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► **To cite this version:**

Marwan Osman, Hiba Al Mir, Rayane Rafei, Fouad Dabboussi, Jean-Yves Madec, et al.. Epidemiology of antimicrobial resistance in Lebanese extra-hospital settings: An overview. *Journal of Global Antimicrobial Resistance*, 2019, 17, pp.123-129. 10.1016/j.jgar.2018.11.019 . anses-04013185

**HAL Id: anses-04013185**

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Submitted on 3 Mar 2023

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## Review

## Epidemiology of antimicrobial resistance in Lebanese extra-hospital settings: An overview



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## ARTICLE INFO

## Article history:

Received 20 September 2018  
Received in revised form 7 November 2018  
Accepted 26 November 2018  
Available online 12 December 2018

## Keywords:

Antimicrobial resistance  
Epidemiology  
Environment  
Carbapenemase  
ESBL  
Lebanon

## ABSTRACT

Antibiotics can truly be considered the symbol of the 20th century's miracle drugs. However, excessive and inappropriate use of antibiotics in human and veterinary medicine has led to repercussions in terms of mortality, morbidity, and financial and societal costs, especially with the lack of novel drugs to combat infections caused by antimicrobial-resistant pathogens. Unfortunately, antimicrobial resistance (AMR) has increased significantly worldwide in the past decades, particularly in developing third-world countries. Hence, various key organisations have made AMR the focus of highly visible reports, conferences and actions. Nevertheless, the majority of investigations were initiated in the developed world. In Lebanon, as in other developing countries, AMR remains responsible for significant morbidity and mortality. Whilst a large number of studies have targeted the AMR crisis in Lebanese clinical settings, its epidemiological situation in animals, foodstuffs and the environment is still unclear in this country. In this context, and in order to better survey, control and prevent the emergence of multidrug-resistant bacterial strains in Lebanese non-clinical settings, this work reviewed the available data on the epidemiology of antimicrobial-resistant bacteria isolated from Lebanese extra-hospital sources.

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## 1. Introduction

With the advent of the 90th anniversary of the discovery of penicillin, antimicrobial resistance (AMR) has become a major public-health issue of global concern and has emerged as one of the principal international healthcare crises of the 21st century [1]. In 2013, the US Centers for Disease Control and Prevention (CDC)

announced that the human race is now in the post-antibiotic era. The World Health Organization (WHO) global AMR surveillance report published in 2014 also warned that the AMR crisis is dire [1,2]. Recently, a high profile report warned that 700 000 annual deaths globally attributed to AMR in 2015 could climb to 10 million deaths in 2050 if nothing is done to reverse the trend [3]. Besides these serious issues, AMR has a negative economic impact on communities, leading to huge annual costs almost similar to those of the global financial crisis [4]. A recent study estimated the GDP loss due to AMR in the Middle East and North Africa (MENA) region, including Lebanon, to range between US\$2 billion and US\$159

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billion per year over 40 years [4]. Unfortunately, Lebanon, like the majority of developing countries, still suffers from high levels of AMR. In this context, and in order to better understand the epidemiology and transmission of AMR in Lebanon, the aim of the present review was to summarise recent findings on the epidemiology of antimicrobial-resistant Gram-negative bacteria isolated from the environment and from animals, mainly swine, cattle and poultry, in Lebanon, a small country in the MENA region sheltering a huge number of refugees and facing large social, health, economic, political and security challenges.

## 2. Desperate situation regarding antibiotics in Lebanon

Despite the implementation of consistent strategies and measures to prevent and control the emergence and spread of AMR in developed countries, this issue continues to grow in a large number of these countries [5]. However, the AMR issue is more complicated in developing countries, such as Lebanon, since numerous factors leading to the emergence and spread of multidrug-resistant (MDR) strains remain uncontrollable. The increasing availability of antibiotics in Lebanon is generally a good thing, however the misuse of these 'wonder drugs' has created and promoted the transmission of antimicrobial-resistant strains of deadly bacteria, particularly in poorer communities such as Syrian and Palestinian refugees and the vulnerable Lebanese population [2]. Besides the availability of antibiotics without prescription in pharmacies, various factors including (i) poor antibiotic awareness both among prescribers and the general public, (ii) extensive antibiotic use in humans, animals and agriculture, (iii) excessive use of antibiotics as growth-promoting factors in livestock, (iv) non-compliance with antibiotic therapy, (v) promotion of antibiotic self-medication, (vi) poor antibiotic stewardship and (vii) inadequate infection control are key drivers of AMR in Lebanon. Moreover, the availability of antibiotics for purchase on websites increases the circulation of counterfeit drugs and decreases the quality of care in the country [6]. Therefore, despite the outstanding progress to develop a national plan of action to combat the spread of AMR in Lebanon, AMR rates are at the higher end of levels reported globally [7]. Several cross-sectional studies showed a high prevalence of inappropriate antibiotic prescription in Lebanon, regardless of doctors' specialty [8,9]. Similarly, large amounts of antibiotics are used in the veterinary, livestock and agriculture fields without surveillance and control, causing a rapid increase in the prevalence of AMR and the use of last-resort antibiotic compounds both in clinical and veterinary fields in Lebanon. On the other hand, a cross-sectional nationwide study conducted last year, in synchronisation with the first Lebanese antibiotic awareness campaign, revealed very insufficient knowledge, poor attitudes and inadequate practices towards antibiotics among the resident populations in Lebanon [10].

