Escherichia coli Antimicrobial Resistance in Humans

Subjects: Infectious Diseases

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To date, the scientific literature on health variables for *Escherichia coli* antimicrobial resistance (AMR) has been investigated throughout several systematic reviews, often with a focus on only one aspect of the One Health variables: human, animal, or environment.

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1. Introduction

Antimicrobial resistance (AMR) is a global problem leading to untreatable infections that occurs by natural selection but is driven by antibiotic exposure in healthcare (humans), agriculture (animals, plants, or food-processing technology), and the environment (sea, soil, drinking water, and wastewater) [1][2][3][4]. The use of antibiotics in humans and animals is perceived as the major contributor to the development of AMR [5]. With AMR increasing and new antibiotic development stagnating, problems due to untreatable infections can be expected to increase health-related burdens, including more extended hospital stays, increased healthcare costs, and death [6]. Investigating the interaction between humans, animals, and the environment, as well as between the different sectors involved (e.g., pharmaceutical industry, food industry, water waste companies), using a One Health approach, is of great importance in mitigating resistance [7].

Escherichia coli (*E. coli*) is a common commensal of the intestinal microbiota in both animals and humans [8][9] that has received significant attention in the literature [10][11] due to increasing AMR [12][13] and death associated with resistance [14][15]. *E. coli* infections are caused by extraintestinal and uropathogenic subtypes [16], with uropathogenic *E. coli* responsible for up to 80% of urinary tract infections [17], the most common infectious disease in the community [18]. Virulence potential varies according to molecular types of bacterial isolates [19]. AMR of *E. coli* is due to both intrinsic (the outer membrane and expression of efflux pumps) and extrinsic mechanisms (the acquisition of mobile genetic elements or through horizontal gene transfer that assists in capturing, accumulating, and disseminating resistance genes [20]). New antimicrobial resistance genes continuously emerge, leading to multidrug resistance [21][22]. *E. coli* can mobilize resistant genes more easily than other bacteria populations and act as a reservoir for AMR genes and mobile genetic elements, and is mainly driven by external factors [12][20]. It is, therefore, essential to understand the community variables leading to AMR of *E. coli*.

2. Human Variables

2.1. Antibiotic Use

Of the human-related variables, antibiotic use was most frequently reported as a variable for AMR (**Table 1**). Most reviews investigating the impact of antibiotic use on AMR *E. coli* reported a positive association ranging from general antibiotic use increasing the odds by 1.5 and use of fluoroquinolones increasing the odds by 19 times (**Table 1**). Longer duration of use was associated with increased odds of AMR *E. coli*, as was the use of multiple courses and mass administration across populations such as HIV-infected adults and young children. The use of β-lactam antibiotics was identified as the most important variable in this category, followed by (fluoro)quinolone- and cephalosporin antibiotics [23]. There were no [15][24] statistical results reported around sulphonamides, trimethoprim [25][26][27], and tetracycline [28][29] use.

Table 1. Human health variables of *E. coli* AMR among community-dwelling populations.

Variable	Subcategory	Number of Participants (Number of Studies Investigating Variable)	Magnitude of Association OR (95% CI)	Importance Rating *
Antibiotic use	General antibiotic use	6 studies (NR)	1.51 (1.17–1.94) [15]	+
		1528 (6 studies)	1.58 ** (1.16–2.16) [24]	
		1297 (5 studies)	1.63 ** (1.19–2.24) [24]	
		449 (1 study)	1.8 (1.0–3.1) [23]	
		88 studies (NR)	2.33 (2.19–2.49) [30]	
		NR (5 studies)	2.65 (1.70–4.12) [31]	
		172 (1 study)	3.1 (1.4–6.7) [23]	
		484 (1 study)	4.0 (1.6–10.0) [23]	
		300 (1 study)	4.6 (1.9–11.0) [23]	

Variable	Subcategory	Number of Participants (Number of Studies Investigating Variable)	Magnitude of Association OR (95% CI)	Importance Rating *
		140 (1 study)	5.6 (2.1–14.8) [23]	
	Trimethoprim and β-lactams	179 (2 studies)	3.2 (0.9–10.8) [25]	0
	Beta-Lactam	290 (1 study)	4.5 (1.8–11.0) [23]	+++
		510 (1 study)	4.6 (2.0–10.7) [23]	
	(Fluoro)Quinolone	449 (1 study)	2.1 (0.6–7.3) [23]	+
		200 (1 study)	2.6 (1.3–5.1) [23]	
		140 (1 study)	9.9 (2.2–44.6) [23]	
	Penicillin	290 (1 study)	19.0 (3.3–111.4) [23]	0
		7170 (1 study)	0.9 (0.5–1.7) [23]	
		408 (1 study)	2.7 (1.2–6.3) [23]	
		74 (1 study)	1.5 (5.4–85.2) [23]	
	Cephalosporin	200 (1 study)	2.2 (1.01–5.0) [23]	+
		408 (1 study)	2.2 (1.1–4.5) [23]	
		200 (1 study)	3.9 (1.8–8.5) [23]	
	Macrolides	7170 (1 study)	1.5 (1.1–2.2) [23]	0
	Nitrofurantoin	7170 (1 study)	1.54 (1.1–2.3)	0

