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Review article

Antibiotic susceptibility among non-clinical *Escherichia coli* as a marker of antibiotic pressure in Peru (2009–2019): one health approach

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HIGHLIGHTS

- In livestock and food >90% of streptomycin and cephalosporin resistance was detected.
- High levels of rifamycin resistance were found in non-clinical samples from humans.
- High levels to quinolones tetracycline and cephalosporins were detected in pets.
- Environmental samples showed 50–70% of resistance to cephalosporins and streptomycin.
- In general, high levels of resistance to ancient antibacterial agents was observed.

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ABSTRACT

Objective: Antimicrobial resistance is an increasing health problem worldwide with serious implications in global health. The overuse and misuse of antimicrobials has resulted in the spread of antimicrobial-resistant microorganisms in humans, animals and the environment. Surveillance of antimicrobial resistance provides important information contributing to understanding dissemination within these environments. These data are often unavailable in low- and middle-income countries, such as Peru. This review aimed to determine the levels of antimicrobial resistance in non-clinical *Escherichia coli* beyond the clinical setting in Peru.

Methods: We searched 2009–2019 literature in PUBMED, Google Scholar and local repositories.

Results: Thirty manuscripts including human, food, environmental, livestock, pets and/or wild animals' samples were found. The analysis showed high resistance levels to a variety of antimicrobial agents, with >90% of resistance for streptomycin and non-extended-spectrum cephalosporin in livestock and food. High levels of rifamycin resistance were also found in non-clinical samples from humans. In pets, resistance levels of 70–>90% were detected for quinolones tetracycline and non-extended spectrum cephalosporins. The results suggest higher levels of antimicrobial resistance in captive than in free-ranging wild-animals. Finally, among environmental samples, 50–70% of resistance to non-extended-spectrum cephalosporin and streptomycin was found.

Conclusions: High levels of resistance, especially related to old antibacterial agents, such as streptomycin, 1st and 2nd generation cephalosporins, tetracyclines or first-generation quinolones were detected. Antimicrobial use and control measures are needed with a One Health approach to identify the main drivers of antimicrobial resistance due to interconnected human, animal and environmental habitats.

1. Introduction

1.1. Antibiotic resistance: origin and where we are

From the last third of the 19th century, efforts to find or synthetize molecules able to efficiently fight infectious diseases were continuous, with the introduction of penicillin into clinical practice in the 1940's [1, 2, 3, 4, 5, 6]. Since then, antimicrobial agents play a crucial role in reducing morbidity and mortality caused by bacterial infections, being indispensable for the practice of modern medicine. Antimicrobial resistance (AMR) is an ancient phenomenon related to a series of mechanisms, which have coevolved in parallel with antibiotics to either avoid self-killing of

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antibiotic-producer microorganisms or to provide a selective advantage to other microorganisms when near an antibiotic source [7, 8]. Nonetheless, different factors, such as the maintenance of a series of additional structures, expression genes or related cellular network alterations, often negatively impact bacterial fitness and result in a selective disadvantage in free-antibiotic environments [9].

Currently, AMR has been reported for all the antimicrobial families, with the presence of pan-resistant microorganisms being considered a major and growing health challenge with serious economic impact [10, 11, 12, 13]. Thus, in 2019, the Center for Diseases Control (CDC) considered that in the USA more than 2.8 million people developed infection by multidrug-resistant (MDR) microorganisms, leading to 35, 000 deaths [14]. Also, it estimated that 4.95 million deaths were associated with bacterial AMR, being 1.27 million deaths attributable to bacterial AMR [15]. While controversial, the most negative forecast has projected that around 10,000,000 deaths worldwide related to antibiotic-resistant microorganisms can be foreseen in 2050 [16], resulting in an economic loss of $ 1.2 trillion worldwide, with a special impact on the most disfavored countries [17]. In 2015, this situation led the World Health Organization to design a worldwide strategy to fight AMR with posterior discussion in a plenary session of United Nations on September 21, 2016 of the problem of antibiotic resistance (https://www.un.org/pga/71/event-latest/high-level-meeting-on-antimicrobial-resistance/). These findings have underlined the absolute need to design strategies and actions to avoid the risk of a full loss of usefulness of antibiotics.

1.2. Antibiotic resistance in low- and middle-income countries

Low- and middle-income countries are characterized by a high burden of infectious diseases, and resistance rates that are even greater than in industrialized countries [18]. The emergence and spread of resistance to antimicrobials in Latin America is not an exception, producing an even greater challenge for the fight against infectious diseases. In these countries, resistance to antimicrobials is multifactorial, and it is especially related to inadequate use of antibiotics, environmental changes and rapid growth of the population, with the majority of people living in large cities and suburbs with poor hygienic conditions and often inadequate sanitation. In addition, basic problems such as malnutrition and anemia, which have a direct impact on the immune system, and even sociocultural attitudes that affect the misuse of medications, also play a role in this scenario [18–21]. It is important to highlight that the lack of regulation and control of access to antibiotics, both by humans and for veterinary use are also key points to be considered. Indeed, the overuse of antibiotics in human and veterinary medicine contributes to high local antibiotic pressure inducing major selective pressure leading to the emergence and spread of resistance [22, 23, 24].

1.3. Antibiotic resistance: situation in Latin America and Peru

Fueled by the above-mentioned aspects, in recent years, antibiotic resistance has been a growing problem in Latin America [25, 26, 27, 28, 29]. The data available suggest that in this region, antibiotic resistance of the most common pathogens has reached unacceptable levels, with reported values of 90–100% resistance to different antimicrobial, such as carbapenems in *Acinetobacter baumannii* [27, 30]. Peru is a upper-middle-income country (https://data.worldbank.org/?locations=PE-XT), with around 33 million inhabitants in 2020; of these ~9.7 million inhabitants (29.7%) live in the Lima department, mostly in the metropolitan area (http://m.inei.gob.pe/media/MenuRecursivo/noticias/notadeprensa006.pdf). The country has 3 clearly delimited geographical areas: the coast, on the western side, the highlands in the center, and the jungle, on the east side of the country. Peru presents clear inequities between rural and urban areas, although these inequities are declining. This scenario as well as the difficult access to health facilities, either because of distance or economical costs, often results in inadequate medical assistance and a lack of effective control of access to antibiotics, contributing to self-medication practices [21, 31].

1.4. Antibiotic resistance beyond clinical data

Different interconnected human, animal and environmental media contribute to the emergence and dissemination of antibiotic resistance, with this concept being the basis of the so-called One Health approach [23]. Thus, the antibiotic resistance levels of these habitats can have a final impact on human health [32]. Data on the relevance of commensal and environmental microorganisms as a reservoir of antibiotic resistance determinants is growing worldwide [33, 34, 35]. Nonetheless, regarding Peru data are scarce, being mostly fragmented and sometimes reported in difficult to access documents.

1.5. Escherichia coli

Escherichia coli ranks among the most relevant human pathogens isolated as a cause of a high diversity of pathogenic process [36, 37, 38, 39, 40, 41, 42], even involving animals [43, 44, 45]. Moreover, it colonizes the gastrointestinal tract of humans and animals as a commensal microorganism, being commonly isolated from foods of animal origin, as well as vegetables, water and soil [42, 46, 47, 48]. Thus, *E. coli* is a good bacterial marker for studies including a variety of sources and would be an excellent marker to draw the antibiotic resistance scenario beyond classical clinical approaches and points of view.

In this scenario, this manuscript aims to provide an overview of the resistance profiles of non-clinical recovered *E. coli* in Peru in relation to the sources from which they were found from 2009-2019.