## 3. Consequences of antibiotic misuse

It is well known that antibiotic use contributes to the selection of resistance by posing selective pressure on antimicrobial resistance genes (ARGs) and bacterial community composition in different environments. Humans and animals discharge in their faeces and urine a large proportion of the administered antibiotic either unchanged or as active metabolites, contaminating external environments. The presence of antibiotics, even at low concentrations, in environments and in treated animals and humans could allow for enrichment and selection of bacteria carrying multidrug resistance plasmids and thereby may contribute to the emergence, maintenance, multiplication and spread of antimicrobial-resistant bacterial pathogens of clinical importance [11,12]. Many studies have found a strong association between

administration of antibiotics in animals and the corresponding rate of resistance towards these antibiotics in bacterial strains isolated from cattle, poultry and pigs [13,14]. On the other hand, humans and animals may also be contaminated with antibiotics indirectly through food and water containing active antibiotic residues. Moreover, a population-based study found a strong association between virulence and AMR in bacterial communities [15]. Remarkably, a recent retrospective clinical study found that low antibiotic concentrations were detected in the urine of patients who had not consumed antibiotics that were capable of selecting antibiotic-resistant *Staphylococcus* species [16].

The exceptional spread of MDR and extensively drug-resistant (XDR) bacteria is highly worrisome as it could lead to serious infections leaving patients and animals with very limited or no therapeutic options [17]. Moreover, ARGs are often located on mobile genetic elements (MGEs), which can be easily transmitted between different hosts including humans, animals and the environment. Indeed, genetic similarities of such ARGs, MGEs and/or clones that are detected in humans, animals and the environment have repeatedly been reported worldwide [18,19]. Genes encoding extended-spectrum  $\beta$ -lactamases (ESBLs), carbapenemases and aminoglycoside-modifying enzymes as well as plasmid-mediated quinolone resistance genes are often located on MGEs, which can be transmitted both within and between different bacterial species and hosts. Unfortunately, all of these antimicrobial-resistant bacteria and genes are now widely disseminated among humans, animals and the environment, and their presence in animals and foodstuffs has also been regularly reported in Lebanon [20–25].

## 4. Epidemiology of antimicrobial resistance in non-clinical settings in Lebanon

Antibiotic misuse in humans is a fundamental issue favouring the emergence, multiplication and spread of resistant strains [12]. Although AMR is generally associated with uncontrolled use of antibiotics in human medicine, antibiotic abuse in the veterinary and agriculture sectors is also reported as a main driver for the rapid evolution of bacterial AMR [25,26]. Animals, food and the environment are generally considered a reservoir of MDR and XDR bacteria, particularly Enterobacteriaceae [24,27]. Nevertheless, the impact of animal reservoirs of AMR on human health has yet to be proven and remains debatable. New research studies suggest that sharing the same ARGs, MGEs and clones constitutes potential evidence of transmission of antimicrobial-resistant bacteria from animals to humans [28]. Bacterial strains carried by animals can be easily transferred to humans through direct contact or by handling or consumption of animal products [29]. Hence the importance of the implementation of a One Health approach to face the current public-health challenges, including the emerging AMR threat, and to provide a strategy to improve the lives of all species. Fortunately, surveillance of AMR in Lebanon has improved during the last years. Moreover, Lebanon has been enrolled in the WHO's Global Antimicrobial Resistance Surveillance System (GLASS) since April 2017. In this context, numerous epidemiological studies were conducted in the last decade in Lebanon that highlighted the worrying situation of AMR in the country and described high rates of methicillin-resistant *Staphylococcus aureus* (MRSA) and differentially resistant Gram-negative bacteria [7,30,31]. One nationwide study performed at 16 Lebanese tertiary-care centres between 2011–2013 reported a rise in the prevalence of common MDR pathogens including MRSA, vancomycin-resistant enterococci, ESBL-producing *Escherichia coli*, and carbapenem-resistant *Acinetobacter* and *Pseudomonas* spp. [7]. Another study performed at El Youssef Hospital Center in North Lebanon between 2015–2017 reported