Variable	Subcategory	Number of Participants (Number of Studies Investigating Variable)	Magnitude of Association OR (95% CI)	Importance Rating *
			[23]	
	Longer duration of course (>7 days vs. <7 days amoxicillin and trimethoprim)	1521 (2 studies)	1.50 (0.76–2.92) [26]	0
		1521 (2 studies)	2.89 (1.44–5.78) [26]	
	Multiple courses (>3 courses vs. 1 course, trimethoprim, amoxicillin, trimethoprim)	1521 (2 studies)	0.4 (0.12–1.31) [26]	
		1521 (2 studies)	3.95 (1.06–14.72) [26]	++
		1521 (2 studies)	3.62 (1.25–10.48) [26]	
	Mass administration	NR (1 study)	3.64 (2.38–5.78) [32]	
		NR (5 studies)	7.8 (3.0–20.2) [27]	
		NR (5 studies)	10.2 (5.9–17.8) [27]	+++
		NR (5 studies)	17.1 (2.3–127.7) [27]	
	Higher dose (each 200 mg trimethoprim tablet extra and 500 mg instead of 250 mg amoxicillin)	1521 (2 studies)	1.01 (1.01–1.02) [26]	
		1521 (2 studies)	2.26 (1.13–4.55) [26]	+
Comorbidities		7170 (1 study)	1.3 (1.01–1.6) [23]	
	Previous/recurrent UTI	408 (1 study)	3.4 (1.8–6.7) [23]	++
		510 (1 study)	3.8 (1.8–8.1) [23]	
	Previous/recurrent pyelonephritis	300 (1 study)	1.7 (0.7–3.9) [23]	–

Variable	Subcategory	Number of Participants (Number of Studies Investigating Variable)	Magnitude of Association OR (95% CI)	Importance Rating *
	Previous catheterization	408 (1 study)	3.3 (1.7–6.6) [23]	+
	Diarrhea symptoms	5144 (7 studies)	1.53 (1.27–1.84) [15]	0
	Diabetes	300 (1 study)	1.7 (0.8–3.4) [23]	++
		290 (1 study)	3.7 (1.1–12.7) [23]	
		484 (1 study)	3.0 (1.1–8.0) [23]	
	Recurrent acute pyelonephritis and a history of diabetes	300 (1 study)	4.2 (1.3–16.9) [23]	+
	Renal or urological disorder	7170 (1 study)	1.6 (1.0–2.5) [23]	–
		484 (1 study)	3.5 (1.0–11.5) [23]	
	History prostatic disease	510 (1 study)	9.6 (2.1–44.8) [23]	+
	Chronic disease	2323 (3 studies)	0.91 (0.13–6.53) [15]	–
Medication use	Immunosuppressive therapy	7170 (1 study)	1.5 (1.1–2.1) [23]	0
	Corticosteroids	172 (1 study)	24.3 (2.4–246.9) [23]	+
	Acid suppressants	4111 (3 studies)	1.31 (0.11–15.5) [15]	0
		NR (4 studies)	1.41 (1.07–1.87) [33]	
Hospitalization	Previous hospitalization	1379 (5 studies)	1.18 ** (0.78–1.81) [24]	+
		1163 (4 studies)	1.28 ** (0.82–	