2. Search method

Articles containing the terms ((*Escherichia coli*) AND Peru) AND antibiotic resistance) were sought in PubMed. The results were complemented by searching in Google Scholar and local academic repositories. Limits were placed on reports (articles or Thesis) published from 2009-2019 in either Spanish or English languages. Only studies reporting numeric or percentual values of antibiotic resistance levels (obtained by disk diffusion or by minimal inhibitory concentration) in *E. coli* recovered from non-clinical (i.e.: *E. coli* does not isolate as a cause of human disease) human sources were considered. When more than one report referred to the same bacterial collection only one was considered for statistical purposes irrespective of complementing the resistance data with information present in other related reports.

Studies reporting resistance data in non-standardized formats such as "median of halo diameter" were not included in the study because of the inability to establish the levels of antibiotic resistance. Although the articles in which the microorganisms were isolated in antibiotic-supplemented media were included in the bibliometric analysis and the data were used in the discussion, they were not used to determine and analyze the levels of resistance due to selection bias. All *E. coli* from healthy people were collectively analyzed irrespective of their pathogenic potential [49]. Finally, intermediate isolates were added to resistant isolates to determine the number of non-susceptible isolates.

3. Results of the bibliometric analysis

The PubMed search resulted in 42 articles fulfilling the search criteria, 10 of which were selected after visual inspection. In addition, 20 other studies were obtained from Google scholar and university repositories: 1 article from a PubMed indexed journal (but not detected using the search strategy), 11 articles published in local or other non-PubMed indexed journals (LJ/NPM) and 8 Doctoral [1], Master [2] or Grade [5] Theses (hereafter called Thesis) extracted from local repositories (Table 1). Thus, a total of 30 different studies were considered. Of these, 7 (23.3%) related to livestock and 7 (23.3%) to the environment. Five (16.7%) studies were

Table 1. Reports of antimicrobial resistance levels in Peruvian non-clinical *Escherichia coli* published from 2009-2019.

Sampling				*E. coli*			
Source		Year[a]	Area	N	R[b]	Ref	Type
Human							
1	Undetermined	2002	Lt	111	89	50c	PM
2	Children	2005	Lt	164	66	51[d]	PM
3	Children	2006–2007	Lm	753	168	49[e]	PM
4	Children	<2009	Cj, Ic Lm, Lt	523	523	52	PM
4	Adults	<2009	Cj; Ic, Lm, Lt	164	164	52	PM
5	Undetermined	2009	Lt	34	29	28[d]	PM
6	Children	2014–2015	Cs, Sm	179	179	53	PM
Sub-Total				1928	1218		
Food							
4	Chicken	<2009	Cj, Ic Lm, Lt	252	252	52	PM
7	Chicken	2012	Lm	159	56	47	PM
7	Pork	2012	Lm	45	22	47	PM
7	Beef	2012	Lm	57	25	47	PM
8	Beef	2015	Lm	154	154	54	TH
Sub-Total				667	509		
Environmental							
9	Sea water	1999–2000	Lm	55	41	55	LJ/ NPM
10	Hospital surfaces	2009–2010	Cj	20	20	56[h]	PM
11	Hospital cell phones	2012	Lm	34	34	57	PM
8	Slaughterhouse	2015	Lm	35	35	54	TH
12	Drinking water (untreated)	2015–2016	Cj	117	117	58	PM
13	Sea water	2016	Pr	108	108	59	TH
14	Sea water	2017	Lm	64	64	60	TH
15	River water (urban area)	2018–2019	Pr	31	31	61	TH
Sub-Total				464	450		
Livestock							
4	Chicken	<2009	Lm	242	242	52	PM
16	Alpaca (*Vicugna pacos*)	2007	Ar, Pn, Cs	30	30	44	LJ/ NPM
17	Pig	2010–2015	Lm	36	36	62	LJ/ NPM
18	Pig	2013	Lm	36	36	63	LJ/ NPM
19	Alpaca (*Vicugna pacos*)	2013	Hc	82	82	64	LJ/ NPM
8	Cattle (feces)	2015	Lm	70	70	54	TH
20	Various[i]	2015	Lm	10	10	65j	PM
21	Chicken	2015–2016	Ar; Ic; Ll, Lm; Uc	185	185	66	LJ/ NPM
22	Chicken	2017	Pr	50	50	67	TH
23	Cattle	2017–2018	Cj	32	32	68	TH
Sub-Total				773	773		
Pets							
4	Various[h]	<2009	Cj, Ic, Lm, Lt	526	526	52	PM
24	Dog	?	Lm	12	12	69	LJ/ NPM
25	Dog	2003–2012	Lm	14	14	43	LJ/ NPM
26	Dog	2012–2017	Lm	45	45	70	LJ/ NPM
27	Dog	2016–2017	Cj	100	100	71	TH
Sub-Total				697	697		
Wild Animals[f]							
28	Northern Caiman Lizard (*Dracaena guianensis*)	2014	Lm	17	17	72	TH
29	Spectacled caiman (*Caiman cocodrilus*)	2014	MdD	7	7	73	LJ/ NPM
20	Common vampire bat (*Desmodus rotundus*)	2015	Lm	5	5	65[g]	PM
30	Monkey (*Ateles*, *Callicebus*, *Lagothrix*)	?	Lt	45	45	74	LJ/ NPM
Sub-Total				74	74		
Overall				4603	3721		

Ar: Arequipa; Cj: Cajamarca; Cs: Cusco; Hc: Huancavelica; Ic: Ica; Ll: La Libertad; Lm: Lima; Lt: Loreto; MdD. Madre de Dios; Pr: Piura; Pn: Puno; Sm: San Martin; Uc. Ucayali. N: Number of isolates; R: Antimicrobial resistant isolates. PM: PubMed journals; TH: Thesis; NPM: non-PubMed indexed journals; LJ: Local journals.
When the same sampling recovered *E. coli* from different sources, these are indicated in different rows. Nonetheless, in several cases the data were reported together to avoid an excessive fragmentation of the Table and because they were mainly analyzed together in the original articles, making it difficult to adjudicate the specific results to specific sampling sources. In these cases, the sampling composition is indicated below. Articles 1, 2, 5 and 20 presented a selective bias and were only considered for bibliometric purposes [28, 50, 51, 65]. a: Sampling year. b: The number of *E. coli* is limited to those for which data on antimicrobial resistance was available. c: Isolates recovered from plates containing antibiotic disks (direct plating method). d: Samples cultured in the presence of 0.12 μg/ml of ciprofloxacin. e: Data about sampling or AMR may also be found in Gomes *et al.*, 2013, Gomes *et al.*, 2019 Ochoa *et al.*, 2009, and Pons *et al.*, 2014 [75, 76, 77, 78]. f: Includes free wild animals [73] and wild animals living in captivity or in semi-captivity [72, 74]. g: The article only reports isolates possessing ESBLs. h: Data about sampling and/or AMR may also be found in Rivera-Jacinto *et al.*, 2015 [79]. i: The sampling including: 20 cows, 8 pigs, 5 sheep, 2 horses and 2 donkeys. j: The article only reports isolates possessing ESBLs (6 from pigs, 4 from cows). h: The sampling included: 224 dogs, 95 cats, 77 guinea pigs, 72 pigs, 64 ducks, 34 cows, 30 rabbits, 27 sheep, 23 turkeys, 15 donkeys, 12 doves, 12 goats, 8 horses, 8 canaries/parrots, 2 geese, 2 monkeys, 1 quail, 1 squirrel, 1 unknown. Note that in Peru guinea pig is considered a food-producing animal, not a pet.

focused on human commensal *E. coli*, while 4 (13.3%) and 3 (10.0%) were analyzed pets and wild animals, respectively, and 1 (3.3%) included meat samples. Finally, 3 (10.0%) studies reporting *E. coli* from different sources were also included. Overall, 4 studies were only considered in the bibliometric analysis because of the above-mentioned selection bias. In the tables, these studies are numbered from 1 to 30 with to facilitate reading and interchangeability of data present in the tables. Five additional studies performing complementary analysis of the same *E. coli* collections were also revised (Table 1).

