

1 ANTIBIOTIC RESISTANCE IN *Escherichia coli* IN HUSBANDRY ANIMALS. THE AFRICAN
2 PERSPECTIVE.

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13 Running headline: Resistant *E. coli* in African livestock

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27 SUMMARY (150-200 word)

28 In the last few years different surveillances have been published in Africa, especially in Northern countries,
29 regarding antimicrobial resistance among husbandry animals. Information is still scarce, but the available
30 data shows a worrying picture. Although the highest resistance rates have been described against
31 tetracycline, penicillins and sulphonamides, prevalence of plasmid mediated quinolone resistance genes
32 and extended-spectrum β -lactamase (ESBL) are being increasingly reported. Among ESBLs, the CTX-M-
33 1 group was dominant in most African surveys. Within this group, CTX-M-15 was the main variant both
34 in animals and humans, except in Tunisia where CTX-M-1 was more frequently detected among *E. coli*
35 from poultry. Certain *bla*_{CTX-M-15}-harboring clones (ST131/B2 or ST405/D) are mainly identified in humans
36 but they have also been reported in livestock species from Tanzania, Nigeria or Tunisia. Moreover, several
37 reports suggest an inter-host circulation of specific plasmids (e.g. *bla*_{CTX-M-1}-carrying IncI1/ST3 in Tunisia,
38 IncY and Inc-untypeable replicons co-harboring *qnrS1* and *bla*_{CTX-M-15} in Tanzania and the worldwide
39 distributed *bla*_{CTX-M-15}-carrying IncF-type plasmids). International trade of poultry meat seems to have
40 contributed to the spread of other ESBL variants, such as CTX-M-14, and clones. Furthermore, first
41 descriptions of OXA-48 and OXA-181-producing *E. coli* have been recently documented in cattle from
42 Egypt, and the emergent plasmid-mediated colistin resistance *mcr-1* gene has been also identified in
43 chickens from Algeria, Tunisia and South Africa. These data reflect the urgent need of a larger regulation
44 in the use of veterinary drugs and the implementation of surveillances programmes in order to decelerate
45 the advance of antimicrobial resistance in this continent.

46 Keywords: *Escherichia coli*, antibiotic resistance, β -lactamases, husbandry animals, Africa.

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48 INTRODUCTION

49 The rapid increase in the rate of antimicrobial-resistant bacteria (AMR) reinforced by the opposite tendency
50 in the development of new active drugs is currently one of the most serious public health threats, as
51 recognized by the World Health Organization (Accessed 26/11/2016
52 <http://www.who.int/drugresistance/documents/surveillancereport/en>). Resistance trends in Gram-negative
53 bacilli are particularly alarming due to limited antibiotic options to treat infections caused by some
54 organisms (especially Enterobacteriaceae, *Pseudomonas aeruginosa* and *Acinetobacter*) that are becoming
55 resistant to nearly all available antimicrobials, including carbapenems.

56 This global emergence of multi-drug resistant bacteria has been attributed to the overuse and misuse of
57 antibiotics, not only in human medicine but also in farming and veterinary sectors. In fact, the worldwide
58 use of antibiotics for animal health and production purposes exceeds the use in humans and most of the
59 drugs designed exclusively for veterinary use are closely related or belong to the same antimicrobial classes
60 of those indicated for humans (Aaerstrup *et al.* 2008; Cantas *et al.* 2013). In Europe, according to the data
61 from 10 countries, the amount of veterinary antimicrobial agents sold in 2007 varied from 18 to 188 mg/kg
62 biomass of food-producing animals (FPA), and were globally predominant the sales of sulphonamides and
63 trimethoprim (alone or in combination), tetracyclines and β -lactams (Grave *et al.* 2010). In Japan, the
64 amounts varied between 132 mg/kg and 153 mg/kg from 2005 to 2010 (Hosoi *et al.* 2013). In general, in
65 developed countries the use of antibiotics is strictly controlled and documented, but this is not the case in
66 developing countries of the African continent where veterinary antimicrobials are often readily sold in
67 shops and markets without prescriptions (Mainda *et al.* 2015).

68 Unfortunately, as expected, it has been demonstrated that the use of antimicrobial agents in husbandry is
69 directly related to the incidence of resistant bacteria in FPA (Baron *et al.* 2014, Chantziaras *et al.* 2014).
70 Selection of these antimicrobial resistant (AMR) bacteria that asymptotically colonize the gut of animals
71 might play an epidemiological role in the spread of resistance between FPA and humans, either through
72 direct contact or consumption of contaminated food. Inter-host transmission is more likely to happen in
73 rural areas of developing countries with mainly subsistence-based agricultural economies, such as some
74 regions in Africa, where people frequently live in close contact with livestock animals.