**Table 1**  
Epidemiology of antimicrobial resistance in non-clinical settings in Lebanon.

Investigation site	Targeted population	Type of sample	Year(s) of survey	No. of isolates		Presence of colistin resistance	Antibiotic resistance (%) among ESBL-producing and/or carbapenem-resistant strains							β-Lactam resistance genes (n)	Reference	
				ESBL-producing	Carbapenem-resistant		TET	NAL	ENR/CIP	TMP	SXT	GEN	STR			CHL
North and South Lebanon (search for MDR bacteria)	Healthy adult cattle	Stool	October 2012–February 2013	<i>Escherichia coli</i> (n=40)	0	No	83	30	18	75	– <sup>a</sup>	23	78	30	<i>bla</i> <sub>CTX-M-15</sub> (24) <i>bla</i> <sub>SHV-12</sub> (10) <i>bla</i> <sub>CTX-M-14</sub> (2) <i>bla</i> <sub>CTX-M-15</sub> + <i>bla</i> <sub>SHV-12</sub> (3) <i>bla</i> <sub>CTX-M-14</sub> + <i>bla</i> <sub>SHV-12</sub> (1)	[24]
South Lebanon (search for MDR bacteria)	Swine	Stool	May 2017	<i>E. coli</i> (n=105) <i>Klebsiella pneumoniae</i> (n=2) <i>Escherichia fergusonii</i> (n=4)	0	<i>mcr-1</i> (n=23)	–	–	78	–	89	42	–	–	[ <i>bla</i> <sub>CTX-M</sub> (83) <i>bla</i> <sub>TEM</sub> (57) <i>bla</i> <sub>SHV</sub> (9) <i>bla</i> <sub>CMY</sub> (13) alone or in combination]	[26]
North Lebanon	Animals (pigs, fowl and cattle)	Stool	2013	–	<i>Acinetobacter baumannii</i> (n=5) <i>Pseudomonas aeruginosa</i> (n=4) <i>E. coli</i> (n=1)	No	–	100	100	–	–	100	–	–	<i>bla</i> <sub>OXA-23</sub> (4) <i>bla</i> <sub>VIM-2</sub> (4) <i>bla</i> <sub>OXA-23</sub> + <i>bla</i> <sub>OXA-58</sub> (1)	[45]
Case report	Poultry (fowl)	Stool	December 2013	–	<i>E. coli</i> (n=1)	No	–	–	–	100	–	100	–	–	<i>bla</i> <sub>OXA-48</sub> + <i>bla</i> <sub>CTX-M-14</sub> + <i>bla</i> <sub>TEM-1</sub> (1)	[27]
Case report (Sidon)	Poultry	Rectal swab	14 August 2015	<i>E. coli</i> (n=1)	0	<i>mcr-1</i> (n=1)	–	–	100	100	100	100	–	–	<i>bla</i> <sub>TEM-135-like</sub> (1)	[52]
Nationwide	Poultry	Rectal swabs	August–December 2015	<i>E. coli</i> (n=103) <i>K. pneumoniae</i> (n=5) <i>Enterobacter cloacae</i> (n=3) <i>E. fergusonii</i> (n=1)	0	No	–	–	62	–	68	71	–	–	<i>bla</i> <sub>CTX-M</sub> (2) <i>bla</i> <sub>TEM</sub> (36) <i>bla</i> <sub>SHV</sub> (17) <i>bla</i> <sub>CTX-M</sub> + <i>bla</i> <sub>TEM</sub> (52) <i>bla</i> <sub>CTX-M</sub> + <i>bla</i> <sub>TEM</sub> + <i>bla</i> <sub>SHV</sub> (5) [ <i>bla</i> <sub>CMY</sub> (152), alone or in combination with other genes]	[25]
Nationwide	Poultry	Faecal samples	September 2017–March 2018	–	–	<i>mcr-1</i> (n=88)	89	–	91	–	84	61	80	95	<i>bla</i> <sub>TEM-1</sub> (84) <i>bla</i> <sub>CTX-M</sub> (31)	[53]
Beqaa Valley	Agri-food environment	Vegetables; knife & board swabs; fresh produce; water	July–August 2013 and July 2014	– (100% of isolates were resistant to cefalotin)	–	No	–	–	–	–	–	–	–	–	–	[34]
North Lebanon	Food	Akkawi cheese	May–June 2011	<i>E. coli</i> (n=3) <i>K. pneumoniae</i> (n=2) <i>Rhanella aquatilis</i> (n=1)	0	No	17	17	17	–	33	50	–	–	–	[35]
North Lebanon	Food	Raw bovine milk	September–November 2015	<i>E. coli</i> (n=7) <i>K. pneumoniae</i> (n=36)	<i>K. pneumoniae</i> (n=1)	No	–	–	–	–	–	–	–	–	<i>bla</i> <sub>CTX-M-15</sub> (38) <i>bla</i> <sub>CTX-M-15</sub> + <i>bla</i> <sub>SHV-12</sub> (4) <i>bla</i> <sub>CTX-M-15</sub> + <i>bla</i> <sub>OXA-48</sub> (1)	[22]
North Lebanon (Tripoli)	Food	Raw meat	April–May 2010	<i>E. coli</i> (n=2)	0	No	100	–	50	–	–	0	–	–	–	[36]
Nationwide	Water	Sewage water	Spring 2016	<i>E. coli</i> (n=21)	0	No	71	–	81	–	81	43	–	–	<i>bla</i> <sub>CTX-M-15</sub> (2) <i>bla</i> <sub>CTX-M-9</sub> (1) <i>bla</i> <sub>CTX-M-15</sub> + <i>bla</i> <sub>OXA-1</sub> (3) <i>bla</i> <sub>CTX-M-15</sub> + <i>bla</i> <sub>OXA-1</sub> + <i>bla</i> <sub>SHV-12</sub> (3) <i>bla</i> <sub>CTX-M-15</sub> + <i>bla</i> <sub>OXA-1</sub> + <i>bla</i> <sub>TEM-1</sub> (1)	[39]

Table 1 (Continued)

Investigation site	Targeted population	Type of sample	Year(s) of survey	No. of isolates		Presence of colistin resistance	Antibiotic resistance (%) among ESBL-producing and/or carbapenem-resistant strains							β-Lactam resistance genes (n)	Reference	
				ESBL-producing	Carbapenem-resistant		TET	NAL	ENR/ CIP	TMP	SXT	GEN	STR			CHL
North and South Lebanon (search for MDR bacteria)	Water	Dug wells; spring water; estuaries	March 2014–January 2015	<i>E. coli</i> (n = 23) <i>K. pneumoniae</i> (n = 4) <i>Citrobacter freundii</i> (n = 1) <i>Citrobacter braakii</i> (n = 1)	<i>E. coli</i> (n = 3) <i>K. pneumoniae</i> (n = 1)	No	67	58	48	58	–	33	42	15	<i>bla</i> <sub>CTX-M-15</sub> + <i>bla</i> <sub>TEM-1</sub> (2) <i>bla</i> <sub>CTX-M-15</sub> + <i>bla</i> <sub>TEM-1</sub> + <i>bla</i> <sub>SHV-12</sub> (1) <i>bla</i> <sub>SHV-12</sub> + <i>bla</i> <sub>OXA-1</sub> (1) <i>bla</i> <sub>CTX-M-27</sub> + <i>bla</i> <sub>TEM-1</sub> (1) <i>bla</i> <sub>CTX-M-14</sub> + <i>bla</i> <sub>OXA-1</sub> (1) <i>bla</i> <sub>CTX-M-15</sub> (24) <i>bla</i> <sub>CTX-M-14</sub> (1) <i>bla</i> <sub>CTX-M-55</sub> (1) <i>bla</i> <sub>SHV-12</sub> (1) <i>bla</i> <sub>OXA-48</sub> (1) <i>bla</i> <sub>OXA-244</sub> (1) <i>bla</i> <sub>OXA-48</sub> + <i>bla</i> <sub>CTX-M-14</sub> (1) <i>bla</i> <sub>OXA-244</sub> + <i>bla</i> <sub>CTX-M-14</sub> + <i>bla</i> <sub>SHV-12</sub> (1) <i>bla</i> <sub>CTX-M-15</sub> + <i>bla</i> <sub>CMY-42</sub> (2)	[23]
Beirut and North Lebanon	Water	Hospital wastewater	August 2011–June 2012	<i>E. coli</i> (n = 45) <i>K. pneumoniae</i> (n = 6)	<i>E. cloacae</i> (n = 2)	No	–	–	–	–	53	41	–	–	[ <i>bla</i> <sub>NDM-1</sub> (2) <i>bla</i> <sub>CTX-M</sub> (45) <i>bla</i> <sub>TEM</sub> (19) <i>bla</i> <sub>SHV</sub> (23) <i>bla</i> <sub>OXA</sub> (29), alone or in combination]	[49]
Akkar District	Water	Dug wells	April–May 2010	<i>E. coli</i> (n = 3) <i>C. freundii</i> (n = 1)	0	No	75	75	50	–	–	67	–	–	–	[37]
Nationwide (search for <i>Acinetobacter</i> spp.)	Agri-food environment	Soil; water; vegetables; seawater fish; cow's milk; animals	September 2014–February 2015	0	<i>Acinetobacter calcoaceticus</i> (n = 2)	No	–	–	0	–	–	–	–	–	<i>bla</i> <sub>OXA-72</sub> (2)	[38,47]
Nationwide (search for <i>Acinetobacter</i> spp.)	Agri-food environment	Soil; animals; food	February 2012–October 2013	0	<i>A baumannii</i> (n = 1) <i>Acinetobacter pittii</i> (n = 1)	No	–	–	–	–	–	–	–	–	<i>bla</i> <sub>OXA-143</sub> (1) <i>bla</i> <sub>OXA-24</sub> (1)	[46]