Thirteen studies (43.3%) included samples collected in the department of Lima while 14 (46.7%) used samples from other Peruvian departments, and an additional 3 (10%) studies analyzed samples from more than one department (2 including samples from Lima) (Table 1, Figure 1). Thus, 50% of the studies included samples from the Lima area, clearly showing that the data generated are strongly influenced by the specificities of the Lima department.

3.1. Overall vision of non-clinical Escherichia coli studies in Peru

The number of analyzed non-clinical *E. coli* during the 2009–2020 period is scarce, with only 3721 isolates with data of antimicrobial

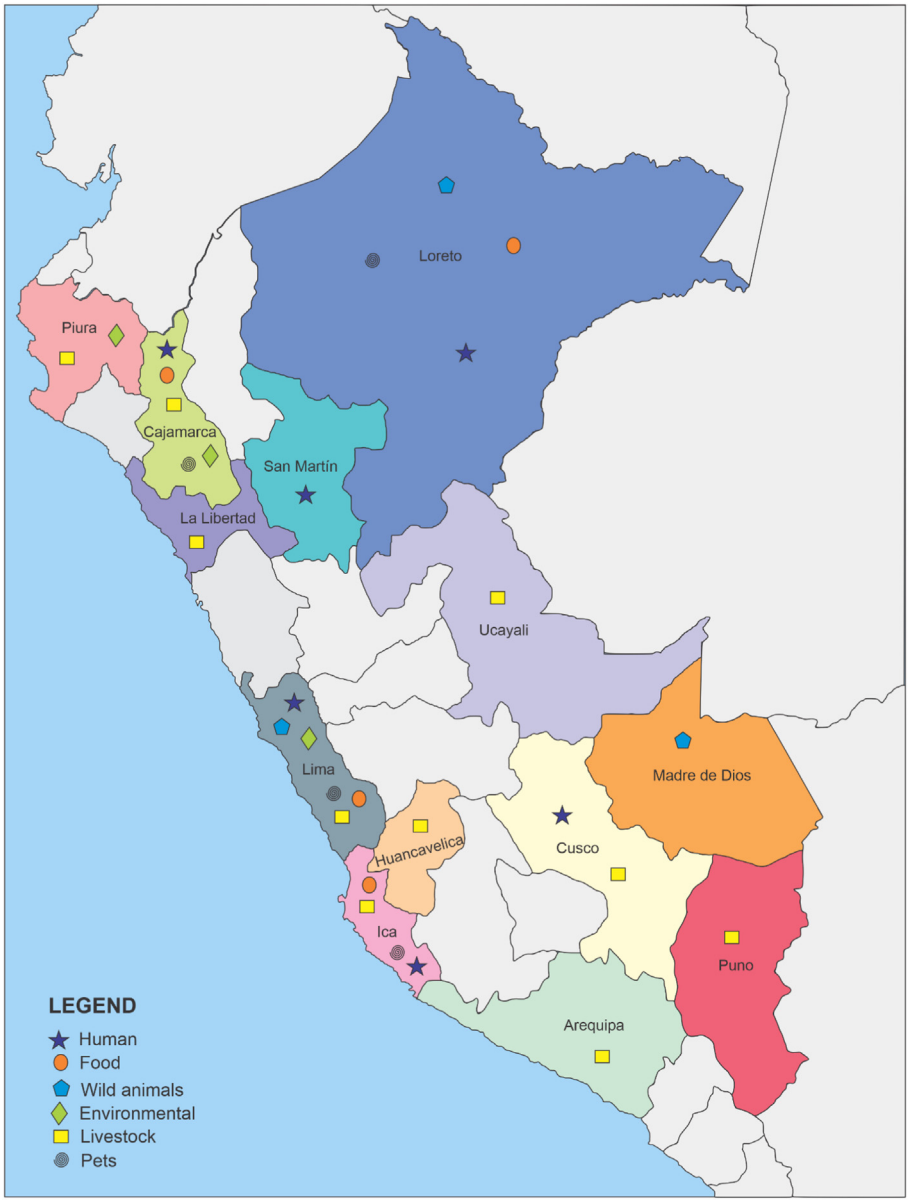

Figure 1. Geographical origin of the studies. The primary politic subdivision of Peru is in Departments. Those Departments from which were analyzed samples, are highlighted in color, and the name has been added in the map. Note that these marks does no preclude the authorship of authors based in these regions. Similarly, the symbols in the map only refers to Department, no to specific areas within each department. Note that in the map Callao, a special Peruvian administrative region, with range equivalent to Department, is included within Lima department. In fact, Callao is surrounded by the sea and the metropolitan area of Lima city.

resistance. Of note, most of them (1218 isolates, 32.7%) being human commensal isolates, with that analyzing wild-animal recovered *E. coli* accounting only for 74 isolates (Table 1). This finding, together the presence of a series of data non-reported in an article format, highlighting the need for new and longer studies.

3.2. Human Commensal Escherichia coli

Three studies reported the AMR levels of human commensal *E. coli*. Of these, 1 analyzed samples from Lima [49], another samples from San Martin and Cusco [53], and the remaining study analyzed samples from 4 Peruvian departments, including Lima [52].

While not included in the analyses of resistance to antimicrobial agents because of the use of antibiotic supplemented media (ciprofloxacin) or colony selection inside halos of antibiotic disks, 3 studies reported resistance levels of *E. coli* from non-pathogenic human samples [28, 50, 51] collected from 2002, 2005 and 2009 respectively in remote areas of the Loreto department.

The studies focused on healthy people ranks among the most ancient of those included in the present study (Table 1). This scenario showing that the number of studies reporting the levels of AMR among human commensal *E. coli* in Peru are scarce and mostly outdated, with all but one referring *E. coli* collected before 2009, with this panorama also extended to the 3 non-included studies [28, 49, 50, 51, 52]. The remaining study analyzing isolates collected on 2014–2015 [53]. This scenario is probably common to a series of low- and middle-income countries for which this type of data is scarce or often unavailable.

Resistance to ancient antimicrobial agents such as ampicillin or cotrimoxazole was high, being of note that these agents are widely used in pediatric population in the area [80]. In this regard, Kalter *et al.* analyzed samples from both children and adults finding ampicillin and cotrimoxazole resistance levels of 53.7% and 51.8% in children and 37.2% and 21.3% in adults, respectively [52]. Macrolides are also used in pediatric populations for the treatment of respiratory infections and diarrhea [80, 81], with analyzed data reporting resistance to azithromycin ranging between 15,6% and 27.4% [53, 76]. In contrast to quinolones, resistance to macrolides in *E. coli* (and other *Enterobacteriales*) is mostly related to transferable mechanisms (especially *mph*A), with a role for efflux pumps rather than to target mutations [76, 82].

Of note, resistance to ancient quinolones, such as nalidixic acid, ranged between 38.7 and 43.0%. Quinolones are usually not used in pediatric populations. Mosquito *et al.* showed that non-diarrheagenic

Table 2. Percentage of antimicrobial resistance in human commensal *Escherichia coli*.

