even though *E. coli* lacks many interesting features appreciated in biotechnology, such as growing at extreme temperatures or pH and the capacity to degrade toxic compounds, pollutants, or difficult to degrade polymers, it is much used in biotechnology also [67]. In **Table 9** contributions of *E. coli* to biology, medicine, and industry are listed.

The following recombinant pharmaceuticals were set up to be in vivo synthesized in *E. coli*: insulin, interleukin-2, human interferon-β, erythropoietin, human growth hormone, human blood clotting factors, pegloticase, taxol, and certolizumab. Further, *E. coli* is also used to produce biofuels and industrial chemicals such as phenol, ethanol, mannitol, and a variety of others [68].

Contribution	Authors	Year
Molecular biology, physiology, and genetics		
Elucidation of the genetic code	Crick FH, Barnett L, Brenner S, and Watts-Tobin RJ	1961
DNA replication	Lehman IR, Bessman MJ, Simms ES, and Kornberg A	1958
Transcription	Stevens A	1960
Life cycle of lytic bacteriophages	Ellis EL and Delbrück M	1939
Gene regulation of the *lac* operon	Jacob F and Monod J	1961
Gene regulation of the *ara* operon	Englesberg E, Irr J, Power J, and Lee N	1965
Discovery of restriction enzymes	Linn S and Arber W	1968
Identification of genes controlling antimicrobial drug tolerance in stationary phase	Hu Y and Coates AR	2005
Role of global regulators and nucleotide metabolism in antibiotic tolerance	Hansen S, Lewis K, and Vulić M	2008
Metabolic control of persister formation	Amato SM, Orman MA, and Brynildsen MP	2013
Swarming motility behavior	Harshey RM and Matsuyama T.	1994
Elucidation of the structure and function of ATP synthase	Capaldi RA, Schulenberg B, Murray J, and Aggeler R	2000
Conjugal DNA transfer	Tatum EL and Lederberg J	1947
Evolution		
Random nature of mutation	Luria SE and Delbrück M	1943
Relationship between genomic evolution and adaptation	Barrick JE, Yu DS, Yoon SH, Oh TK, Schneider D, Lenski RE, and Kim JF	2009
Role of adaption, chance, and history in evolution	Travisano M, Mongold JA, Bennet AF, and Lenski RE	1995
Adaptive mutation	Cairns J, Overbaugh J, and Miller S	1988
Role of historical contingency in evolution	Blount ZD, Borland CZ, and Lenski RE	2008
Origin of novel traits	Blount ZD, Barrick JE, Davidson CJ, and Lenski RE	2012
Long-term fitness trajectories	Wiser MJ, Ribeck N, and Lenski RE	2013
Effect of sexual recombination on adaptation	Cooper TF	2007
Predator-prey interactions (bacteriophage)	Chao L and Levin BR	1977
Genetic engineering and biotechnology		
Molecular cloning and recombinant DNA	Cohen S, Chang A, Boyer H, and Helling R	1973
Generating precise deletions and insertions	Link AJ, Phillips D, and Church GM	1997
Gene replacement	Herring CD, Glasner JD, and Blattner FR	2003

Table 9.
Contributions of E. coli to biology, medicine, and industry [68–70].

4. Conclusion

To conclude, *E. coli* is a truly versatile microorganism possessing many facets—it is a well-known commensal bacterium, but some strains can be also pathogenic, even causing mortality, especially if the pathogenic strain acquired multiple resistance genes. However used as a probiotic it can improve health and in it can be

employed as a good working "workhorse" in the laboratory as well as in biotechnological settings. The differentiation between commensal and pathogenic strains is not easy, as among the healthy gut microbiota pathogenic strains are hidden, and also commensal strains can become pathogenic due to horizontal gene transfer of mobile genetic elements possessing virulence genes [71]. Even though *E. coli* has been the object of research now for already more than 100 years, its versatility warrants new possibilities for investigation also in the future.

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Conflict of interest

The author has no conflict of interest.

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