ESBL, extended-spectrum β-lactamase; TET, tetracycline; NAL, nalidixic acid; ENR, enrofloxacin; CIP, ciprofloxacin; TMP, trimethoprim; SXT, trimethoprim/sulfamethoxazole; GEN, gentamicin; STR, streptomycin; CHL, chloramphenicol; MDR, multidrug-resistant.

<sup>a</sup> Indicates not available.

that 35.7% and 1.1% of uropathogenic *E. coli* were ESBL-producers and ertapenem-resistant, respectively [32]. Another study also carried out in North Lebanon at Nini Hospital reported that 24.4% of cancer patients were colonised with carbapenem-resistant Gram-negative bacteria [33]. Despite the large number of published studies targeting the epidemiology of AMR among the human population in Lebanese hospital settings, the epidemiological situation of antibiotics in animals, food and the environment is still unclear. In the current review, the PubMed, ScienceDirect, Scopus and Google Scholar databases were searched for investigations published between 2008–2018 using the keywords ‘AMR’; ‘antibiotic resistance’; ‘ESBL’; ‘carbapenemase’; ‘mcr’; ‘Lebanon’; ‘extra-hospital’; ‘environment’; ‘animals’; ‘water’ and ‘vegetables’. The retrieved studies were first screened using title and abstract; and all eligible studies were retained for full-text assessment. Only indexed original research papers were included in the review (Table 1). According to our records; very few investigations have targeted the AMR issue in Lebanese non-clinical settings. However; during the last decade; the prevalence of ESBL-; AmpC  $\beta$ -lactamase- and carbapenemase-producing Gram-negative bacteria has become widely reported in animals; food and the environment in Lebanon. Interestingly; the majority of investigations were conducted either in overcrowded urban regions or in rural regions with high agricultural production (Fig. 1). Recently; Diab et al. reported the first ESBL-producing *E. coli* in animals in the country [24]. The same paper also described massive colonisation of the Lebanese bovine sector with ESBL-

producing *E. coli*; with a prevalence of 23% among healthy adult cattle and 84% among randomly selected cattle farms [24]. In contrast to worldwide findings; the enzymes responsible for the ESBL phenotype found in Lebanon were mostly CTX-M-15; followed by other ESBL types such as SHV-12; CTX-M-9; CTX-M-14; CTX-M-27 and CTX-M-55 [22–24,27,39]. Globally; CTX-M-1 is the most identified enzyme responsible for the ESBL phenotype in livestock; followed by CTX-M-14 [19,40,41]. However; recent data highlighted the presence of the *bla*<sub>CTX-M-15</sub> gene in non-clinical contexts [23,39]. In Lebanon as well as worldwide; CTX-M-15 remains the most widespread ESBL disseminated both in hospitals and the community [41,42]. Interestingly; multilocus sequence typing (MLST) and pulsed-field gel electrophoresis (PFGE) results revealed high genetic diversity of CTX-M-15-producing strains circulating in Lebanon. The isolated *E. coli* strains belonged to ST10; ST58; ST69; ST155; ST617 and ST1303; which have been observed both in humans and animals; and to ST162; ST196; ST218; ST457; ST515; ST540; ST746; ST1140; ST1294; ST1303; ST2325; ST2450; ST4252; ST4623; ST5204; ST5442 and ST5728; which have no common history [24]. However; none of the isolated strains belonged to ST131; ST405 or ST648 clones; which are the most responsible for the spread of CTX-M-15 in humans. Similarly; water contamination by ESBLs and carbapenemases is potentially a major risk to public health in Lebanon. A recent nationwide study reported a high diversity of *E. coli* STs in sewage water in Lebanon; including ST38; ST90; ST617; ST4144; ST4608; ST6222; ST6450; ST6470; ST6480 and ST6894

Pheno-type	Bacterial host	Antibiotic resistance gene	Symbol	Origin(s)
CST-R	E	<i>mcr-1</i>	◆	
	E	<i>bla</i> <sub>CTX-M-9</sub>	★	
ESBL	E	<i>bla</i> <sub>CTX-M-14</sub>	■	
	E	<i>bla</i> <sub>CTX-M-15</sub>	▲	
	E	<i>bla</i> <sub>CTX-M-27</sub>	★	
	E	<i>bla</i> <sub>CTX-M-55</sub>	★	
	E	<i>bla</i> <sub>SHV-12</sub>	●	
	E	<i>bla</i> <sub>TEM-135-like</sub>	◆	
	Carbapenemase	E	<i>bla</i> <sub>OXA-48</sub>	☆
E		<i>bla</i> <sub>OXA-244</sub>	▼	
E		<i>bla</i> <sub>NDM-1</sub>	▴	
P		<i>bla</i> <sub>VIM-2</sub>	○	
A		<i>bla</i> <sub>OXA-23</sub>	×	
A		<i>bla</i> <sub>OXA-24</sub>	□	
A		<i>bla</i> <sub>OXA-58</sub>	▶	
A		<i>bla</i> <sub>OXA-72</sub>	○	
A		<i>bla</i> <sub>OXA-143</sub>	◇	