Articles	3	4	4	6
Sample	Ch	Ch	A	Ch
No	168	523	164	179
Year	2006–2007	<2009	<2009	2014–2015
Antimicrobial Resistance				
Amp	76.8	53.7	37.2	51.4
A/C				15.1
Ctx				5.6
Cxm				7.7
Fox				2.8
Cro		0.0	0.6	4.5
Imp				4.0
Tc	56.5			
Sxt	62.5	51.8	21.3	50.8
Chl	22.0			
Azm	27.4[a]			15.6
Nal	38.7			43.0
Cip	13.1	1.5	1.8	9.0
Gm				3.4
Nit				2.3
Rfx	93.2[b]			
Other				
MDR	50.1			

Year: Sampling year. Ch: Children; A: Adults; Amp: Ampicillin; A/C: Amoxicillin plus clavulanic acid; Ctx: Cefotaxime; Cxm: Cefuroxime; Fox: Cefoxitin; Cro: Ceftriaxone; Imp: Imipenem; Tc: Tetracycline; Sxt: Cotrimoxazole; Chl: Chloramphenicol; Azm: Azithromycin; Nal: Nalidixic acid; Cip: Ciprofloxacin; Gm: Gentamicin; Nit: Nitrofurantoin; Rfx: Rifaximin; MDR: Multidrug Resistance. a Eighty-four isolates analyzed [76]. b Seventy-four isolates analyzed, all with a MIC ≥32 μg/L [75].

E. coli were significantly more resistant to ancient quinolones than diarrheogenic *E. coli*, recovered from either ill or healthy children [49]. Furthermore, while transferable mechanisms of quinolone resistance have been described in the area [83], including in several of above-mentioned isolates [77], resistance to these antimicrobial agents is largely mediated by chromosomal mutations [77, 84], suggesting an exogenous origin of these isolates. High levels of quinolone resistance in microorganisms from other sources, such as food-samples [47] could make this a plausible option.

Except for tetracycline, resistance levels to other antimicrobial agents were almost negligible, including resistance to carbapenems as shown in samples from other sources (Table 2).

3.3. *Escherichia coli* recovered from food

The studies on food samples were all focused on pre-marketed (meat food in slaughterhouses) or marketed meats (chicken, beef and pork) with no study reporting data on vegetables or other foodstuffs. Three studies were included in the analysis [47, 52, 54]: 2 from Lima and 1 including samples from Lima and 3 other Peruvian regions (Cajamarca, Ica, Loreto) (Table 1, Figure 1).

All the studies showed high levels of resistance to ampicillin, tetracycline, nalidixic acid and ciprofloxacin, ranging from 19.5% to 96.4%, irrespective of the meat sample. Meanwhile, resistance levels to other antimicrobial agents varied among different studies and samples. For instance, resistance to cotrimoxazole ranged from 1.2% in beef samples to 100% in chicken samples [47, 54]. Similarly, resistance to chloramphenicol varied from 8% in beef samples to 83.9% in chicken samples [47]. Regarding furazolidone, the resistance levels of 35.7% and 31.8% were of note in chicken and pork samples, respectively.

Table 3. Percentage of antimicrobial resistance in *Escherichia coli* from marketed foods.

	Articles				
	4	7	7	8	7
General Data					
Sample	C	C	B	B	P
No	252	56	25	154	22
Year	<2009	2012	2012	2015	2012
Antimicrobial Resistance (%)					
Amp	46.0	94.6	44.0	65.6	95.4
A/C		41.1	16.0		4.5
Kf		91.7			
Cro	0.8				
Tc		94.6	56.0	20.1	90.9
Sxt		100.0	20.0	1.2	54.5
Smz	52.5				
Chl		83.9	8.0	54.5	
S				91.5	
Azm		39.3	8.0		0.0
Nal		94.6	44.0	38.3	77.3
Cip	20.6	96.4	48.0	19.5	81.8
Ak				22.7	
Gm				14.9	
Fur		35.7	4.0		31.8
Other					
MDR		98.2	28.0		86.4
ESBL		59.4[c]	0.0[d]		
pAmpC		6.2[c]	5.0[d]		

Year: sampling year. Amp: ampicillin; A/C: amoxicillin plus clavulanic acid; Kf: cefalotin; Cro: ceftriaxone; Tc: tetracycline; Sxt: cotrimoxazole; Smz: sulfamethoxazole; Chl: chloramphenicol; S: streptomycin; Azm: azithromycin; Nal: nalidixic acid; Cip: ciprofloxacin; Ak: amikacin; Gm: gentamicin; Fur: furazolidone; MDR: multidrug-resistant; ESBL: extended-spectrum β-lactamases, pAmpC: plasmid-encoded AmpC; C: chicken; B: Beef; P: pork. a Following the order described in Table 1. b Sampling year. c Thirty-two samples analyzed. d Twenty samples analyzed.

Azithromycin resistance of 39.3% was relevant among chicken samples. Cephalothin, sulfamethoxazole, streptomycin, amikacin and gentamicin were only tested in one type of meat sample, showing resistance values ranging from 14.9% to 98.7%. Of note, while used until 2019 in veterinary medicine in Peru [85], none of the studies provided data about colistin resistance. Finally, resistance to ceftriaxone in chicken meat was low with 0.8% [52]. MDR values ranged from 28.0% to 98.2% among beef and chicken samples, respectively (Table 3).

Overall, the analysis of the studies showed high levels of AMR which may be related to food-production systems, with chicken generally showing the highest levels of resistance to the antimicrobial agents tested. This finding agrees with the high levels of poultry production in Peru (>1.5 million of Tm in 2018) [86]. Further, Kalter *et al.* [52] reported that chicken samples from the Lima area showed higher levels of resistance to ampicillin and ciprofloxacin than those collected from other Peruvian regions. This finding, together the high levels of resistance to these and other antimicrobial agents observed in other studies using samples from Lima [47, 54], suggest that chickens consumed in Lima were grown in the presence of higher levels of antimicrobial agents. In this sense, antibacterial agents such as enrofloxacin, a member of the quinolone family, or ampicillin and amoxicillin (both β-lactam agents), have been largely used in poultry [87, 88]. Regarding Peru, while updated data of specific antibiotic usage on poultry are lacking, studies analyzing the presence of antibiotic residue in marketed chicken meat have described the presence of enrofloxacin traces in 56% of the samples analyzed [89].

The presence of extended-spectrum β-lactamases (ESBL) and pAmpC was sought in a subset of chicken (32 samples) and beef (20 samples), showing significant differences related to the sample source. Thus, 59.4% of chicken samples presented ESBL-producing *E. coli*, while none was detected from beef samples. Meanwhile, 6.8% and 5% of pAmpC-producing *E. coli* were detected in chicken and beef samples, respectively. This finding again agrees with a high antibiotic pressure in poultry farms. Likewise, the presence of other microorganisms such as MDR *Salmonella enterica* serovar Infantis carrying ESBL has been observed in chicken meat marketed in Lima [47], presenting the same clone in both chicken meat and ill children [90].

All these findings highlight the potential role of marketed meat in Peru as a diffusor of pathogenic microorganisms as well as AMR determinants. While most *E. coli* would be not pathogenic and would remain unnoticed, they, or any of their AMR genes, might be incorporated into the human gut microbiota and thereby act as a hidden AMR reservoir [34].

3.4. Environmental Escherichia coli

Of a total of 8 studies [54, 55, 56, 57, 58, 59, 60, 61], 3 were developed with sea water, 1 with river water and another with untreated water used for all household purposes. The remaining 3 studies were developed in hospital surfaces, personal devices of health workers, and over devices and surfaces of a slaughterhouse. All studies but 3 were performed in Lima, while 2 were performed in Cajamarca samples (hospital surfaces and drinking water respectively) and 1 in Piura analyzing river water.

