Antimicrobial Resistance in Escherichia coli

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Public healthcare systems all over the world are faced with a great challenge in this respect. Obviously, there are many bacteria that can cause infections in humans and animals alike, but somehow it seems that the greatest threat nowadays comes from the *Enterobacteriaceae* members, especially *Escherichia coli*.

Keywords: antimicrobial resistance ; antibiotics ; public health ; microbiology ; E. coli

1. Introduction

Scientists all over the world have studied *Escherichia coli* and it appears to be the most thoroughly investigated and best understood of all model microorganisms [1][2][3][4]. We already know that it is one of the first bacteria that colonizes the human gut immediately after birth [5][6][7]. On the other hand, *E. coli* is often the main culprit of infections in the gastrointestinal tract [8], as well as other parts of human and animal organisms [9][10]. In more precise terms, *E. coli* typically causes urinary infections [11][12], but it can also lead to many other serious infections and conditions, such as: appendicitis [13], pneumonia [14], meningitis [15], endocarditis [16], gastrointestinal infections [17], etc. Research findings have shown us that *E. coli* can cause infections in all age groups and those infections can be acquired in the general population, i.e., community-acquired, as well as related to healthcare institutions [18][19][20].

After Alexander Fleming had discovered penicillin in 1928, the whole course of medicine changed [21][22]. The revolutionary discovery of antibiotics made it possible for doctors to treat extremely severe cases of infectious diseases, which had previously been a very common cause of death [23][24]. That completely changed after antibiotics had been introduced and soon penicillin became the most widely used antibiotic in the world, saving millions of lives [25][26][27].

Unfortunately, only several years after doctors started using it in hospitals, the first cases of penicillin resistance by *Staphylococcus aureus* were identified [28]. Obviously, bacteria have managed to develop a system that can protect them and make them resistant to antibiotics [29]. Sadly, the situation with bacteria evolving resistance is getting worse day by day and we have literally come to a point when we can speak of the antimicrobial resistance presenting a worldwide problem [30][31][32][33][34][35][36].

When we speak about *E. coli*, the fact that it has been put on the World Health Organization's (WHO) list that contains 12 families of bacteria that present the biggest danger to human health [37][38]. Ever since the first reported cases, *E. coli's* resistance to antibiotic treatment has been continuously growing [39][40][41][42].

Scientific literature offers an abundance of research studies into the nature and behavior of *E. coli* [43][44][45][46]. The results point to several extremely interesting facts. This bacterium undoubtedly has considerable influence on human and animal lives [47][48], for the simple reason that it lives inside the gut and can very easily spread from fecal matter to the mouth [49][50]. Being the commensal bacteria of human and animal gut, it happens to be in close contact with numerous other bacteria [51]. However, perhaps the most fascinating thing about *E. coli* is its ability to pass on its genetic-resistant traits to microorganisms who share the same living environment, as well as to acquire resistance genes from them [52][53][54].

According to Poirel et al. [52] *E. coli* present a bacterium with a special place in the microbiological world since it can cause severe infections in humans and animals, and on the other hand represents a significant part of the autochthonous microbiota of the various hosts. The main apprehension is a transmission of virulent and resistant *E. coli* among animals and humans through various pathways. *E. coli* is a most important reservoir of resistance genes that may be accountable for treatment failures in both human and veterinary medicine [52]. An increasing number of resistance genes has been identified in *E. coli* isolates in the past 10 years, and many of these resistance genes were acquired by horizontal gene transfer. In the enterobacterial gene pool, *E. coli* acts as a donor and as a recipient of resistance genes and thereby can acquire resistance genes from other bacteria but can also pass on its resistance genes to other bacteria. Antimicrobial resistance in *E. coli* is considered one of the foremost disputes in both humans and animals at a global scale and needs to be considered as a real public health concern.