2.2. Comorbidities, Medication Use, and Hospitalization

Variable	Subcategory	Number of Participants (Number of Studies Investigating Variable)	Magnitude of Association OR (95% CI)	Importance Rating *
			2.03) [24]	
		7170 (1 study)	1.7 (1.3–2.3) [23]	
		172 (1 study)	2.9 (1.3–6.6) [23]	
		7170 (1 study)	3.9 (2.6–5.8) [23]	
		449 (1 study)	3.9 (1.2–12.7) [23]	
	Prior surgery	172 (1 study)	2.8 (1.9–8.0) [23]	0
Living standards	Lower socioeconomic status	2775 (1 study)	1.33 (1.07–1.75) [34]	+
		2775 (1 study)	2.47 (1.08–5.66) [34]	
	Day-care attendance	NR (6 studies)	1.49 (1.17–1.91) [31]	0
	Living in Northern vs. Southern Europe	7170 (1 study)	0.4 (0.2–0.7) [23]	0
Travel	International travel	1887 (6 studies)	4.06 ** (1.33–2.41) [24]	+++
		834 (1 study)	21 (4.5–97) [23]	
	To Asia	NR (4 studies)	1.78 (0.64–4.98) [15]	++
		NR (12 studies)	14.16 (5.50–36.45) [35]	
		370 (1 study)	30.0 (6.3–147.2) [36]	

Variable	Subcategory	Number of Participants (Number of Studies Investigating Variable)	Magnitude of Association OR (95% CI)	Importance Rating *
	To Africa	NR (3 studies)	0.94 ** (0.14–6.17) [24]	–
	To India	182 (3 studies)	2.4 ** (1.26–4.58) [24]	+
		NR (3 studies)	3.80 (2.23–6.47) [15]	
	Inflammatory bowel disease	5253 (20 studies)	2.09 (1.16–3.77) [37]	0
	Diarrhea	NR (4 studies)	1.65 (1.02–2.68) [15]	+
		5253 (20 studies)	1.69 (1.25–2.30) [37]	
		NR (12 studies)	2.02 (1.45–2.81) [35]	
		430 (1 study)	31.0 (2.7–358.1) [36]	
Health while traveling	Contact with healthcare while traveling	5253 (20 studies)	1.53 (1.09–2.15) [37]	0
	Antibiotic use	5253 (20 studies)	2.38 (1.88–3.00) [37]	+
		NR (12 studies)	2.78 (1.76–4.39) [35]	
		NR (4 studies)	2.81 (1.47–5.36) [15]	
		99 (1 study)	3.0 (1.4–6.7) [36]	
		99 (1 study)	5.0 (1.1–26.2) [36]	
Traveler demographics	Backpackers compared to other travelers	5253 (20 studies)	1.46 (1.20–1.78) [37]	0

Variable	Subcategory	Number of Participants (Number of Studies Investigating Variable)	Magnitude of Association OR (95% CI)	Importance Rating *
	Vegetarian diet	5253 (20 studies)	1.41 (1.01–1.96) [37]	+
		NR (3 studies)	1.92 (1.13–3.26) [15]	
	Diet associated with risk (pastry, meals from stalls, etc.)	NR (12 studies)	1.27 (0.67–2.41) [35]	−
	Street food consumption	NR (2 studies)	0.92 (0.49–1.74) [15]	
		NR (2 studies)	1.37 (1.08–1.73) [15]	+
		NR (2 studies)	2.09 (1.30–3.38) [15]	
	Raw vegetable consumption	NR (2 studies)	0.34 (0.12–0.93) [15]	
		NR (2 studies)	0.58 (0.33–1.07) [15]	−
	[15][35][36]	[15][24] NR (2 studies)	2.18 (1.29–3.68) [15]	[23][24]
	Consuming bottled water	5253 (20 studies)	1.29 (0.50–3.34) [37] [15] [37]	[36] [36]
Protective measures while traveling [35][37]	General protective measures (disposable gloves, bottled water, etc.) [37]	NR (12 studies)	0.83 (0.61–1.13) [35]	−
	Meticulous hand hygiene [15]	5253 (20 studies)	1.10 (0.81–1.49) [37]	−
	Probiotics	5253 (20 studies)	1.06 (0.78–1.45) [37]	−

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4. Animal and Environmental Variables

Of the animal-related variables, pets and farming were investigated in reviews for increasing the odds of AMR *E. coli* amongst community-dwelling populations (**Table 3**). All reviews reporting on pet owners reported no increased odds of AMR *E. coli*. No statistical results were reported on farming. Amongst the types of farms, poultry in the Netherlands has been identified as a probable source of genetic AMR *E. coli* transmission in two reviews identified through whole-genome sequencing [38][39]. Looking at the environmental-related variables, swimming in freshwater

* Importance rating refers to the statistical significance of a potential variable and/or effect size estimate in relation to *E. coli* AMR; i.e., the amount of studies within the reviews that found statistically significant results with +++ very strong association, ++ strong association, + moderate association, 0 weak association and – No association. ** Risk ratio (95% CI) instead of odds ratio presented.

doubled the risk of AMR *E. coli* infection in one systematic review [23] (**Table 3**). No variables were identified as important in both categories.