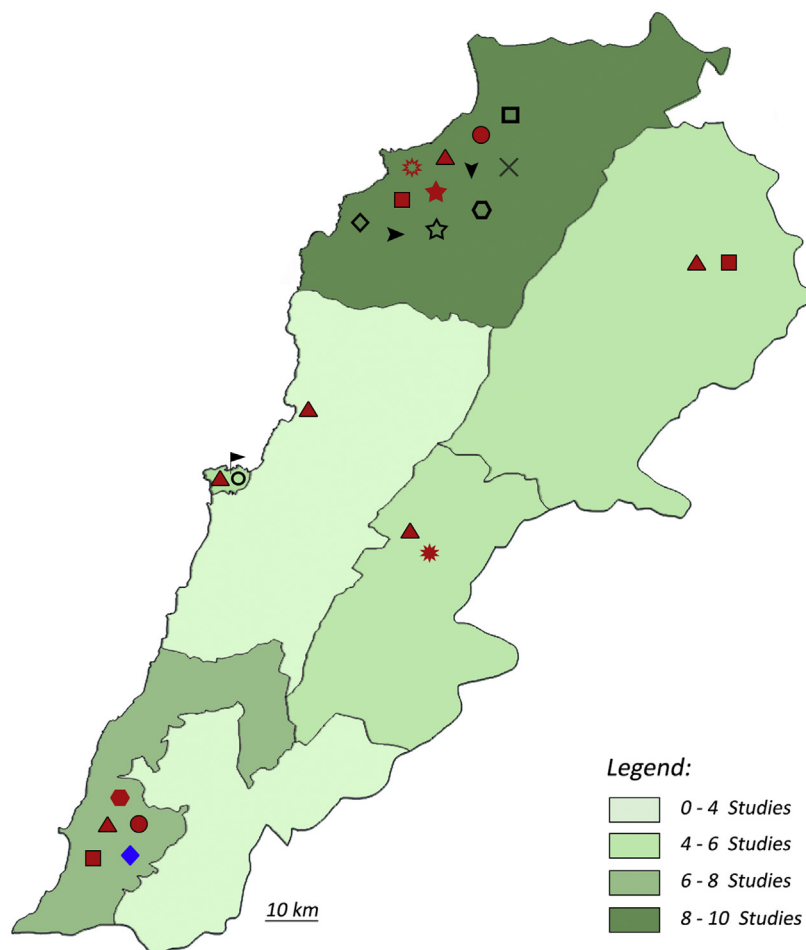


Fig. 1. Geographical distribution of reported extended-spectrum  $\beta$ -lactamases (ESBLs), carbapenemases and *mcr-1* genes and their corresponding producing Gram-negative bacteria and sources in Lebanon. CST-R, colistin-resistant; E, Enterobacteriaceae; P, *Pseudomonas aeruginosa*; A, *Acinetobacter* spp.

[39]. Another study conducted in North and South Lebanon also described very similar findings associated with high ESBL levels (59%) in water sampled from estuaries [23]. As described above; CTX-M-15 was the predominant ESBL identified in water sources including estuaries; wells and springs. None the less; this study described for the first time the presence of *E. coli* isolates belonging to ST131 and ST405 clones that are commonly reported in clinical settings [43]. Interestingly; well and spring water in Lebanon; particularly in rural areas; is directly intended for human and animal consumption without any further treatment. In addition; estuary water is commonly used to water animals and/or irrigate crops. Moreover; a cross-sectional study conducted on poultry farms at a national level revealed the presence of STs common to both humans and animals; particularly ST155 [25]. Surprisingly; none of the aforementioned studies reported the occurrence of *bla*<sub>CTX-M-15</sub>; which is mainly associated with animal sources. All of these findings are in agreement with the proposition that livestock; poultry and water in Lebanon are inhabited by genetically diverse *E. coli* carrying and disseminating *bla*<sub>CTX-M-15</sub> plasmids in different genetic backgrounds and imply an association with clinical isolates [44].

Regarding carbapenemases, Al Bayssari et al. published the first description of *bla*<sub>VIM-2</sub>-carrying *Pseudomonas aeruginosa* and *bla*<sub>OXA-23</sub>-carrying *Acinetobacter baumannii* strains isolated from Lebanese livestock and poultry [45]. Moreover, they also detected the co-occurrence of *bla*<sub>OXA-23</sub> and *bla*<sub>OXA-58</sub> in the same strain of *A. baumannii* isolated from fowl. Similarly, Rafei et al. identified a *bla*<sub>OXA-143</sub>-harbouring *A. baumannii* and a *bla*<sub>OXA-24</sub>-harbouring *Acinetobacter pittii*, both from horses [46]. In addition, two *Acinetobacter calcoaceticus* strains carrying the *bla*<sub>OXA-72</sub> carbapenemase gene have also been isolated from vegetables [47]. Furthermore, a case report showed the presence of *E. coli* OXA-48 clone ST38 in a Lebanese fowl (*Gallus domesticus*). This latter represents an emerging human clone in the Mediterranean basin region but has also been identified as an OXA-244-producer in estuaries water in Lebanon [23,27,43]. Furthermore, an OXA-48-producing *Klebsiella pneumoniae* ST530 was recently detected in raw bovine milk [22]. In addition, *E. coli* and *K. pneumoniae* strains harbouring *bla*<sub>OXA-48</sub> were also reported in estuary water, confirming the diversity of bacterial species producing OXA-48 and their probable endemic status in Lebanon [20,22,27,48]. Likewise, a recent study reported for the first time NDM-1-producing *Enterobacter cloacae* in Lebanon [49]. The NDM-1 enzyme was previously detected in Lebanon among *A. baumannii* and *A. pittii* isolated from clinical samples, but not in Enterobacteriaceae [50,51]. Besides, Gram-negative bacteria producing ESBLs and carbapenemases are co-resistant to other veterinary and clinically-licensed antibiotics (Table 1), making the AMR situation worse.