Barrios-Villa et al. [55] have observed increased evidence demonstrating the association between Crohn's Disease (CD), a type of Inflammatory Bowel Disease (IBD), and non-diarrheagenic Adherent/Invasive *E. coli* (AIEC) isolates. Genomes of five AIEC strains isolated from individuals without IBD were sequenced and compared with AIEC prototype strains (LF82 and NRG857c), and with extra-intestinal uropathogenic strain (UPEC CFT073). Non-IBD-AIEC strains showed an Average Nucleotide Identity up to 98% compared with control strains. Blast identities of the five non-IBD-AIEC strains were higher when compared to AIEC and UPEC reference strains than with another *E. coli* pathotypes, suggesting a relationship between them [55]. In the same study, Barrios-Villa et al. [55], an incomplete Type VI secretion system was found in non-IBD-AIEC strains; however, the Type II secretion system was complete. Several groups of genes reported in AIEC strains were searched in the five non-IBD-AIEC strains, and the presence of *fimA*, *fliC*, *fuhD*, *chuA*, *irp2*, and *cvaC* were confirmed. Other virulence factors were detected in non-IBD-AIEC strains, which were absent in AIEC reference strains, including EhaG, non-fimbrial adhesin 1, PapG, F17D-G, YehA/D, FeuC, IucD, CbtA, VgrG-1, Cnf1, and HlyE. Based on the differences in virulence determinants and single-nucleotide polymorphisms (SNPs), it is plausible to suggest that non-IBD AIEC strains belong to a different pathotype.

Meanwhile, genomic analysis of *E. coli* strains isolated from diseased chicken in the Czech Republic [56] showed that multiresistant phenotype was detected in most of the sequenced strains with the predominant resistance to β-lactams and quinolones being associated with TEM-type beta-lactamase genes and chromosomal *gyrA* mutations. The phylogenetic analysis proved a huge variety of isolates that were derived from all groups. Clusters of closely related isolates within ST23 and ST429 indicated a possible local spread of these clones. Moreover, the ST429 cluster carried $bla_{\text{CMY-2,-59}}$ genes for AmpC β-lactamase and isolates of both clusters were well-equipped with virulence-associated genes, with significant variations in allocation of specific virulence-associated genes among phylogenetically distant lineages. Zoonotic APEC STs were also identified, such as ST117, ST354, and ST95, showing numerous molecular elements typical for human ExPEC [56].

As already stated, antibiotic resistance found in microorganisms presents a big challenge for medical practice in the whole world [57][58][59][60][61]. This is to a great extent the consequence of wrong or uncritical consumption of antibiotics.

In a study by Abdelhalim et al. [62], from 17 Crohn's disease patients and 14 healthy controls *E. coli* strains were isolated, 59% and 50% of them were identified as AIEC strains. It was discovered that *chuA* and *ratA* genes were the most significant genetic markers associated with AIEC compared to non-AIEC strains isolated from Crohn's disease patients and healthy controls $p = 0.0119, 0.0094$, respectively. Most *E. coli* strains obtained from Crohn's disease patients showed antibiotic resistance (71%) compared to healthy controls (29%) against at least one antibiotic. Investigation have demonstrated significant differences between AIEC strains and non-AIEC strains in terms of the prevalence of *chuA* and *ratA* virulence genes and the antibiotic resistance profiles. Furthermore, AIEC strains isolated from Crohn's disease patients were found to be more resistant to β-lactam and aminoglycoside antibiotics than AIEC strains isolated from healthy controls [62].

E. coli strains isolated from animals in Tunisia [63] revealed occurrence of plasmid-mediated quinolone resistance between themselves. With 51 nalidixic acid-resistant isolates, 9 PMQR genes were harbored (5 co-harbored *qnrS1* and *qnrB1*, 3 harbored *qnrS1* and 1 harbored *qnrB1*). Two types of mutation in the QRDR of GyrA were observed: S83L and D87N. For the QRDR of ParC, the substitution S80I was observed as well, while A class 1 integron was found in isolates, respectively. The *tetA* or *tetB* gene was observed and both were co-harbored by two isolates. The *sul1*, *sul2*, and *sul3* genes were discovered, respectively. According to the presence of specific virulence genes, the nine strains were classified as UPEC, EAEC, and EPEC [63]. All mentioned highlight the plausible role of the avian industry as a reservoir of human pathogenic *E. coli* strains.

Yu et al. [64] have investigated the prevalence and antimicrobial-resistance phenotypes and genotypes of *E. coli* isolated from raw milk samples from mastitis cases in four regions of China. A total of 83 strains of *E. coli* were isolated and identified, but without any significant differences in the number of *E. coli* isolates detected among the two sampling seasons in the same regions. Nevertheless, a significant difference in *E. coli* prevalence was found among the four different regions. The isolates were most frequently resistant to penicillin (100%), acetylspiramycin (100%), lincomycin (98.8%), oxacillin (98.8%), and sulphamethoxazole (53%). All the *E. coli* strains were multiresistant to three antimicrobial classes, and the most frequent multidrug-resistance patterns for the isolates were resistant to three or four classes of drugs simultaneously [64].