75 Because of the growing problem of antibiotic resistance worldwide, the number of studies focusing on the
76 epidemiology of AMR bacteria, with special attention to extended-spectrum beta-lactamase (ESBL),
77 plasmidic AmpC beta-lactamase (pAmpC) and carbapenemase-production in Enterobacteriaceae, has
78 increased over the last few years. The majority of these reports have been carried out in *Escherichia coli*,
79 generally considered a useful indicator of antimicrobial resistance due to its medical importance and its
80 presence in a wide range of hosts. This allows comparisons of prevalence between different populations
81 and the evaluation of antimicrobial resistance transmission from animals to humans and vice versa (van der
82 Bogaard and Stobberingh 2000). Despite limited resources, the incidence of AMR Enterobacteriaceae in
83 Africa, and more specifically ESBL producers, has been also studied at the local level in different countries.
84 There are also some reviews about the general situation in the whole continent but most of them are
85 concentrated in human clinical and community settings (Storberg, 2012; Sangare *et al.* 2015, Sekyere *et al.*

86 2016). In the present review, we aim to describe the situation of AMR *E. coli* in FPA and food of animal
87 origin in Africa, with particular focus on ESBL/pAmpC producing isolates.

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89 LITERATURE SEARCH STRATEGY AND DATA EXTRACTION

90 A literature search was conducted in PubMed database for original articles reporting data on AMR *E. coli*
91 from African countries. The review was limited to studies published in English between January 2007 and
92 November 2016. We used combinations of relevant keywords such as: A) "*Escherichia coli*"; B)
93 "antimicrobial resistance", "antibiotic resistance", "antimicrobial usage", "antibiotic usage", "ESBL",
94 "extended-spectrum beta-lactamases", "carbapenemases"; C) General ("livestock animals", "farm
95 animals", "husbandry", "food-producing animals") and specific animal descriptors (eg, "poultry",
96 "chickens", "swine", "pigs", "cattle"); D) "Africa" and the names of each African nation. References of
97 articles were reviewed to identify any other relevant publication and, additionally, an online search was
98 carried out to consult documents from International Organizations (e.g., WHO, OIE).

99 The first author, country, year of sampling, sample type, sample size, animal health status, prevalence and
100 distribution of antimicrobial resistance, resistance genes/mechanisms and molecular typing data were
101 extracted from all the included studies.

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103 ANTIMICROBIAL USAGE IN LIVESTOCK AND RESISTANCE PATTERNS IN *E. coli*

104 Antimicrobial agents can be used in animal husbandry not only for the treatment and prevention of
105 infectious diseases but also, at low and sub-therapeutic doses, as growth promoters. Although their use
106 allows to protect animal health and welfare with lower incidence of disease and also contributes to food
107 safety, there is evidence to suggest that are leading to the spread of antimicrobial resistance (Chantziaras *et*
108 *al.* 2014) with important public health implications. In this sense, on the basis of precautionary principles,
109 European Union banned in 2006 the use of all growth-promoting antibiotics (Hao *et al.* 2014).
110 Unfortunately, this preventive measure has not been taken all over the world, and antimicrobial agents are
111 still used for this purpose in many developed and developing countries.

112 In general, the use and control of antimicrobials in the developing world, including countries of the African
113 continent, remains largely unregulated (Maron *et al.* 2013). According to The World Organisation for
114 Animal Health (Accessed 26/11/2016 <http://www.oie.int/>) in many countries, mainly developing and
115 emerging ones, do not yet have relevant legislation concerning appropriate conditions for the use of

116 veterinary products, including antimicrobials. In some cases, legislation is totally non-existent and where
117 it does exist it is very often not properly applied. As some African studies focused on the antimicrobial
118 usage in livestock indicate, there is an irrational use due to the unregulated access and even administration
119 of veterinary drugs (Adesokan *et al.* 2015; Eagar *et al.* 2012; Mainda *et al.* 2015). Even though in many
120 African countries it is illegal for any person who is not a registered veterinarian to administer antibiotics,
121 there are no strict control measures and often farmers purchase and administer a drug without veterinary
122 prescription and supervision (Adesokan *et al.* 2015, Mainda *et al.* 2015). Unfortunately, the use of
123 antimicrobials in animals by untrained personnel is not confined to developing and emerging countries
124 (Accessed 26/11/2016 <http://www.oie.int/>).

125 Furthermore, it is also important to note that the first study estimating the global trends in antimicrobial use
126 in livestock production found that the global consumption of antimicrobials will increase in the future and
127 this rise is likely to be driven by the growth in consumer demand for livestock products in middle-income
128 countries and a shift to large-scale farms where antimicrobials are used routinely (Van Boeckel *et al.* 2015).

129 The data of different surveys conducted in Nigeria (Adesokan *et al.* 2015), Zambia (Mainda *et al.* 2015)
130 and South Africa (Eager *et al.* 2012) about the sales of antimicrobials for farm animals indicate that, even
131 considering variations between countries or animal species (mammals or poultry), tetracyclines and beta-
132 lactams (mainly penicillins) are among the first four leading antibiotics commonly employed in livestock
133 animal production. Sulphonamides and macrolides are also frequently consumed antimicrobials, this last
134 group (with reference specifically to tylosin) has been reported as the most extensively sold in South Africa
135 for treatment and prevention of veterinary diseases and also, at sub-therapeutic levels, as a registered growth
136 promoter (Eager *et al.* 2012). Equally worrisome is the veterinary overuse of fluoroquinolones (critically
137 important in human medicine) in some African regions, as it has been documented in a survey conducted
138 in south-western Nigeria (Adesokan *et al.* 2015).