Relevant levels of resistance of ampicillin were detected (Table 4). High levels of ampicillin resistance of river and drinking water [58, 61] is of special concern. In fact, *E. coli* from river water presented high levels of ampicillin (80.6%) and cotrimoxazole (41.9%) resistance. *E. coli* from river water also showed significant levels of resistance to other antibiotics such as cefotaxime (35.5%) and gentamicin (19.4%) [61]. In a scenario of uncontrolled access to antibacterial agents, the presence of these levels of resistance to ancient (and relatively cheap) antimicrobial agents such as ampicillin in water sources, seems to be related to

Table 4. Antimicrobial resistance levels in environmental *Escherichia coli*.

	Articles							
	8	9	10	11	12	13	14	15
General Data								
Sample	Slt	SW	HS	HS	DW	SW	SW	RW
No	35	41	20	34	117	108	64	31
Year	2015	1999–2000	2009–2010	2012	2015–2016	2016	2017	2018–2019
Antimicrobial Resistance (%)								
Amp	80.0	19.5	60.0	—	51.3	—	48.5	80.6
Amx	—[a]	17.1	—	—	—	—	—	—
A/C	—	—	—	—	9.4	—	—	—
Spz	—	0.0	—	—	—	—	—	—
Atm	—	2.4	25.0	—	—	—	—	25.8
Kf	100.0	—	75.0	—	—	—	—	—
Ctx	—	—	20.0	—	5.1	36.1	—	35.5
Cro	—	—	20.0	—	—	—	—	35.5
Fox	—	—	10.0	8.8	3.2	—	—	—
Caz	—	0.0	10.0	—	—	23.1	—	16.1
Fep	—	—	20.0	—	—	25.9	—	—
Mem	—	—	—	—	—	0.0	—	—
Tc	40.0	17.1	—	—	32.5	—	40.4	—
Sxt	17.1	17.1	—	44.1	19.8	19.4	31.3	41.9
Chl	25.7	2.4	—	—	11.1	—	9.9	—
S	71.5	—	—	—	—	—	—	—
Azm	—	—	—	—	6.8	—	—	—
Nal	75.7	7.3	—	—	14.5	—	50.0	—
Nor	—	0.0	—	—	—	—	—	—
Cip	31.4[b]	0.0	—	61.8	9.4	8.3	—	9.7
Ak	14.3	4.9	—	5.9	—	—	—	0.0
Gm	17.1	0.0	—	32.4	2.6	—	—	19.4
Km	—	2.4	—	—	—	—	—	—
Tob	—	—	—	47.1	—	—	—	—
Nit	—	—	—	—	5.1	—	—	—
Other								
MDR	—	9.1	—	35.3	19.7	—	26.6	—
ESBL	—	—	20.0	55.9	5.1	18.5		16.1
pAmpC	—	—	—	—	—	—	—	—

Year: sampling year; Slt: Slaugterhouse (devices and surfaces); SW: Sea water; HS: Hospital surfaces (in study 32 referring to medical personal devices); DW: Drinking water; RW: River water; Y: Year; Amp: Ampicillin; Amx: Amoxicillin; A/C: Amoxicillin plus clavulanic acid; Spz Sulperazone (cefoperazone plus sulbactam); Atm: Aztreonam; Kf: cefalotin; Ctx: cefotaxime; Cro: Ceftriaxone; Fox: Cefoxitin; Caz: Ceftazidime; Fep: Cefepime; Mem: Meropenem; Tc: Tetracycline; Sxt: Cotrimoxazole; Chl: Chloramphenicol; S: Streptomycin; Azm: Azithromycin; Nal: Nalidixic acid; Nor: Norfloxacin; Cip: Ciprofloxacin; Ak: Amikacin; Gm: Gentamicin; Km: Kanamycin; Tob: Tobramycin; Nit: Nitrofurantoin; MDR: Multidrug Resistance; ESBL: Extended-Spectrum β-Lactamases; pAmpC: Plasmid encoded AmpC. a Not reported/not determined/cannot be extrapolated from data. b All intermediate.

Table 5. Percentage of antimicrobial resistance in livestock samples.

	Articles								
	4	8	16	17	18	19	21	22	23
General Data									
Sample	Ch	Ct	Alp	Pig	Pig	Alp	Ch	Ch	Ct
No	242	70	30	36	36	82	185	50	32
Year	<2009	2015	2007	2010–15	2013	2013	2015–16	2016	2017–18
Antimicrobial Resistance (%)									
Amp	12.4	71.4	70.0*		100				
Amx								0.0	
A/C				69.4			90.2		
Atm				38.9					
Kf		97.2			100				
Ctx				41.7					
Cro	0.8			33.3		28.0*			
Fox				25.0					
Caz				47.2		22.0			
Fep				44.4					
Oxt			94.0*			37.0*	95.0	54.0	40.6
Dox								36.0*	
Tc		38.6			100.0				
Sxt		12.9	6.0		80.6	2.0	87.5	0.0	0.0
Sulfa	12.8								
Chl		7.1	70.0*		44.4				
Flor							65.8		
S		88.6	75.0*		94.4				
Nal		78.5		88.9	94.4				
Cip	2.5	34.3*		47.2	33.3	26.0*			
Enr			12.0			61.0*	83.4	0.0	0.0
Ak		37.1		16.7	11.1*	41.0*			
Gm		47.2	55.0*	44.4	19.4	5.0			
Km				27.8					
Nm			94.0	58.3					37.5
Tob				97.2					
Nit						91.3			
Fos						12	62.7		
Col							21.3		
Other									
MDR									
ESBL				0.0			38.4		
pAmpC				3.0					

Year: sampling year; Alp: Alpaca; C: Chicken; Ct: Cattle; Y: Year; Amp: Ampicillin; Amx: Amoxicillin; A/C: Amoxicillin plus clavulanic acid; Atm: Aztreonam; Kf: cefalotin; Ctx: cefotaxime; Cro: Ceftriaxona Fox: Cefoxitin; Caz: Ceftazidime; Fep: Cefepime; Mem: Oxt: Oxytetracycline; Dox: doxyciline; Tc: Tetracycline; Sxt: Cotrimoxazole; Sulfa: Sulfamethoxazole; Chl: Chloramphenicol; Flor: Florfenicol; S: Streptomycin; Azm: Azithromycin; Nal: Nalidixic acid; Cip: Ciprofloxacin; Enr: Enrofloxacin; Ak: Amikacin; Gm: Gentamicin; Km: Kanamycin; Nm: Neomycin; Tob: Tobramycin; Nit: Nitrofurantoin; Fos: Fosfomycin; Col: Colistin; MDR: Multidrug Resistance; ESBL: Extended-Spectrum β-Lactamases; pAmpC: Plasmid encoded AmpC. *Most of them being intermediate.

anthropogenic activities such as discharge of antimicrobial agents in the environment (either directly or through human/animal excretion), or contamination with fecal antibiotic-resistant microorganisms. In this sense, the problematic of industrial, agrarian and urban discharges in the Piura River has been highlighted [91].

Although only 3 studies focused on surfaces and devices, the *E. coli* from these studies presented overall higher levels of AMR, probably reflecting the specificities of the study settings, a hospital and a slaughterhouse. In hospital environments the use of antimicrobial agents is intense, resulting in direct antimicrobial pressure over microorganisms and the subsequent selection of AMR [92]. Indeed, isolation of MDR, extensively resistant (XDR) and even pan-drug resistant (PDR) microorganisms is frequent worldwide and is of special concern [17, 77, 93, 94, 95]. This finding is extrapolated to Peru, in which the levels of AMR among microorganisms causing infections are extremely high [30, 82, 96]. In this regard, the presence of highly resistant *E. coli*, including 66% of ESBL-producer *E. coli* in the personal devices of intensive care unit health care workers (i.e. mobile phones) highlights the ease with which a MDR microorganism may be transported within different hospital areas or outside hospitals [57].