On the other hand, a case report published in January 2018 showed the emergence of an *mcr-1* plasmid-mediated colistin-resistant *E. coli* strain isolated from Lebanese poultry [52]. The isolated strain belonged to ST515, which was lately observed in Lebanese livestock [24]. In the same year, the same research group reported 23 colistin-resistant *E. coli* strains harbouring the *mcr-1* gene isolated from pigs [26]. Of the 23 colistin-resistant strains, only 4 were ESBL-producers whilst the remaining strains were susceptible to the majority of  $\beta$ -lactams [26]. A nationwide study carried out between September 2017 and March 2018 in three main poultry farms in Lebanon revealed widespread resistance to colistin, with an alarming percentage of *E. coli* isolates harbouring the *mcr-1* gene (98%) [53].

The level of colistin usage in farms and veterinary medicine remains unclear. However, unpublished data have revealed the heavy use of this compound both in humans and animals in Lebanon. Hence, further studies including a large number of human, animal and environmental samples are urgently required.

In conclusion, the AMR issue is not only confined to clinical settings but is also disseminated in the community. Animals as well as foodstuffs and the environment are significant reservoirs of AMR in Lebanon. Although few epidemiological studies have been conducted, the available data are highly worrisome indicating that MDR and XDR bacteria are ubiquitous in Lebanon. Besides, it is suggested that the dissemination of resistant clones in the community may have a zoonotic origin since the same clones were found both in clinical and non-clinical samples in Lebanon. Moreover, the presence of antimicrobial-resistant Gram-negative bacteria in the environment suggests potential contamination either by human or animal activities and represents a prominent public-health issue in Lebanon. Hence the importance of a One Health concept based on whole-genome sequencing surveillance data of microbes in humans, animals and the environment in order to address the AMR issue by developing comprehensive and integrative measures and effective preventive and control strategies. Moreover, awareness movements involving stakeholders, policy-makers and health actors need to be initiated in order to stop using antibiotics without prescription and even to ban antibiotic use in the veterinary sector.

## Acknowledgment

The authors would like to thank Halima El Cheikh for assistance in the design of the figure.

## Funding

HAM was supported by PhD fellowships from the Azm & Saade Association and the Lebanese Association for Scientific Research (LASER).

## Competing interests

None declared.

## Ethical approval

Not required.

## References

- [1] Prestinaci F, Pezzotti P, Pantosti A. Antimicrobial resistance: a global multifaceted phenomenon. *Pathog Glob Health* 2015;109:309–18.
- [2] Ventola CL. The antibiotic resistance crisis: part 1: causes and threats. *P T* 2015;40:277–83.
- [3] de Kraker ME, Stewardson AJ, Harbarth S. Will 10 million people die a year due to antimicrobial resistance by 2050? *PLoS Med* 2016;13:e1002184.
- [4] GBD 2015 Healthcare Access and Quality Collaborators. Healthcare access and quality index based on mortality from causes amenable to personal health care in 195 countries and territories, 1990–2015: a novel analysis from the Global Burden of Disease Study 2015. *Lancet* 2017;390:231–66.
- [5] European Centre for Disease Prevention and Control (ECDC). Antimicrobial resistance surveillance in Europe 2016. Stockholm, Sweden: ECDC; 2017 <https://ecdc.europa.eu/en/publications-data/antimicrobial-resistance-surveillance-europe-2016>. [Accessed 19 March 2019].
- [6] Kelesidis T, Falagas ME. Substandard/counterfeit antimicrobial drugs. *Clin Microbiol Rev* 2015;28:443–64.
- [7] Chamoun K, Farah M, Araj G, Daoud Z, Moghnieh R, Salameh P, et al. Surveillance of antimicrobial resistance in Lebanese hospitals: retrospective nationwide compiled data. *Int J Infect Dis* 2016;46:64–70.
- [8] Farah R, Lahoud N, Salameh P, Saleh N. Antibiotic dispensation by Lebanese pharmacists: a comparison of higher and lower socio-economic levels. *J Infect Public Health* 2015;8:37–46.
- [9] Saleh N, Awada S, Awwad R, Jibai S, Arfoul C, Zaiter L, et al. Evaluation of antibiotic prescription in the Lebanese community: a pilot study. *Infect Ecol Epidemiol* 2015;5:27094.
- [10] Al Omari S, Al Mir H, Wrayde S, Merhabi S, Dhaybi I, Jamal S, et al. First Lebanese antibiotic awareness week campaign: knowledge, attitudes and practices towards antibiotics. *J Hosp Infect* 2019;101:475–9, doi:<http://dx.doi.org/10.1016/j.jhin.2018.07.009>.