In Egypt, Farhat et al. [65] have investigated the antimicrobial resistance patterns, the distribution of phylogenetic groups, and the prevalence and characteristics of integron-bearing *E. coli* isolates from outpatients with community-acquired urinary tract infections. A total of 134 human urine samples were positive for *E. coli*, from which a total of 80 samples were selected for further analyses. Most of the isolates (62.5%) proved multidrug resistance profiles. Group B2 was the most

predominant phylogenetic group (52.5%), followed by group F (21.25%), Clade I or II (12.5%), and finally isolates of unknown phylogroup (13.75%). Of the 80 selected isolates, 7 of them carried class 1 integrons, which contained 3 different types of integrated gene cassettes, conferring resistance to streptomycin, trimethoprim, and some open reading frames of unknown function [65].

Low hygiene levels, lack of clean water, or poor sanitary conditions can create perfect conditions for the development and transmission of infections [66]. In addition to that, Farhani et al. [67] have total of 80 *E. coli* isolates, separated into 51 different genotypes. Using the Multi Locus VNTR Analysis (MLVA) profiles, a minimum spanning tree (MST) algorithm showed two clonal complexes with 71 isolates and only 9 isolates were stayed out of clonal complexes in the form of a singleton. High genotypic diversity was seen among *E. coli* strains isolated from hospital wastewaters; however, many isolates showed a close genetic relationship. Authors have concluded that MLVA as a rapid, inexpensive, and useful tool could be used for analysis of the phylogenetic relationships between *E. coli* strains [67].

Extended-spectrum beta-lactamases (ESBLs) are specific enzymes, which show resistance to almost all beta-lactam antibiotics [68], including penicillin [69], cephalosporin [70], etc. [71]. Cases of infections in which ESBLs are produced usually have quite an unpredictable course. *E. coli* is an example of a multidrug-resistant and ESBL-producing bacterium that can be the source of extremely severe infections [72][73][74]. As has previously been stated, some strains of *E. coli* can also cause very serious medical conditions connected with urinary and gastrointestinal tract and central nervous system [75]. On the other hand, the side effects of a prolonged usage of antibiotics include the occurrence of antibiotic resistance [76][77][78]. Today we have evidence that people can get antibiotic-resistant *E. coli* directly or indirectly from the environment [79][80]. Therefore, it is very important that we first evaluate the existence of drug-resistant *E. coli* in our surroundings and based on such findings try to outline the human and veterinary healthcare guidelines [81][82][83][84][85][86].

2. Usage of Antibiotics in Different Countries of EU Region and Spread of *E. coli* Resistance to Antibiotics

It is absolutely clear to us today that the antibiotic resistance of *E. coli* and some other bacteria involves a combination of different factors [87][88]. Research results indicate that *E. coli* exhibits the strongest resistance to the longest used and most commonly prescribed antibiotics [89][90][91]. This is exactly the case with sulfonamides, which were first used in humans around 1930s [92]. Some twenty years later, the first resistant strains of *E. coli* appeared and with time this resistance only grew stronger. It has also been found that low-income [93] and mid-income countries (Table 1) are regions with the highest antibiotic-resistance rates and it is precisely in these regions that we see the highest consumption of antibiotics [94]. On the other hand, high-income nations show a lower rate of antibiotic resistance, resulting from lower usage of antibiotics. In some high-income countries the consumption is high, for example in Belgium, France, and Italy. This is even more complex when comparing to low-income countries where on one hand the consumption may be high but the availability of many of the more advanced antimicrobials is limited [95].

Table 1. The consumption of total antibiotics in Defined Daily Doses, in DDD per 1000 inhabitants per day in countries of European region based on WHO database [93].