Table 3. Animal and environmental variables of *E. coli* AMR among community-dwelling populations.

Animal	Subcategory	Number of Studies Investigating Variable (Number of Participants)	Magnitude of Association OR (95% CI)	Importance of Rating *
Pets	Pet owner	963 (5 studies)	1.39 ** (0.89–2.18) [24][40]	–
		9403 (12 studies)	1.18 ** (0.83–1.68) [40]	
		5159 (4 studies)	1.15 (0.33–4.06) [15]	
	Dog owner	9403 (12 studies)	0.88 ** (0.56–1.40) [40]	–
	Cat owner	9403 (12 studies)	1.16 ** (0.58–2.34) [40]	–
	Rodent owner	9403 (12 studies)	1.34 ** (0.43–4.18) [40]	–
	Bird owner	9403 (12 studies)	0.91 ** (0.38–2.18) [40]	–
Environment				
Freshwater	Swimming	290 (1 study)	2.1 (1.02–4.3) [23]	0

5. Temporal Relationship Variable and AMR *E. coli*

* Importance rating refers to the statistical significance of a potential variable and/or effect size estimate in relation to *E. coli* AMR; i.e., the amount of studies within the reviews that found statistically significant results with 0 weak association and – No association ** Risk ratio (95% CI) instead of odds ratio presented.

Eleven reviews investigated the temporal relation of variables and outcomes of AMR *E. coli* with antibiotic use and travel as subcategories (**Table 4**). Reviews showed that resistance after antibiotic use can persist for up to 12 months [15][26][41]. All cut-off points before one year were consistently associated with increasing the odds of AMR *E. coli* varying from 1.4 to 13.2. The risk of AMR *E. coli* after traveling abroad is highest in the first six weeks but decreases over time [37]. Six months [32][41] after antibiotic use was identified as the most important variable for AMR *E. coli*, followed by one and three months [32][41][42].

Table 4. Temporal relationship of variables for *E. coli* AMR among community-dwelling populations.

Variable	Subcategory	Number of Studies Investigating Variable (Number of Participants)	Magnitude of Association OR (95% CI)	Importance of Rating *
Time after antibiotic use	One week	129 (2 studies)	7.1 (4.2–12) [25]	0

Variable	Subcategory	Number of Studies Investigating Variable (Number of Participants)	Magnitude of Association OR (95% CI)	Importance of Rating *
	Two weeks	NR (6 studies)	1.08 (0.6–1.96) [42]	+
		NR (1 study)	6.12 (3.18–11.76) [41]	
	One month	NR (6 studies)	1.38 (1.16–1.64) [42]	++
		93 (1 study)	1.8 (0.9–3.6) [25]	
		NR (1 study)	6.20 (2.14–15.96) [41]	
		NR (2 studies)	8.38 (2.84–24.77) [41]	
		1208 (3 studies)	11.21 (7.13–17.63) [32]	
	Two months	14,348 (5 studies)	2.5 (2.1–2.9) [26]	+
		NR (1 study)	5.08 (2.70–9.56) [42]	
	Three months	NR (6 studies)	1.65 (1.36–2.0) [42]	++
		NR (1 study)	3.38 (2.05–5.55) [41]	
		1208 (3 studies)	10.64 (3.79–29.92) [32]	
	Six months	NR (1 study)	3.16 (1.65–6.06) [41]	+++
		1208 (3 studies)	4.76 (1.52–14.90) [32]	
		NR (1 study)	13.23 (7.84–22.31) [41]	
	12 months 11, 51, 54, 59, 60	14,348 (5 studies)	1.33 (1.2–1.5) [26]	+
		NR (1 study)	0.94 (0.57–1.56) [41]	
		10,079 (13 studies)	1.84 (1.35–2.51)	

Variable	Subcategory	Number of Studies Investigating Variable (Number of Participants)	Magnitude of Association OR (95% CI)	Importance of Rating *
			[15]	
		NR (1 study)	1.89 (1.04–3.42) [41]	
	Over 12 months	NR (1 study)	0.94 (0.57–1.56) [41]	–
Time after return from travel	Six weeks	290 (1 study)	16.4 (3.4–78.8) [23]	+
	Between six weeks and two years	290 (1 study)	2.2 (1.1–4.3) [23]	0

* Importance rating refers to the statistical significance, potential clinical, epidemiological, or economic importance, relation to *E. coli* AMR, and number of studies within the review that found statistically significant results. + very strong association, + strong association, 0 moderate association, – weak association.

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