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.

Keywords: antimicrobial resistance ; antibiotics ; One Health ; risk factor ; community ; human ; Escherichia coli

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		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]	
	General antibiotic use	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]	
		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]	
		290 (1 study)	19.0 (3.3–111.4) [23]	
	Penicillin	7170 (1 study)	0.9 (0.5–1.7) [23]	0
		408 (1 study)	2.7 (1.2–6.3) [23]	
	Cephalosporin	74 (1 study)	1.5 (5.4–85.2) [23]	+
		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) [23]	0
	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]	

Variable	Subcategory	Number of Participants (Number of Studies Investigating Variable)	Magnitude of Association OR (95% CI)	Importance Rating *
	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]	
	Previous/recurrent UTI	7170 (1 study)	1.3 (1.01–1.6) [23]	++
		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]	–
	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
Comorbidities	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]	–
	Immunosuppressive therapy	7170 (1 study)	1.5 (1.1–2.1) [23]	0
Medication use	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]	

Variable	Subcategory	Number of Participants (Number of Studies Investigating Variable)	Magnitude of Association OR (95% CI)	Importance Rating *
Hospitalization	Previous hospitalization	1379 (5 studies)	1.18 ** (0.78–1.81) [24]	+
		1163 (4 studies)	1.28 ** (0.82–2.03) [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
Diet	Vegetarian	6802 (5 studies)	1.60 (1.0043–2.5587) [15]	0
	Raw milk	226 (1 study)	7.54 (2.41–23.45) [15]	+
	Fish	290 (1 study)	0.6 (0.5–0.9) [23]	0
Sex and age	Older age	300 (1 study)	2.0 (1.02–3.5) [23]	0
	Male sex	NR (9 studies)	0.96 (0.74–1.24) [31]	0
		7170 (1 study)	1.6 (1.2–2.1) [23]	

* 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.

2.2. Comorbidities, Medication Use, and Hospitalization

Urogenital comorbidities increased the odds of AMR *E. coli*, as did some non-urogenital conditions (**Table 1**), with the most important variables being previous/recurrent urinary tract infection (UTI) [23] and diabetes [23]. There were mixed results for variables indicating increased vulnerability, with a positive association for previous hospitalization [24] and corticosteroid use [23], mixed results for acid suppressants [15][33], and no association for increased odds of AMR *E. coli* in those with chronic disease [15] or renal and urological disorders [23].

2.3. Diet, Sex, Age, and Living

Vegetarian diet, older age (>55 years) [23], and children attending day-care [31] increased the odds of AMR *E. coli* varying from 1.5 to 2.0 (**Table 1**). Raw milk [15] and lower socioeconomic status [34] were found to be the most important variables in this category. A weekly fish meal and living in Northern Europe compared to Southern Europe were found to reduce the risk of infection of AMR *E. coli* [23] (**Table 2**).

Table 2. Human living and travel 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 *
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]	
		NR (4 studies)	1.78 (0.64–4.98) [15]	
	To Asia	NR (12 studies)	14.16 (5.50–36.45) [35]	++
		370 (1 study)	30.0 (6.3–147.2) [36]	
	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]	

Variable	Subcategory	Number of Participants (Number of Studies Investigating Variable)	Magnitude of Association OR (95% CI)	Importance Rating *
Traveler demographics	Backpackers compared to other travelers	5253 (20 studies)	1.46 (1.20–1.78) [37]	0
	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]	–
		NR (2 studies)	2.18 (1.29–3.68) [15]	
Protective measures while traveling	Consuming bottled water	5253 (20 studies)	1.29 (0.50–3.34) [37]	–
	General protective measures (disposable gloves, bottled water, etc.)	NR (12 studies)	0.83 (0.61–1.13) [35]	–
	Meticulous hand hygiene	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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3. Travel

The last human-related variable was travel, with destination, health while traveling, traveler demographics, protective measures, and household transmission as subcategories (**Table 2**). International travel [23][24] increased the odds of AMR *E. coli*, with Asia [15][35][36] and India [15][24] as travel destinations having the highest risks and were found to be the most important variables in this category. Reviews reporting on bowel-related diseases while traveling reported a positive association with odds for AMR *E. coli* ranging from 1.6 [15] to 31 [36]. Antibiotic use while traveling showed a positive association in all reviews, increasing odds from 2.4 [37] to 5 [36]. There were no conclusive results around food consumption while traveling on the odds of AMR *E. coli*, with a vegetarian diet increasing the odds by 1.4 [37], raw vegetable consumption showing mixed results and odds after street food consumption varying from approximately 1.4 to 2.1 [15]. Protective measures while traveling were proven ineffective [35][37]. International travel, followed by travel to Asia, travel to India, antibiotic use while traveling, vegetarian diet, and street food consumption were identified as important variables.

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 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

* 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.

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

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
	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]	

Variable	Subcategory	Number of Studies Investigating Variable (Number of Participants)	Magnitude of Association OR (95% CI)	Importance of Rating *
	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) [15]	
	Over 12 months	NR (1 study)	1.89 (1.04–3.42) [41]	–
		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 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.

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