Country	DDD/1000 Inhabitants Per Day	Country	DDD/1000 Inhabitants Per Day
Albania	16.41	Kosovo	20.18
Armenia	10.31	Kyrgyzstan	17.94
Austria	12.17	Latvia	13.30
Azerbaijan	7.66	Lithuania	15.83
Belarus	17.48	Luxemburg	22.31
Belgium	25.57	Malta	21.88

Bosnia and Herzegovina	17.85	Montenegro	29.33
Bulgaria	20.25	Netherlands	9.78
Croatia	20.28	Norway	16.97
Cyprus	27.14	Poland	24.30
Czech Republic	17.18	Portugal	17.72
Denmark	17.84	North Macedonia	13.42
Estonia	12.13	Romania	28.50
Finland	18.52	Russia	14.82
France	25.92	Serbia	31.57
Georgia	24.44	Slovakia	24.34
Germany	11.49	Slovenia	13.48
Greece	33.85	Spain	17.96
Hungary	16.31	Sweden	13.73
Iceland	17.87	Tajikistan	21.95
Ireland	23.27	Turkey	38.18
Italy	26.62	United Kingdom	20.47
Kazakhstan	17.89	Uzbekistan	8.56

In the 2017 revision of the WHO Model List of Essential Medicines, antibiotics in the list were grouped into three AWaRe categories: Access, Watch, and Reserve. According to the WHO AWaRe categories [96], the classification showed that the Access group antibiotics accounted for more than 50% of total consumption both in Serbia and Spain [93]. The size of the population (in thousands) living in the European Region in 2015 was 912,984, respectively. Of the 53 Member States of the region, none is a low-income country, 20 are middle-income countries, and 33 are high-income countries. The median proportional consumption of the Access group values ranged between 61% in Spain to 64% in Serbia. The median proportion of Watch group antibiotics related to total consumption values ranging from less than 34% in Serbia and 28.5% in Spain. Reserve group antibiotics were only rarely used. The most widely used Reserve group antibiotics were intravenous fosfomycin, followed by cefepime, colistin, linezolid, and daptomycin. The antibiotics assigned to the Other group varied from 1.5% in Serbia to 9.5% in Spain (Figure 1). Overall consumption of antibiotics in these 46 countries ranged from 7.66 to 38.18 DDD per 1000 inhabitants per day. The overall absolute weight (not adjusted by population size) varied from 2.18 ton (Iceland) to 1195.69 tons (Turkey) per year.

Figure 1. Proportional consumption of antibiotics by AWaRe categorization, % [93][96].

It is a widespread opinion among scientists that antibiotic resistance has developed as the result of human activity and commonly applied treatment with antibiotics [97]. On the other hand, studies of bacteria living inside human body and other environmental bacteria helped us discover many other resistance factors that did not develop over time as a reaction to antibiotics, but were probably part of bacteria genomes in the first place [98][99][100]. Scientists often refer to those characteristics as the intrinsic resistance of bacteria [101]. It presents a great advantage of that particular bacteria strain, as its main task is to inhibit or eliminate other bacteria that live in the same environment and compete for food [102][103][104]. Hence, intrinsic resistance is different from the extrinsic antibiotic resistance, which was triggered primarily by human action [105]. In times of constantly growing antibiotic resistance and in a situation when we seem not to have any readily available antibacterial agents, it is extremely important to thoroughly study the intrinsic resistance of bacteria. That could lead to the development of a new method of fight against bacterial resistance [106]. If we could manage somehow to inhibit the factors that intrinsic resistance is composed of, perhaps bacteria would then become highly sensitive to antibiotics again. *E. coli* and other gram-negative bacteria have two important characteristics, which are the foundations of their intrinsic resistance. Namely, they have a protective impermeable membrane and a large number of efflux pumps, which successfully remove all unwanted substances from inside the cell [107][108][109].

Antibiotic resistance is an ecosystem problem threatening the interrelated human–animal–environment health under the “One Health” framework. Resistant bacteria arising in one geographical area can spread via cross-reservoir transmission to other areas worldwide either by direct exposure or through the food chain and the environment. Drivers of antibiotic resistance are complex and multisectoral particularly in lower- and middle-income countries. These include inappropriate socio-ecological behaviors; poverty; overcrowding; lack of surveillance systems; food supply chain safety issues; highly contaminated waste effluents; and loose rules and regulations. Iskandar et al. [110] have investigated the drivers of antibiotic resistance from a “One Health” perspective. They have summarized the results from many researches that have been conducted over the years and shown that the market failures are the leading cause for the negative externality of antibiotic resistance that extends in scope from the individual to the global ecosystem. Iskandar et al. [110] highlighted that the problem will continue to prevail if governments do not prioritize the “One Health” approach and if individual’s accountability is still denied in a world struggling with profound socio-economic problems.