Meanwhile, the high levels of resistance to antimicrobial agents such as ampicillin (80%), cephalothin (100%), nalidixic acid (75.7%) or tetracycline (40%), among others, detected in *E. coli* from a slaughterhouse environment, probably reflect environmental contamination by antimicrobial-resistant microorganisms colonizing sacrificed livestock. This finding is supported by the available literature about AMR levels of *E. coli* from both livestock and food-marketed meats (see sections 3 and 3.2 respectively). Curiously, while 31.5% of the isolates from slaughterhouse surfaces were ciprofloxacin intermediate, no ciprofloxacin-resistant was isolated. Nevertheless, 75.5% of isolates showed nalidixic

acid resistance (Table 4). Of note, the phenotype Nal^R, $Cip^{I/S}$ (or another fluoroquinolone) is usually related to the presence of a single mutation in *gyrA* [84, 97] and is associated with enhanced facility to drive to selection of additional target mutations and therapeutic failure when fluoroquinolones are used [97, 98, 99].

In general, the levels of resistance to amikacin and meropenem were low or null. The analysis of *E. coli* or other *Enterobacteriales* of clinical origin, also showed that amikacin retains good activity in Peru [26, 96]. Meanwhile, the presence of carbapenem-resistant clinical isolates of *E. coli* has been described but remains low [82, 100, 101]. Therefore, although only one of the studies analyzed reported susceptibility data of meropenem, the good activity of amikacin and meropenem against environmental *E. coli* seems to reflect the overall picture of resistance to these antimicrobial agents in Peru.

3.5. Livestock recovered Escherichia coli

Several studies were focused on a variety of livestock, with data about chicken in 3 studies, and of pigs, cattle and alpacas in 2 studies each; thus, 9 studies were considered in the analysis [44, 52, 54, 62, 63, 64, 66, 67, 68]. Of these, only 3 were total or partially developed using samples from Lima (Table 1, Figure 1). Another study was not included due to bacterial selection bias [65].

While a high variety of tested antibiotics was observed (total of 30 antimicrobial agents tested), none was included in all studies, with only members of the quinolone family being tested in all studies, highlighting the relevance of these agents in veterinary medicine during the last decade in Peru.

Resistance to the antibiotics tested was common and high in all studies except in the oldest isolates recovered from chicken prior to 2009, showing the highest resistance to ampicillin and sulfamethoxazole with 12.5% and 12.8%, respectively [52] (Table 5).

Interestingly, as mentioned above, Kalter *et al.* also analyzed marketed chicken meat, detecting substantially higher levels of resistance to these agents (see section 3.2), suggesting differences in antibiotic use between household and industrially raised chicken [52]. The other 2 studies in industrially raised chicken [66, 67] collected in 2016 and 2017–2018, respectively, showed dissimilar results. The study by Vilchez-Chiara showed high resistance levels to tetracyclines (oxytetracycline and doxycycline) but full susceptibility to amoxicillin, enrofloxacin and cotrimoxazole [67], while Ceino-Gordillo *et al.* described overall high levels of resistance to all the antibacterial agents tested, reaching 95% and 90.2% in the cases of oxytetracycline and amoxicillin plus clavulanic acid [66]. The only difference between the two studies was the geographic origin of the samples.

While only reported in one out of 9 studies [66], 23.1% of resistance to colistin is worrisome. Colistin is considered as a last resort antibacterial agent in hospital settings, being used when no other alternative is available [102]. Although colistin is currently forbidden for veterinary applications in a growing number of countries, it has been used in veterinary settings for years [103, 104]. In Peru, veterinary uses of colistin were forbidden in December 2019 [85], after the *E. coli* collection of Ceino-Gordillo *et al.* [66]. This finding might explain Ceino-Gordillo *et al.* data, but the analysis of isolates collected from 2020 onwards is of special relevance to determine the stability or reversion of these resistance levels. There are no data about molecular mechanisms underlying resistance to colistin in these isolates, which if mediated through *mcr* genes is at risk of being horizontally disseminated to pathogenic microorganisms [105].

Of note were the high levels of resistance to quinolones detected in 6 out of 9 studies. In several cases resistance to nalidixic acid was higher than 78% and up to 94% [63] Although the emergence of transferable mechanisms of quinolone resistance has slightly altered the scenario [8], these resistance levels are mostly related to the presence of mutations in quinolone targets [84, 97, 106], which might not imply the surpassing of fluoroquinolone resistance breakpoints, but have been associated with enhanced levels of therapeutic failures during fluoroquinolone treatments [99]. Of note, in other microorganisms, such as *Campylobacter* spp., isolation of quinolone-resistant isolates in clinical settings was parallel to the increasing levels of quinolone resistance among poultry isolates following the introduction of enrofloxacin in veterinary medicine [22].

Five reports showed >30% of aminoglycoside intermediate or resistant isolates. The presence of intermediate isolates either to aminoglycosides or other antibacterial agents was frequent among *E. coli* recovered from livestock samples, especially in the 2 studies using *E. coli* recovered from Alpacas. Thus, Luna *et al.* reported ~70%, ~70%, ~65%, ~55% and ~40% of intermediate isolates to oxytetracycline, streptomycin, ampicillin, chloramphenicol and gentamicin, respectively, and Barrios-Arpi *et al.* reported 50%, 29%, 28%, 26% and 22% of intermediate levels of resistance to enrofloxacin, amikacin, oxytetracycline, ceftriaxone and ciprofloxacin, respectively [44, 64]. The high number of isolates exhibiting intermediate resistance levels to a series of unrelated antibiotics might be related to the presence of subinhibitory antibiotic

Table 6. Percentage of antimicrobial resistance in *Escherichia coli* from pets.

	Articles				
	4	24	25	26	27
Sample	V	Dog	Dog	Dog	Dog
No	526	12	14[b]	45[c]	100
Year	<2009	?	2003–2012	2012–2017	2016–2017
Antimicrobial Resistance (%)					
Amp	13.5	91.7			53
Amx		75.0			
Pen		100.0			
A/C		25.0	46.0	52.6	
Kf		91.7			
Cfx		91.7	50.0		47.0
Fox		41.7[d]			
Cro	0.9	33.3[d]		45.2	
Imp		8.3[d]			
Oxt		75.0		75.0	
Dox		58.3		70.6	
Tc					33.0
Sxt	9.1	25.0[d]	75.0	63.4	41.0
Chl		33.3[d]		78.6	
S					61.0
Nal				91.7	
Cip	1.7	33.3	60.0	51.3	
Enr		41.7	46.0	77.5	10.0
Ak			0.0	20.6	
Gm		25.0	33.0	63.6	40.0
Tob			29.0		
Nit				70.0	

V: various; Year: sampling year; Amp: Ampicillin; Amx: Amoxicillin; Pen: Penicillin; A/C: Amoxicillin plus clavulanic acid; Atm: Aztreonam; Kf: cefalotin; Cfx: cefalexin; Fox: Cefoxitin; Cro: Ceftriaxone; Imp: Imipenem; Oxt: Oxytetracycline; Dox: Doxycycline; Tc: Tetracycline; Sxt: Cotrimoxazole; Chl: Chloramphenicol; S: Streptomycin; Nal: Nalidixic acid; Cip: Ciprofloxacin; Enr: Enrofloxacin; Ak: Amikacin; Gm: Gentamicin; Tob: Tobramycin; Nit: Nitrofurantoin. a The sampling included: 224 dogs, 95 cats, 77 guinea pigs, 72 pigs, 64 ducks, 34 cows, 30 rabbits, 27 sheep, 23 turkeys, 15 donkeys, 12 doves, 12 goats, 8 horses, 8 canaries/parrots, 2 geese, 2 monkeys, 1 quail, 1 squirrel, 1 unknown. Note that in Peru guinea pig is considered a food-producing animal, not a pet. Data were classified in the pet category because of the high percentage of dogs (31.7%) and cats (13.4%). In the article, data of resistance were not disaggregated by species [52]. b The number of isolates analyzed for each antimicrobial differed, varying from 6 isolates in the case of gentamicin to 13 for amoxicillin plus clavulanic acid and enrofloxacin. c The number of isolates analyzed for each antimicrobial differed, varying from 12 isolates in the case of nalidixic acid and oxytetracycline to 40 for enrofloxacin. d All intermediate.