139 In a study carried out in Ghana, 395 commercial livestock keepers who practice intensive or extensive
140 farming were interviewed about their antibiotic usage practice (Donkor *et al.* 2012). Most of the farmers
141 used veterinary drugs mainly for disease prevention, followed by the dual purpose of prevention and
142 treatment, only treatment and, less often, also for growth promotion. Of course, it is important to mention
143 that the data collected from livestock keepers were self-reported, which may pose certain limitations.
144 Another significant aspect to consider is the antibiotic administration bias commonly employed in livestock
145 production, which is obviously different from those used in human medicine. A survey conducted in South

146 Africa showed that in-feed dosage forms constituted almost 70% of the total of antimicrobial dosages sold
147 in this country (Eager *et al.* 2012). This practice favors that an entire group of animals be medicated at the
148 same time contrary to the individual treatment given to patients.

149 Moreover, recent data from Nigeria show a significant increasing trend in the veterinary antimicrobial
150 consumption, which is not proportional to the annual livestock rate in the area (Adesokan *et al.* 2015).
151 Regarding the type of livestock species, some studies suggest a relatively higher rate of antimicrobial usage
152 among chickens, which is expressed in the more elevated percentage of resistant isolates detected among
153 this particular animal population (Ben Sallem *et al.* 2012b, Donkor *et al.* 2012, Adenipekun *et al.* 2015). A
154 European report based on data gathered from seven countries also showed higher resistance rates in poultry
155 (Chantziaras *et al.* 2014). This may be explained, in part, by the fact that antibiotic usage is even higher in
156 intensive farming, more common in poultry, where animals are reared in close proximity.

157 In general, although resistance percentages vary significantly among regions and studied animal
158 populations, the highest rates have been reported for tetracycline (10.6%-95%), ampicillin (6.02%-95.7%)
159 and trimethoprim/sulfamethoxazole (4.49%-80%) (Wesonga *et al.* 2010, Donkor *et al.* 2012, Adelowo *et al.*
160 *et al.* 2014, Adenipekun *et al.* 2015, Mainda *et al.* 2015, Rugumisa *et al.* 2016). African studies on food of
161 animal origin (retail chicken or turkey meat, beef and pork carcasses) also report that resistance levels to
162 these antimicrobials are among the most relevant ones (Soufi *et al.* 2009; Odwar *et al.* 2014; Luanda *et al.*
163 2016; Mrutu *et al.* 2016). This is not surprising since these drugs have been in use the longest time both in
164 human and veterinary medicine (Tadesse *et al.* 2012). Their combined resistance, often due to the co-
165 location of different determinants in the same mobile genetic elements (plasmids, transposons and/or
166 integrons) has contributed to the selection of multi-drug resistant (MDR) isolates worldwide (Wesonga *et al.*
167 *et al.* 2010, Tadesse *et al.* 2012, Adenipekun *et al.* 2015). The presence and diversity of integrons in *E. coli*
168 from poultry, poultry meat and cattle have been studied in various reports from Africa (Soufi *et al.* 2009,
169 Ben Slama *et al.* 2010, Inwezerua *et al.* 2014, Maamar *et al.* 2016) and showed high rates of prevalence of
170 class 1 and class 2 integrons (60%) containing, as commonly occur, trimethoprim (*dfr*) and streptomycin
171 (*aad*) resistance encoding genes.

172 Regarding other antimicrobial classes, such as quinolones and cephalosporins, the picture is even more
173 worrying due to their vital importance in the treatment of a wide variety of infections in humans and the
174 fact that resistance against them leaves few therapy options. Livestock as reservoirs of ESBL-producer
175 bacteria will be discussed in the following sections because of its relevance in terms of emerging resistance

176 properties and the substantial literature available. Some studies performed in Tunisia and Nigeria reported
177 unexpected high prevalence of resistance to quinolones among cattle (61.2%) (Grami *et al.* 2014) and
178 poultry (42-55%) (Fortini *et al.* 2011, Adelowo *et al.* 2014), since this antimicrobial class was introduced
179 later than others in livestock and is relatively expensive. Resistance to quinolones and fluoroquinolones is
180 mainly driven by chromosomal mutations at the quinolone resistance determining region (QRDR) of DNA
181 gyrase and topoisomerase IV. However, plasmid-mediated quinolones resistance mechanisms (PMQR)
182 (such as, *qnr* proteins, *aac(6)-Ib-cr* aminoglycoside acetyltransferase and efflux pump proteins like QepA
183 or OqxAB) have been progressively detected and contribute to an increase in the MIC of quinolones and
184 fluoroquinolones. In Nigeria, a country where previous studies had reported a high prevalence of PMQR
185 genes in clinical samples from humans (Ogbolu *et al.* 2011), an important study was carried out in poultry
186 and pigs to characterize PMQR determinants and associated plasmids and clones (Fortini *et al.* 2011). The
187 resulting data, which identified four PMQR gene variants (*qnrB10*, *qnrB19*, *qnrS1* and *qepA1*) located on
188 five different plasmid types (IncHI2, ColE, IncI1, IncN and IncX2), suggested that FPA can act as reservoirs
189 of PMQR determinants. In particular, this work demonstrated the wide circulation in the area of *qnrS1* gene
190 harbored mainly in IncX2, IncN and IncI1 plasmids, *qnrB19* in small ColE-like plasmids and *qepA1* in
191 plasmids of HI2 incompatibility group. Moreover, the same IncI1-ST12 plasmid harboring *qnrS1* was
192 detected in commensal *E. coli* isolates from poultry in the mentioned study and in *Salmonella* strains in
193 other independent work carried out previously in Nigeria (Fashae *et al.* 2010). Regarding other remarkable
194 aspect of this study, all the strains carried the *bla*_{TEM-1} gene and one was positive for CTX-M-15 beta-
195 lactamase. In fact, association between *qnr* or *aac(6)Ib-cr* and *bla* genes has been frequently reported
196 worldwide, including some African countries (Mnif *et al.* 2012, Ben Sallem *et al.* 2014, Inwezerua *et al.*
197 2014, Kilani *et al.* 2015, Belmahdi *et al.* 2016, Ojo *et al.* 2016, Seni *et al.* 2016).