Dsani et al. [111] investigated the spread of *E. coli* isolates from raw meat in Greater Accra region in Ghana, to antibiotics resistance, respectively. Usually, raw meat can be contaminated with antibiotic resistant pathogens and consumption of meat contaminated with antibiotic resistant *E. coli* is associated with grave health care consequences. In their research, *E. coli* was detected in half of raw meat samples. Isolates were resistant to ampicillin (57%), tetracycline (45%), sulfamethoxazole-trimethoprim (21%), and cefuroxime (17%). Multidrug resistance (MDR) was identified in 22% of the isolates. The $bla_{TEM\ gene}$ was detected in 4% of *E. coli* isolates [111]. Dsani et al. [111] concluded that levels of microbial contamination of raw meat in their research were unacceptable and highlighted that meat handlers and consumers are at risk of foodborne infections from *E. coli* including ESBL producing *E. coli*, which is resistant to nearly all antibiotics in use.

According to Hassan et al. [112], a last resort antibiotic is colistin. Colistin is crucial for managing infections with carbapenem-resistant *Enterobacteriaceae*. The recent emergence of mobile-colistin-resistance (*mcr*) genes has jeopardized the efficiency of this antibiotic. Aquaculture is a foremost contributor to the evolution and dissemination of *mcr*. Nevertheless, data on *mcr* in aquaculture are narrow. In Lebanon, a country with developed antimicrobial stewardship the occurrence of *mcr-1* was evaluated in fish. Mobile-colistin-resistance-*1* was detected in 5 *E. coli* isolated from fish intestines. The isolates were classified as multidrug-resistant and their colistin minimum inhibitory concentration ranged between 16 and 32 µg/mL. Whole genome sequencing analysis showed that *mcr-1* was carried on transmissible

IncX4 plasmids and that the isolates harbored more than 14 antibiotic resistance genes. The isolates belonged to ST48 and ST101, which have been associated with *mcr* and can occur in humans and fish and help in spreading of antibiotic resistance of *E. coli*.

While, Montealegre et al. [113] have showed how high genomic diversity and heterogeneous origins of pathogenic and antibiotic-resistant *E. coli* in household settings represent a challenge to reducing transmission in low-income settings. Transmission of *E. coli* between hosts and with the environment is believed to happen more frequently in regions with poor sanitation. Montealegre et al. [113] performed whole-genome comparative analyses on 60 *E. coli* isolates from soils and fecal from cattle, chickens, and humans, in households in rural Bangladesh. Results suggest that in rural Bangladesh, a high level of *E. coli* in soil is possible led by contributions from multiple and diverse *E. coli* sources (human and animal) that share an accessory gene pool relatively unique to previously published *E. coli* genomes. Thus, interventions to reduce environmental pathogen or antimicrobial resistance transmission should adopt integrated “One Health” approaches that consider heterogeneous origins and high diversity to improve effectiveness and reduce prevalence and transmission [113].

It has been confirmed that wastewater treatment plant effluents are influenced by hospital wastewaters [114] in Germany. Alexander et al. [114] quantified the abundances of antibiotic resistance genes and facultative pathogenic bacteria as well as one mobile genetic element in genomic DNA via qPCR from 23 different wastewater treatment plant effluents in Germany. Total of 12 clinically relevant antibiotic resistance genes were categorized into frequently, intermediately, and rarely occurring genetic parameters of communal wastewaters. Taxonomic PCR quantifications of 5 facultative pathogenic bacteria targeting *E. coli*, *P. aeruginosa*, *K. pneumoniae*, *A. baumannii*, and enterococci were performed.

Since communal wastewater treatment plants are the direct link to the aquatic environment, wastewater treatment plants should be monitored according to their antibiotic resistance genes and facultative pathogenic bacteria abundances and discharges to decide about the need of advanced treatment options. Critical threshold volumes of hospital wastewaters should be defined to discuss the effect of a decentralized wastewater treatment, because they can serve as an excellent reservoir in spreading of *E. coli* resistance to antibiotic.

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