- [11] Gullberg E, Albrecht LM, Karlsson C, Sandegren L, Andersson DI. Selection of a multidrug resistance plasmid by sublethal levels of antibiotics and heavy metals. *mBio* 2014;5:e01918-14.
- [12] Alhomoud F, Aljamea Z, Almahasnah R, Alkhalifah K, Basalelah L, Alhomoud FK. Self-medication and self-prescription with antibiotics in the Middle East—do they really happen? A systematic review of the prevalence, possible reasons, and outcomes. *Int J Infect Dis* 2017;57:3–12.
- [13] Chantziaras I, Boyen F, Callens B, Dewulf J. Correlation between veterinary antimicrobial use and antimicrobial resistance in food-producing animals: a report on seven countries. *J Antimicrob Chemother* 2014;69:827–34.
- [14] Ter Kuile BH, Kraupner N, Brul S. The risk of low concentrations of antibiotics in agriculture for resistance in human health care. *FEMS Microbiol Lett* 2016;363: pii:fnw210.
- [15] Zhang L, Levy K, Trueba G, Cevallos W, Trostle J, Foxman B, et al. Effects of selection pressure and genetic association on the relationship between antibiotic resistance and virulence in *Escherichia coli*. *Antimicrob Agents Chemother* 2015;59:6733–40.
- [16] Lerbech AM, Opintan JA, Bekoe SO, Ahiabu MA, Tersbol BP, Hansen M, et al. Antibiotic exposure in a low-income country: screening urine samples for presence of antibiotics and antibiotic resistance in coagulase negative staphylococcal contaminants. *PLoS One* 2014;9:e113055.
- [17] Tartari E, Abbas M, Pires D, de Kraker MEA, Pittet D, World Health Organization SAVE. LIVES: clean your hands global campaign—fight antibiotic resistance—it's in your hands". *Clin Microbiol Infect* 2017;23:596–8.
- [18] Dahmen S, Metayer V, Gay E, Madec JY, Haenni M. Characterization of extended-spectrum  $\beta$ -lactamase (ESBL)-carrying plasmids and clones of Enterobacteriaceae causing cattle mastitis in France. *Vet Microbiol* 2013;162:793–9.
- [19] Haenni M, Chatre P, Metayer V, Bour M, Signol E, Madec JY, et al. Comparative prevalence and characterization of ESBL-producing Enterobacteriaceae in dominant versus subdominant enteric flora in veal calves at slaughterhouse, France. *Vet Microbiol* 2014;171:321–7.
- [20] Beyrouthy R, Robin F, Dabboussi F, Mallat H, Hamze M, Bonnet R. Carbapenemase and virulence factors of Enterobacteriaceae in North Lebanon between 2008 and 2012: evolution via endemic spread of OXA-48. *J Antimicrob Chemother* 2014;69:2699–705.
- [21] Beyrouthy R, Robin F, Hamze M, Bonnet R. IncFIIk plasmid harbouring an amplification of 16S rRNA methyltransferase-encoding gene *rmtH* associated with mobile element ISCR2. *J Antimicrob Chemother* 2017;72:402–6.
- [22] Diab M, Hamze M, Bonnet R, Saras E, Madec JY, Haenni M. OXA-48 and CTX-M-15 extended-spectrum  $\beta$ -lactamases in raw milk in Lebanon: epidemic spread of dominant *Klebsiella pneumoniae* clones. *J Med Microbiol* 2017;66:1688–91.
- [23] Diab M, Hamze M, Bonnet R, Saras E, Madec JY, Haenni M. Extended-spectrum  $\beta$ -lactamase (ESBL)- and carbapenemase-producing Enterobacteriaceae in water sources in Lebanon. *Vet Microbiol* 2018;217:97–103.
- [24] Diab M, Hamze M, Madec JY, Haenni M. High prevalence of non-ST131 CTX-M-15-producing *Escherichia coli* in healthy cattle in Lebanon. *Microb Drug Resist* 2017;23:261–6.
- [25] Dandachi I, Sokhn ES, Dahdouh EA, Azar E, El-Bazzal B, Rolain JM, et al. Prevalence and characterization of multi-drug-resistant Gram-negative bacilli isolated from Lebanese poultry: a nationwide study. *Front Microbiol* 2018;9:550.
- [26] Dandachi I, Fayad E, El-Bazzal B, Daoud Z, Rolain JM. Prevalence of extended-spectrum  $\beta$ -lactamase-producing gram-negative bacilli and emergence of *mcr-1* colistin resistance gene in Lebanese swine farms. *Microb Drug Resist* 2019;25:233–40.
- [27] Al Bayssari C, Olaitan AO, Dabboussi F, Hamze M, Rolain JM. Emergence of OXA-48-producing *Escherichia coli* clone ST38 in fowl. *Antimicrob Agents Chemother* 2015;59:745–6.
- [28] Madec JY, Haenni M, Nordmann P, Poirel L. Extended-spectrum  $\beta$ -lactamase/AmpC- and carbapenemase-producing Enterobacteriaceae in animals: a threat for humans? *Clin Microbiol Infect* 2017;23:826–33.
- [29] Tang KL, Caffrey NP, Nobrega DB, Cork SC, Ronskley PE, Barkema HW, et al. Restricting the use of antibiotics in food-producing animals and its associations with antibiotic resistance in food-producing animals and human beings: a systematic review and meta-analysis. *Lancet Planet Health* 2017;1:e316–27.
- [30] Jamal S, Atrouni AA, Rafei R, Dabboussi F, Hamze M, Osman M. Molecular mechanisms of antibiotic resistance in *Acinetobacter baumannii*, with a special focus on its epidemiology in Lebanon. *J Glob Antimicrob Resist* 2018;15:154–63.
- [31] El Moujabber G, Osman M, Rafei R, Dabboussi F, Hamze M. Molecular mechanisms and epidemiology of resistance in *Streptococcus pneumoniae* in the Middle East region. *J Med Microbiol* 2017;66:847–58.
- [32] Osman M, Mallat H, Hamze M, Achkar M. Prevalence and antibiotic susceptibility patterns of bacteria causing urinary tract infections in Youssef Hospital Center: first report from Akkar governorate, North Lebanon. *Int Arab J Antimicrob Resist* 2017;7. doi:<http://dx.doi.org/10.3823/802>.