198 It is also important to highlight the detection of *E. coli* isolates carrying the emerging plasmid-mediated
199 colistin resistance gene *mcr-1* in chickens from Algeria (Olaitan *et al.* 2016), South Africa (Perreten *et al.*
200 2016) and three poultry farms from Tunisia (Grami *et al.* 2016). Tunisian isolates, collected from chickens
201 imported from France, were further characterized and demonstrated to carry *bla*_{CTX-M-1} and *mcr-1* genes co-
202 localised on the same IncHI2-type plasmid. This plasmid was also found in veal calves in France (Haenni
203 *et al.* 2016) and food samples in Portugal (Tse *et al.* 2016), highlighting the impact of food animal trade on
204 the dissemination of *mcr-1*-mediated colistin resistance. This polymyxin is currently considered a last-
205 resort antibiotic for the treatment of highly resistant pathogenic bacteria in human medicine. However, it

206 has been also extensively used in animal production worldwide (Rhouma *et al.* 2016) leading to a potential
207 selection of resistant strains which reflects, once again, the urgent need of a better control in the global
208 market of veterinary drugs.

209 Regarding surveillances performed on specific pathogenic strains, such as Shiga-toxin producing
210 *Escherichia coli* O157, a high prevalence of MDR isolates (>90%) were reported in two studies conducted
211 in South Africa (Ateba and Bezuidenhout 2008, Iweriebor *et al.* 2015). In both cases, elevated rates of
212 resistance against sulphametoxazol and tetracycline were reported, but even more alarming was the
213 detection of *bla*_{CTX-M} and *bla*_{CMY} genes encoding third-generation cephalosporin resistance (Iweriebor *et al.*
214 2015). Healthy domestic ruminants, particularly cattle and sheep, are considered natural reservoirs of these
215 pathogens, associated to clinical diseases such as diarrhea, haemorrhagic colitis or haemolytic uraemic
216 syndrome in humans. Thus, indirect selection of MDR isolates can contribute to an emergence of
217 pathogenic strains posing a risk to public health.

218

219 ESBL, PLASMID-MEDIATED AMP^c AND CARBAPENEMASE PRODUCING *E. coli* IN

220 HUSBANDRY ANIMALS

221 The first description of ESBL-producing *Escherichia coli* from livestock origin in the African continent
222 dates back to 2011 (Fortini *et al.* 2011). Since then, many surveillance reports have been published,
223 especially in Northern Africa, reflecting an increased effort to understand the role of animals as reservoirs
224 of ESBL and establish good control measures to avoid the spread of these bacteria.

225 Regarding data from Table 1, which collects all the published studies on ESBL-producing *E. coli* among
226 African livestock and derived-food, the prevalence of these resistant bacteria among healthy animals was
227 highly variable depending on the study (from 0% to 42.8%). This variability can be explained, in part, to
228 differences in the methodology used. Of course, other factors like specific selective driving forces
229 (antimicrobial usage), farming practices, geographical particularities such as the predominance of specific
230 clones, and even the studied animal breed (local/exotic) or age have demonstrated to affect the carriage
231 percentages of ESBL among animals (Reist *et al.* 2013, Seni *et al.* 2016). It is also important to mention
232 that most of the surveys were carried out among poultry in comparison with other FPA species such as
233 cattle or pigs. Although the vast majority of analyzed samples were faeces, one study conducted in Algeria
234 (not considered in the previously given prevalence estimation because of the small number of samples
235 included) reported the presence of ESBL-*E.coli* in the reproductive and gastrointestinal tract of 9 broiler

236 breeding roosters (Mezhoud *et al.* 2015). Considering the few data available on diseased animal population
237 (Table 2), the number of studies among cattle and poultry is more homogeneous and mainly focused on
238 chickens suffering from colibacillosis and cattle with clinical or subclinical mastitis. The prevalence of
239 ESBL-producing *E. coli* among sick poultry varied from 0 to 24.7% and for cattle was reported between 0
240 and 10% (although the number of studied *E. coli* strains was considerably lower in cattle).