Table 7. Percentage of antimicrobial resistance in *Escherichia coli* from wild animals.

	Articles		
	28	29	30
Sample	NC	SC	M
No	17	7	45
Year	2014	2014	?
Antimicrobial Resistance			
Amp		28.6	
A/C			26.7
SAM			8.0
Atm		28.6	
Kf			62.2
Cxm	46.7		
Fox		0.0	
Oxa	53.3		
Cro	40.0		6.6
Tc	60.0		46.7
Sxt	20.0[a]		15.5
Chl		100.0	28.9
S	6.7[a]		
Nal	60.0	14.3	
Cip	6.7[a]	0.0	
Enr	13.3[a]		28.9
Ak			20.0
Gm	6.7	0.0	
Nm	46.7		
Tob			40.0
Nit	26.7		

Year: sampling year; *Callicebus* spp., and *Lagothrix* spp.); Amp: Ampicillin; A/C: Amoxicillin plus clavulanic acid; Atm: Aztreonam; Kf: cefalotin; Cxm: Cefuroxime; Fox: Cefoxitin; Oxa: Oxacillin; Cro: Ceftriaxone; Tc: Tetracycline; Sxt: Cotrimoxazole; Chl: Chloramphenicol; S: Streptomycin; Nal: Nalidixic acid; Cip: Ciprofloxacin; Enr: Enrofloxacin; Ak: Amikacin; Gm: Gentamicin; Nm: Neomycin; Tob: Tobramycin; Nit: Nitrofurantoin. a Mostly intermediate.

concentrations favoring the selection of non-specific low-level resistance mechanisms, such as overexpression of efflux pumps or other adaptative responses, or to external factors, such as the presence of environmental contaminants (e.g: heavy metals, chemicals, solvents), which might favor similar scenarios [107, 108, 109]. In this sense, a study analyzing the mechanisms of rifaximin resistance in 74 commensal and 136 diarrheogenic isolates from a periurban area of Lima showed an unusual scenario, with 100% of the isolates having a minimal inhibitory concentration (MIC) ≥32 mg/L [75], when studies on *E. coli* with a very diverse geographical origin only showed the presence of a few *E. coli* isolates presenting a maximum MIC of ≥32 mg/L [40, 110, 111, 112]. This atypical resistance pattern was related to the presence of overexpressed efflux pumps in 95.2% of the isolates, with only 9 out of 200 (4.5%) isolates having MICs ≥32 mg/L after the use of an efflux pump inhibitor [75]. Of note, the presence of heavy metals such as arsenic, chrome, cadmium, lead, mercury or zinc, and other toxics such as polycyclic aromatic hydrocarbon has been widely described in different Peruvian areas [113, 114, 115, 116].

The presence of ESBLs was reported in 3 studies [62, 65, 66], which were not considered in the analysis of AMR because the samples were directly screened for ESBL-producing *Enterobacteriaceae*. These studies showed the presence of ESBLs in samples from chickens, cows and pigs, reporting the presence of $bla_{\text{CTX-M-14}}$, $bla_{\text{CTX-M-15}}$ and $bla_{\text{CTX-M-26}}$ [62,65,66].

3.6. Pet-isolated Escherichia coli

Five studies reported data about AMR in *E. coli* recovered from pets. Of this, four were focused on dogs [43, 69, 70, 71], while the remaining study considered a diversity of animals, including pets such as dogs, and also ducks and guinea pigs, which are consumed, or others including donkeys used in the agrarian setting [52]. Three of these studies were developed in Lima [43, 69, 70], one in Cajamarca (Northern Peru) [71], and the remaining study tested samples from 4 Peruvian regions, including Lima [52]. As with *E. coli* of other origins, the number and type of antibiotics tested varied among the different studies, with AMR data of a total of 22 different antibacterial agents (Table 6).

Four of the studies reported high levels of AMR [43, 69, 70, 71], with the remaining study of samples collected prior to 2009, described 13.5% of resistance to ampicillin as the highest value [52]. Intermediate isolates were especially frequent in the study by Vega *et al* [69], with no specific reason to explain this difference, other than the above-commented possible misuse of antibacterial agents or higher exposure to environmental pollution. In this regard is of note that Vega *et al.* reported *E. coli* isolates recovered from dog samples collected in shelters (therefore not living in a household as a personal pet) in periurban areas of Lima [69], including areas with deficient access to drinking water (https://www.inei.gob.pe/media/MenuRecursivo/publicaciones_digitales/Est/Lib1411/cap01_01.pdf).

Neither susceptibility to ceftazidime, cefotaxime or cefepime, nor data about ESBLs or pAmpC was available. Nevertheless, 2 of the studies described levels of intermediate or resistance of 33.3% and 45.2% to cefotaxime [69, 70], suggesting the presence of these enzymes.

Excluding the article of Kalter *et al.* [52], in general, the levels of resistance detected ranged from 25% to 91.7%. Thus, as described in *E. coli* from other sources, resistance to quinolones was high, with a maximum of 91.7% of nalidixic acid resistance reported by García *et al* [70]. Along the same line, levels of resistance of up to 75% to tetracyclines (oxytetracycline) or between 50% and 100% for ancient penicillins and first-generation cephalosporins were reported. The most noticeable exception was the presence of 0% of resistance to amikacin observed by Lujan-Roca *et al.* [43], and 8.3% of non-susceptibility to imipenem (all isolates were intermediate) described by Vega *et al* [69]. These data agree with those related to environmental *E. coli.*

3.7. Escherichia coli recovered from wild Animals

Only 3 studies, one in Lima and the other two in the jungle area of Peru, reported data of susceptibility to antimicrobial agents in *E. coli* from wild animals [72, 73, 74] (Table 7).

Of note, while classified as "wild", only one study involved free-ranging animals (*Caiman cocodrilus*) [73], while another 2 studies analyzed samples from animals living in captivity or semi-captivity [72, 74]. Another study, including bats (*Desmodus rotundus*) was not considered because of the presence of selective bias [65].

In a few cases, AMR levels >60% were detected, with nalidixic acid and tetracycline reaching this level in samples collected from Northern Caimans living in semi-captivity in San Juan del Lurigancho [72]. In addition, as in other cases, resistance levels to antimicrobial agents such as ancient β-lactam agents or several aminoglycosides were also high. Of note the study by Castañón also detected a high number of intermediate isolates, in agreement with the results of Vega *et al.* in shelter dogs in the same area [69], supporting the presence of local specificity favoring the natural selection of *E. coli* presenting low levels of AMR.