- [33] Christophy R, Osman M, Mallat H, Achkar M, Ziedeh A, Moukaddem W, et al. Prevalence, antibiotic susceptibility and characterization of antibiotic resistant genes among carbapenem-resistant Gram-negative bacilli and yeast in intestinal flora of cancer patients in North Lebanon. *J Infect Public Health* 2017;10:716–20.
- [34] Faour-Klingbeil D, Kuri V, Fadlallah S, Matar GM. Prevalence of antimicrobial-resistant *Escherichia coli* from raw vegetables in Lebanon. *J Infect Dev Ctries* 2016;10:354–62.
- [35] Dabboussi F, El Omari K, Mouzawak M, Al Bayssari C, Hamze M. Recherche de *Salmonella*, *Listeria* et de bactéries résistantes aux céphalosporines de troisième génération dans du fromage Akkawi au nord du Liban [*Salmonella*, *Listeria* and third-generation cephalosporin-resistant bacteria tested in Akkawi cheese in northern Lebanon]. *Lebanese Sci J* 2012;14:3–14.
- [36] Hamze M, Dabboussi F, Chami J, Makhoul J. Qualité microbiologique et recherche des bactéries résistantes aux antibiotiques dans 40 échantillons de viande hachée commercialisés dans la ville de Tripoli-nord Liban [Microbiological quality and research of antibiotic-resistant bacteria in 40 minced meat samples marketed in the city of North Tripoli, Lebanon]. *Microbiol Hyg Alim* 2011;23:28–34.
- [37] Hamze M, Dabboussi F, Abdou T, Radwan M, Awad Z. Étude sur la qualité bactériologique et recherche des bactéries multirésistantes aux antibiotiques dans 50 puits à Akkar au nord du Liban [Study on the bacteriological quality and research of multidrug-resistant bacteria in 50 wells in Akkar, northern Lebanon]. *Cahiers de l'ASEES* 2010;15:45–53.
- [38] Al Atrouni A, Kempf M, Eveillard M, Rafei R, Hamze M, Joly-Guillou ML. First report of OXA-72-producing *Acinetobacter calcoaceticus* in Lebanon. *New Microbes New Infect* 2016;9:11–2.
- [39] Tokajian S, Moghnieh R, Salloum T, Arabaghian H, Alouisi S, Moussa J, et al. Extended-spectrum  $\beta$ -lactamase-producing *Escherichia coli* in wastewaters and refugee camp in Lebanon. *Future Microbiol* 2018;13:81–95.
- [40] Hordijk J, Wagenaar JA, van de Giessen A, Dierikx C, van Essen-Zandbergen A, Veldman K, et al. Increasing prevalence and diversity of ESBL/AmpC-type  $\beta$ -lactamase genes in *Escherichia coli* isolated from veal calves from 1997 to 2010. *J Antimicrob Chemother* 2013;68:1970–3.
- [41] Ewers C, Bethe A, Semmler T, Guenther S, Wieler LH. Extended-spectrum  $\beta$ -lactamase-producing and AmpC-producing *Escherichia coli* from livestock and companion animals, and their putative impact on public health: a global perspective. *Clin Microbiol Infect* 2012;18:646–55.
- [42] Moubareck C, Daoud Z, Hakime NI, Hamze M, Mangeny N, Matta H, et al. Countrywide spread of community- and hospital-acquired extended-spectrum  $\beta$ -lactamase (CTX-M-15)-producing Enterobacteriaceae in Lebanon. *J Clin Microbiol* 2005;43:3309–13.
- [43] Tokajian S, Salloum T, Eisen JA, Jospin G, Farra A, Mokhbat JE, et al. Genomic attributes of extended-spectrum  $\beta$ -lactamase-producing *Escherichia coli* isolated from patients in Lebanon. *Future Microbiol* 2017;12:213–26.
- [44] Ribeiro-Santos R, Andrade M, Ramos de Melo N, Sanches-Silva A. Use of essential oils in active food packaging: recent advances and future trends. *Trends Food Sci Technol* 2017;61:132–40.
- [45] Al Bayssari C, Dabboussi F, Hamze M, Rolain JM. Emergence of carbapenemase-producing *Pseudomonas aeruginosa* and *Acinetobacter baumannii* in livestock animals in Lebanon. *J Antimicrob Chemother* 2015;70:950–1.
- [46] Rafei R, Hamze M, Pailhories H, Eveillard M, Marsollier L, Joly-Guillou ML, et al. Extrahuman epidemiology of *Acinetobacter baumannii* in Lebanon. *Appl Environ Microbiol* 2015;81:2359–67.
- [47] Al Atrouni A, Hamze M, Rafei R, Eveillard M, Joly-Guillou ML, Kempf M. Diversity of *Acinetobacter* species isolated from different environments in Lebanon: a nationwide study. *Future Microbiol* 2016;11:1147–56.
- [48] Beyrouthy R, Robin F, Coughnoux A, Dalmasso G, Darfeuille-Michaud A, Mallat H, et al. Chromosome-mediated OXA-48 carbapenemase in highly virulent *Escherichia coli*. *J Antimicrob Chemother* 2013;68:1558–61.
- [49] Daoud Z, Farah J, Sokhn ES, El Kfoury K, Dahdouh E, Masri K, et al. Multidrug-resistant Enterobacteriaceae in Lebanese hospital wastewater: implication in the one health concept. *Microb Drug Resist* 2018;24:166–74.
- [50] Rafei R, Dabboussi F, Hamze M, Eveillard M, Lemarie C, Mallat H, et al. First report of *bla*<sub>NDM-1</sub>-producing *Acinetobacter baumannii* isolated in Lebanon from civilians wounded during the Syrian war. *Int J Infect Dis* 2014;21:21–3.
- [51] Al Atrouni A, Joly-Guillou ML, Hamze M, Kempf M. Emergence of NDM-1 and OXA-72 producing *Acinetobacter pittii* clinical isolates in Lebanon. *New Microbes New Infect* 2016;12:43–4.
- [52] Dandachi I, Leangapichart T, Daoud Z, Rolain JM. First detection of *mcr-1* plasmid-mediated colistin-resistant *Escherichia coli* in Lebanese poultry. *J Glob Antimicrob Resist* 2018;12:137–8.
- [53] Hmede Z, Kassem II. The colistin resistance gene *mcr-1* is prevalent in commensal *Escherichia coli* isolated from preharvest poultry in Lebanon. *Antimicrob Agents Chemother* 2018;62. doi:<http://dx.doi.org/10.1128/AAC.01304-18> pii: e01304-18.