241 Focusing on the diversity of ESBL enzymes among *E. coli* isolates from African livestock, those belonging
242 to CTX-M-1 group have demonstrated to be more abundant than other ESBL groups or types (SHV or TEM
243 ESBLs). In the majority of the surveys, *bla*_{CTX-M-15} was the most common ESBL gene detected with the
244 exception of Tunisia, where many works reported CTX-M-1 as the main enzyme among poultry (Ben
245 Sallem *et al.* 2012b, Mnif *et al.* 2012, Maamar *et al.* 2016) (Fig. 1A). In Tunisia, CTX-M-1 has also been
246 found as the most prevalent variant among ESBL-producing *E. coli* of healthy humans' intestinal
247 microbiota (Ben Sallem *et al.* 2012a), whereas CTX-M-15 is the predominant enzyme among clinical
248 ESBL-producer isolates (Dahmen *et al.* 2010, Ben Slama *et al.* 2011). In fact, *bla*_{CTX-M-15} is in general the
249 most frequently found ESBL gene among African hospital strains, regardless of the country (Storberg
250 2014). In Algeria, a study carried out in slaughtered broilers showed a high prevalence of *bla*_{SHV-12}
251 (Belmahdi *et al.* 2016). However, most of the isolates carrying this *bla* gene were taken from chickens
252 belonging to the same farm and showed equal sequence type, suggesting a possible spread of a specific
253 clone in this farm more than a picture of the situation in the country. It is also remarkable, the high rate of
254 plasmid AmpC (pAmpC) beta-lactamase, belonging in all cases to CMY-2 variant, identified among
255 commensal *E. coli* from healthy chickens in Tunisia (Ben Sallem *et al.* 2012b, Mnif *et al.* 2012, Maamar *et*
256 *al.* 2016), Algeria (Belmahdi *et al.* 2016) and septicemic broilers in Egypt (Ahmed *et al.* 2013). CMY-2,
257 together with DHA-1, is the most frequently detected pAmpC variant among human clinical isolates in
258 Africa (Storberg 2014).

259 Considering carbapenemase production among *E. coli* isolates in the African continent, although many
260 descriptions have been reported in humans (Robin *et al.* 2010, Moquet *et al.* 2011, Barguigua *et al.* 2013,
261 Leski *et al.* 2013, Mushi *et al.* 2014) and the hospital environment (Chouchani *et al.* 2011) over the last
262 five years, it has not been until very recently when the first carbapenemase-producing *E. coli* was detected
263 in pets (Yousfi *et al.* 2016) and livestock animals (Braun *et al.* 2016). This last study, conducted in different
264 dairy cattle farms from Egypt, reported 4 *E. coli* strains harboring *bla*_{OXA-48} and one carrying *bla*_{OXA-181}
265 carbapenemase genes, all of them phenotypically resistant to meropenem and imipenem. It is also important

266 to mention the detection of an ertapenem-resistant ESBL-*E. coli* strain in a chicken from Nigeria. However,
267 no carbapenemase was detected in this strain. The resistant phenotype was attributed to a synergistic effect
268 between CTX-M-15 production and dysfunctionality of outer membrane proteins (Ojo *et al.* 2015).
269 Although CTX-M-15 was the predominant ESBL enzyme detected among livestock in many African
270 countries such as Nigeria, Tanzania or Egypt, only in two surveillances this *bla* gene was shown to be
271 associated with the human epidemic clone ST131. These ST131-CTX-M-15-producing *E. coli* isolates were
272 identified in a healthy swine from Tanzania (Seni *et al.* 2016) and the blood of 3 septicemic broilers from
273 Egypt (Ahmed *et al.* 2013). ST405-D strains, which have also been considered vehicles driving CTX-M-
274 15 worldwide and are frequently associated with clinical conditions in humans (Ben Slama *et al.* 2011,
275 Alghoribi *et al.* 2015, Day *et al.* 2016), were also identified among healthy chickens and cattle in Tunisia
276 and Nigeria, respectively. Other clones, such as those belonging to ST10 Complex (ST10 or ST617), are
277 equally highly distributed among various livestock species and humans in many African countries like
278 Nigeria (Aibinu *et al.* 2012, Ojo *et al.* 2016) or Tanzania (Mshana *et al.* 2016, Seni *et al.* 2016). Concerning
279 the distribution of ESBL/pAmpC producing *E. coli* strains according to the major phylogenetic groups (A,
280 B1, B2, D), the majority of the studies showed a dominance of phylogroups A and B1 over isolates from
281 healthy FPA and derived meat (Ben Slama *et al.*, 2010, Schaumburg *et al.* 2014, Abdallah *et al.* 2015,
282 Rasmussen *et al.* 2015, Maamar *et al.* 2016, Seni *et al.* 2016). Although phylogroup D has also been
283 detected quite frequently among ESBL/AmpC producers from healthy poultry (Mnif *et al.* 2012),
284 phylogroup B2 was present at lower rates in all the studies considered in this review. Regarding publications
285 on diseased animals, few of them provide a phylogenetic analysis of the ESBL isolates, making it difficult
286 to generalize.

287 However, epidemiology of ESBL involves not only a clonal spread of bacteria but also the horizontal
288 transfer of *bla* genes via plasmids and/or other transferable genetic structures. In this sense, although
289 molecular information on mobile elements is scarce in Africa, there are some works that prove the
290 importance of specific plasmids in the geographical and even interspecies dissemination of ESBL
291 determinants (Grami *et al.* 2015, Ojo *et al.* 2016, Seni *et al.* 2016). In this regard, as it has been previously
292 shown in other continents, the dominance of IncF-type plasmids carrying the *bla*_{CTX-M-15} gene among *E. coli*
293 from human and animal origin has been also reported in Africa (Grami *et al.* 2014, Ojo *et al.* 2016, Seni *et*
294 *al.* 2016). But this emergent CTX-M-15 encoding gene has been also associated with other less common
295 replicon plasmids such as IncY-type, which have shown to be very prevalent in animal isolates from