Despite the differences inherent to sampling species, the limited number of studies, and the difficulty in comparing studies using different antimicrobial agents, overall, the results suggest higher levels of resistance in animals living in captivity than in those in free-ranging conditions. The most notorious exception was chloramphenicol, with 100% of resistance in free-ranging *C. cocodrilus*, and no clear reason for this finding [73].

None of the 3 studies analyzed the presence of ESBLs or other specific AMR determinants. Nevertheless, in a study using selective media for the detection of ESBL-carrying *E. coli,* Benavides *et al.* [65], detected the presence of $bla_{\text{CTX-M-15}}$ in *E. coli* recovered from fecal swabs from bats,

AF[a]	Livestock N[b] = 763	Environmental N[b] = 464	Food N[b] = 509	Human N[b]= 1034	Pets N[b] = 697	Wild Animals N[b] = 69
AMG	5.0 - 97.2	0.0 - 47.1	14.9 - 22.7	3.4	0.0 - 63.6	0.0 - 46.7
AMG (S)	88.6 - 94.4	71.5	91.5	N.D.	61.0	6.7
CBP	N.D.	0.0	N.D.	4.0	8.3	N.D.
nesCph	97.2 - 100	75.0 - 100.0	98.7	7.7	47.0 - 91.7	46.7 - 62.2
ESC	0.8 - 47.2	10 - 36.1	0.8 - 59.4 [c]	0 - 5.6	0.9 - 45.2	6.6 - 40.0
CPH	25.0	3.2 - 10	N.D.	2.8	41.7	0.0 - 53.3
Q [d]	78.5 - 94.4	5.4 - 75.7	38.3 - 94.6	38.7 - 43.0	91.7	14.3 - 60.0
FQ	0.0 - 83.4	0.0 - 61.8	19.5 - 96.4	1.5 - 13.1	1.7 - 77.5	0.0 - 28.9
FPI	0.0 - 87.5	12.7 - 44.1	1.2 - 100.0	21.3 - 62.5	9.1 - 75.0	15.5 - 20.0
MB	38.9	1.8 - 25.8	N.D.	N.D	N.D.	28.6
PEN	0.0 - 100	12.7 - 80.0	44.0 - 95.4	37.2 - 76.8	13.5 - 100.0	28.6
PEN+I	69.4 - 90.2	0.0 - 9.4	4.5 - 41.1	15.1	25.0 - 52.6	8.0 - 26.7
PHE	7.1 - 70.0	1.8 -25.7	8 - 83.9	22.0	33.3 - 78.6	28.9 - 100
POL	21.3	N.D.	N.D.	N.D.	N.D.	N.D.
PHO	12 - 62.7	N.D.	N.D.	N.D.	N.D.	N.D.
TET	36 - 100	12.7 - 40.4	20.1 - 94.6	56.5	33.0 - 75.0	46.7 - 60.0
NIT	91.3	5.1	4 - 35.7	2.3	70.0	26.7
RF	N.D.	N.D.	N.D.	93.2	N.D.	N.D.
MCR	N.D.	6.8	0 - 39.3	15.6 - 27.4	N.D.	N.D.

0-1%	>1%-10%	>10-30	>30-50	>50-70	>70-90	>90

Figure 2. Overall data of antimicrobial resistance in *Escherichia coli* (2009–2019). AF: Antimicrobial agents' families; N: Number; AMG: Aminoglycosides (amikacin. gentamicin, kanamycin neomycin, tobramycin) excepting streptomycin; AMG (S): Aminoglycosides (only streptomycin); CBP: Carbapenems (ertapenem, imipenem, meropenem); nesCph: non extended-spectrum cephalosporins (cefazolin, cefalotin; cefalexin; cefuroxime); ESC: Extended-spectrum cephalosporins (ceftazidime, cefotaxime, cefepime, ceftriaxone); CPH: Cefamicins (cefoxitin, oxacillin); Q/FQ: Quinolones (nalidixic acid) and Fluoroquinolones (ciprofloxacin, norfloxacin, enrofloxacin); FPI: Folate pathway inhibitors (cotrimoxazole, sulfamethoxazole); MB: Monobactams (aztreonam); PEN: Penicillins (ampicillin, amoxicillin); PEN + I: Penicillins plus inhibitors of β-Lactamases (amoxicillin plus clavulanic acid, sulperazone); PHE: Phenicols (chloramphenicol, florfenicol); POL: Polymyxins (colistin); PHO: Phosphonic acids (fosfomycin); TET: Tetracyclines (tetracycline, doxycycline, oxytetracycline); NIT: Nitrofurans (furazolidone; nitrofurantoin); RF: Rifamycins (rifaximin); MCR: Macrolides (azithromycin); N.D.: No data. The numbers represent the minimum and the maximum percentage of resistance to any of the tested antibacterial agents belonging to each family. The mean values of resistance are represented by colors; to establish this value the maximum mean value of any of the antimicrobial agents belonging to a specific family was considered. Note that these approaches result in a sub estimation of the real levels of resistance to antibacterial agent families. [a] Following the classification of Magiorakos *et al* [119]. Families not considered by Magiorakos *et al.* were reported following standard schemes. [b] Overall number of isolates included in each group. Note that not all isolates were tested for all antimicrobial agents. [c] Maximum value inferred from prevalence of ESBL reported by Ruiz-Roldán *et al.* [47]. [d] Resistance to quinolones is a risk factor for the development of resistance and therapeutic failure when using fluoroquinolones [97].

showing that the spread of ESBLs in Peru has extended to free-ranging animals.

3.8. Limitations

Among the limitations of the present analysis two are of special relevance: the lack of uniformity and the outdating of most of the samples analyzed. Thus, the lack of uniformity in reporting data inherent to the different origins of the studies makes data comparison difficult. In addition, several reports included isolates obtained more than 20 years ago and were, thus, outdated with respect to the inferred current situation. The later finding highlights the scarcity of recent data in Peru, being especially notable among human commensal *E. coli,* and the need to perform new AMR surveillances to provide at least of a partial vision of the current AMR panorama. These data are of special relevance in the current scenario of the COVID-19 pandemic, in which the use of antimicrobial agents has incremented worldwide in both hospital and community settings, especially in countries with over-the-counter access to antimicrobial agents, such as Peru, leading to higher selective pressure towards increasing AMR levels [21, 117, 118].

4. Conclusion

The levels of AMR reported in Peru between 2009 and 2019 are of concern, especially regarding ancient antibacterial agents such as streptomycin, 1st and 2nd generation cephalosporins, tetracyclines or first-generation quinolones (Figure 2).

The high levels of AMR and the detection of relevant resistance levels to other agents such as 3rd and 4th generation cephalosporins or fluoroquinolones, as well as the detected resistance to polymyxins (although only data from livestock samples were available) suggests the need to implement effective controls regarding access to antibacterial agents as well as the development of educational campaigns to increase population awareness of the relevance of prudent use of antibacterial agents and the risks derived from an abusive use.

The unusual number of *E. coli* isolates presenting intermediate levels of resistance to a series of unrelated agents strongly suggests the presence of an atypical scenario in which factors such as heavy metals or chemical pollutants might play a role in the constitutive overexpression of efflux pumps.

Finally, the data available were scarce, partially outdated and, in several cases, difficult to access, alerting to the need to perform new and extensive surveillance to dispose of a real current scenario leading to more efficient use of antibacterial agents.

Declarations

Author contribution statement

All authors listed have significantly contributed to the development and the writing of this article.

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Data included in article/supplementary material/referenced in article.

Declaration of interest's statement

The authors declare no conflict of interest.

Additional information

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