296 Tanzania. Interestingly, in the same surveillance, the presence of an Inc-untypeable plasmid, co-harboring
297 *bla*_{CTX-M-15} and *qnrS1* genes and genetically homologous to a previously described one from human origin
298 in Nigeria, was detected in various animals. In Tunisia, where CTX-M-1 enzyme is broadly disseminated
299 among poultry, two molecular studies confirmed its frequent association with IncII/ST3 plasmids (Grami
300 *et al.* 2014; Ben Sallem *et al.* 2014). One of these surveys showed a comparison of clonal lineages and
301 plasmids from healthy humans, animals and pets in Tunisia and demonstrated that *bla*_{CTX-M-1}-carrying
302 IncII/ST3 plasmids and *bla*_{CMY-2}-carrying IncII/ST12 plasmids play a crucial role in the spread of these
303 β -lactamases among different host and ecosystems (Ben Sallem *et al.* 2014). Likewise, the other work
304 concluded that examined *bla*_{CTX-M-1}-harboring IncII/ST3 plasmids of *E. coli* from Tunisian poultry and
305 pets were identical or highly similar to those reported in various animal species in Europe (Dahmen *et al.*
306 2012) and in some humans infected with *S. enterica* (Cloeckert *et al.* 2010), highlighting the international
307 role of these mobile elements in CTX-M-1 epidemiology. In addition to plasmid promiscuity, the spread of
308 CTX-M determinants is also favored by flanking transposable elements, which can co-mobilise *bla* genes.
309 This is the case of *ISEcp1* element, usually located immediately upstream *bla*_{CTX-M} and *bla*_{CMY-2} genes.
310 Occasionally, it appears truncated by other insertion sequences such as IS26 (Jouini *et al.* 2007), IS10 (Ben
311 Sallen *et al.* 2012) or IS5 (Maamar *et al.* 2016), which could affect the mobilization and/or the expression
312 of the β -lactamase gene (Lahlaoui *et al.* 2014, Maamar *et al.* 2016).

313

314 ESBL, PLASMID-MEDIATED AMP_c AND CARBAPENEMASE PRODUCING *E. coli* IN ANIMAL- 315 DERIVED FOOD

316 There are a wide number of papers in Africa concerning the microbiological quality of different types of
317 food derived from FPA (milk, cheese, meat, eggs, etc). Most of them are focused on the detection of
318 pathogenic bacteria (especially *E. coli* 0157) in order to determine the rate of contamination of the studied
319 product (Bankole *et al.* 2014, Ombarak *et al.* 2016) or even to analyze the resistance and/or virulence
320 patterns of bacteria present in milk collected from cattle suffering mastitis (Ahmed *et al.* 2011, Kateete *et*
321 *al.* 2013). However, there are just a few articles regarding the prevalence and characterization of
322 ESBL/pAmpC *E. coli* among food-products derived from healthy animals in different countries of the
323 African continent. Remarkable data extracted from these reports is summarized below the dotted lines in
324 Table 1.

325 All the studies but two, which included different animal species (Jouini *et al.* 2007, Ben Slama *et al.* 2010),
326 were carried out on meat samples or swabs collected from poultry carcasses. This fact may be a reflection
327 of the religious and cultural factors which influence the diet of people in many African countries. General
328 prevalence of ESBL/pAmpC *E. coli* among meat products was an average of 16.3%, although the risk of
329 cross-contamination at the slaughterhouses should be considered. This percentage is significantly lower
330 than those reported in many European countries such as Spain (84%-93.3%) (Egea *et al.* 2012, Ojer-Usoz
331 *et al.* 2013) or the Netherlands (76.8%) (Overdeest *et al.* 2011), which may indicate that resistance rates
332 are higher in industrial large-scale meat production.

333 Figure 1B shows the diversity of ESBL/pAmpC types detected among poultry (chicken and turkey), beef
334 and sheep meat in different countries from Africa. Comparing with the distribution of enzymes detected
335 among *E. coli* isolates from faecal poultry microbiota, a higher percentage of CTX-M-14 was identified
336 among derived meat products. It is important to consider different factors that can help to understand these
337 differences. Firstly, it is difficult to elucidate the animal, human or environmental origin of the isolates due
338 to the fact that contamination could take place at all the stages of the food processing chain including
339 processing, packing and distribution. Moreover, there are studies that demonstrate the contribution of
340 imported meat from industrialized countries to the emergence of ESBL and multidrug resistant isolates in
341 developing countries (Schaumburg *et al.* 2014, Rasmussen *et al.* 2015). One of these works, carried out in
342 Ghana, showed a significantly higher rates of ESBL/pAmpC-*E. coli* in imported chicken meat (32.9%)
343 compared to locally reared chickens (13.9%). CTX-M-15 was the most frequently detected ESBL variant.
344 However, *bla*_{CTX-M-2} was also identified in two samples, one of them from an imported chicken thigh from
345 Brazil, where this CTX-M enzyme is well known to be the most prevalent, together with CTX-M-15, among
346 clinical isolates (Rocha *et al.* 2016). In the other study, conducted in Gabon, only imported frozen chicken
347 meat samples were screened and a predominance of CTX-M-14, followed by CTX-M-1, was detected.
348 Interestingly, all ESBL-*E. coli* isolates were identified in meat imported from Spain and, consequently, the
349 distribution of ESBL-type was shown to be in accordance to the proportion of CTX-M subtypes described
350 in this country (Egea *et al.* 2012, Ojer-Usoz *et al.* 2013).

351 Regarding studies on food from healthy animals, only two performed a molecular study of the clonal
352 lineages associated with the spread of ESBLs (Jouini *et al.* 2013, Rasmussen *et al.* 2015). Considering data
353 from both reports, a high clonal diversity was observed, being slightly prevalent *E. coli* isolates belonging
354 to ST155, ST10 and ST38. These sequence types have been previously identified in humans and livestock

355 animals (Ben Sallem *et al.* 2012a, Day *et al.* 2016), also associated to CTX-M-1 group ESBLs, suggesting
356 a potential implication of the food chain in the spread of these resistant clones among different settings.
357 Although none of the studies performed in Africa have reported carbapenemase-producing *E. coli* isolates
358 among food derived from livestock animals, it is important to highlight the detection of twelve NDM-
359 producing *Klebsiella* isolates in retail chicken meat samples from Egypt (Abdallah *et al.* 2015). Moreover,
360 a recent study conducted in the same country has demonstrated a high rate of carbapenemase-producing
361 *Klebsiella pneumoniae* strains, harboring *bla*_{NDM}, *bla*_{OXA-48} and/or *bla*_{KPC} genes in broiler chickens (35%),
362 drinking water (25%) and humans living in contact with chickens (56%) (Hamza *et al.* 2016). Further
363 studies based on multilocus sequence typing (MLST) or whole-genome sequencing should be performed
364 to determine the potential inter-host transmission of these strains through direct contact and/or ingestion of
365 derived contaminated meat.

366

367 CONCLUSIONS

368 The increasing rate of antimicrobial resistance bacteria is a global problem that affects both human and
369 animal ecosystems. In the African region, the real magnitude of this issue is difficult to estimate due to the
370 fact that antimicrobial resistance surveillance programmes are limited to a few countries (Ndihokubwayo
371 *et al.* 2013). The potential inter-host spread of resistant clones or even their encoding determinants through
372 direct contact or ingestion of contaminated food pose a worrisome public health risk. Although in the last
373 decade the number of surveys in Africa has increased, available information is still scarce in many
374 countries, especially in Southern and Eastern Africa. Moreover, further molecular studies are required to
375 characterize the prevailing clonal lineages and plasmids harboring resistance encoding genes in this
376 continent. The combination of factors such as the uncontrolled use of antimicrobials in livestock
377 production, certain farming practices and manure management systems as well as close contact with animal
378 may favor the selection of AMR bacteria and transmission from animals to humans and vice versa.
379 Additionally, international livestock and derived meat trade is leading to an emergence in the dissemination
380 of resistant strains and genetic determinants. Resistance to “old” antimicrobials, such as tetracycline,
381 penicillins or sulphonamides, which has been in use for a long time both in human and veterinary medicine
382 is not surprising. However, in the last years a significant increase in the prevalence of resistance to other
383 clinically critical drugs (i.e. quinolones and 3rd/4th generation cephalosporins) has been reported among
384 commensal *E. coli* from healthy livestock species. In most cases, resistance to both antimicrobial families

385 is co-selected and disseminated not only by clonal spread, but also horizontally via plasmids carrying *qnr*
386 or *aac(6)Ib-cr* and *bla* genes (especially, of the CTX-M group). Worryingly, carbapenem and colistin
387 resistant *E. coli* strains are also emerging among husbandry animals in Africa, which demonstrate the urgent
388 need of a better control of the usage of veterinary drugs and the implementation of effective surveillance
389 programmes to stop the dissemination of MDR *E. coli* strains.

390

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645 *Conflicts of interest:* Do not exist in relation with this manuscript.

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648 FIGURE LEGENDS:

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650 **Fig 1.** Husbandry animal species (A) and food products (B), prevalence of ESBL/pAmpC producing *E. coli*
651 (%) and distribution of ESBL/pAmpC enzymes detected in the African continent. Prevalence at each
652 location was calculated considering the global data of published studies [prevalence (%) / number of samples
653 (number of studies considered at each location)]. ESBL/pAmpC enzymes are ordered, from left to right,
654 with respect to its detection frequency. ^a Rectal samples from cattle (n=210) and environmental samples
655 from the stalls (n=56) were considered. ^b Only a few samples were sequenced (n=25); ^c Imported and locally
656 produced chicken meat; ^d Imported chicken meat.

Table 1. Summarize of data extracted from prevalence studies on ESBL/pAMPc producing *E. coli* in healthy husbandry animals and derived food products in Africa.

Region	Country	Study Period	Animal species	Type of sample	Detection test	Sample size (number of animals)	ESBL/pAmpC-producing <i>E. coli</i> prevalence (% of total animals/samples tested)	ESBL/pAmpC enzymes (% in relation with total n° of ESBL/pAmpC)	MLST (number of ESBL/pAmpC-producing <i>E. coli</i> isolates)	Reference
Northern Africa	Tunisia	2010	Chickens	Faeces	Double disk test PCR Sequencing	136	42	CTX-M-1 (58.2), CTX-M-15 (6.0), CMY-2 (37.3)	NS ^a (025b-ST131 clone discarded by PCR)	Mnif <i>et al.</i> 2012
	Tunisia	2011	Sheep, chickens, cattle, horse, rabbit, dromedaries	Faeces	Double disk test PCR Sequencing	80	13.8	CTX-M-1 (81.8), CMY-2 (18.2)	NS ^a	Ben Sallem <i>et al.</i> 2012
	Tunisia	2013	Chickens	Faeces	Double disk test PCR Sequencing	65	26.1	CTX-M-15 (88.2), CTX-M-1 (5.8), unknown (5.8)	NS ^a	Kilani <i>et al.</i> 2015
	Tunisia	2013	Chickens	Faeces	Double disk test PCR Sequencing	137	35	CTX-M-1 (60.4), CTX-M-15 (10.4), CTX-M-14 (2.1), CMY-2 (27.1)	ST2197 (9), ST58 (7), ST405 (6), ST155 (3), ST93 (3), ST349 (3), ST542 (2), ST1196 (2), ST212 (2), ST117 (2), ST4968 (1), ST1431 (1), ST350 (1), ST1056 (1)	Maamar <i>et al.</i> 2016
	Algeria	NS ^a	Chickens	Gastrointestinal and Reproductive tracts	Double disk test PCR	9	55.5	CTX-M-type (100)	NS ^a	Mezhoud <i>et al.</i> 2015
	Algeria	2014	Chickens	Intestinal swabs	Double disk test PCR Sequencing	61	32.8	SHV-12 (70), CTX-M-1 (10), CMY-2 (20)	ST744 (4), ST38 (1), ST1011 (12), ST2179 (1), ST5086 (2)	Belmahdi <i>et al.</i> 2016
	Egypt	2014	Cattle	Rectal swabs	VITEK® 2 Multiplex microarray assays	266 (210 from cattle, 56 environmental samples from the stalls)	42.8 2.25 (carbapenemase-producing <i>E. coli</i>)	CTX-M-15 (46.4), CTX-M-9 (2.7), TEM-type (40.5), SHV-type (0.4), CMY-type (9.9) Carbapenemase encoding genes: OXA-48 (83.3, n=5), OXA-181 (16.7, n=1)	NS ^a	Braun <i>et al.</i> 2016
	Tunisia	2007	Chickens, cattle, horses, turkeys, sheep, fishes	Faeces/Meat	Double disk test PCR Sequencing	78	12.8 (ESBLs were only detected in food samples, representing 26% of them)	CTX-M-1 (60), CTX-M-14 (20), CTX-M-8 (10), SHV-5 (10)	NS ^a	Jouini <i>et al.</i> 2007
	Tunisia	2007	Chickens, turkeys, sheep, cattle, fishes, horse	Meat	Double disk test PCR Sequencing	79	16.4	CTX-M-1 (92.8), CMY-2 (7.2)	NS ^a	Ben Slama <i>et al.</i> 2010
	Tunisia	2009	Chickens, Turkeys	Meat	Double disk test PCR	55	0	-	NS ^a	Soufi <i>et al.</i> 2009
Egypt	2013	Chickens	Meat	Double disk test PCR Sequencing	112 Enterobacteriaceae (38 <i>E. coli</i>)	61.6% of the meat samples (10/38 <i>E. coli</i> isolates; 26.3%)	Among all Enterobacteria isolates: CTX-M-15 (63.8), other types belonging to CTX-M-1-group (4.3), CTX-M-9 group (2.9), SHV-type (36.2)	NS ^a	Abdallah <i>et al.</i> 2015	

^a NS: Not specified.

Table 1. Cont

Region	Country	Study Period	Animal species	Type of sample	Detection test	Sample size (number of animals)	ESBL/pAmpC-producing <i>E. coli</i> prevalence (% of total animals/samples tested)	ESBL/pAmpC enzymes (% in relation with total n° of ESBL/pAmpC)	MLST (number of ESBL/pAmpC-producing <i>E. coli</i> isolates)	Reference
Eastern Africa	Tanzania	2014	Sheep, goats, chickens, pigs, cattle, dogs	Rectal/Cloacal swabs	VITEK® 2 Whole-Genome Sequencing (25 <i>ESBL-E. coli</i> isolates)	600	20.8	Among the 25 sequenced <i>ESBL-E. coli</i> isolate: CTX-M-15 (100)	Among the 25 sequenced <i>ESBL-E. coli</i> isolate: ST617 (7; cattle, chicken, dog, pig), ST1303 (3; cattle, pig), ST2852 (3; pig, dog), ST131 (2; pig, dog)	Seni <i>et al.</i> 2016
	Zambia	2013-2014	Cattle	Faeces	-	376	0	-	-	Mainda <i>et al.</i> 2015
	Zambia	NS ^a	Chickens	Poultry swabs samples collected at the slaughterhouse	Double disk test PCR	384	20.1	CTX-M-type (92.2), SHV-type (9.1), TEM-type (29.9)	NS ^a	Chishimba <i>et al.</i> 2016
Western Africa	Ghana	2007	Humans, chickens, sheep, goats, pigs	Faeces	-	268	0	-	NS ^a	Donkor <i>et al.</i> 2012
	Nigeria	2006	Chickens, pigs	Faeces	PCR Sequencing	200	0.5	CTX-M-15 (100)	NS ^a	Fortini <i>et al.</i> 2011
	Nigeria	NS ^a	Cattle, pigs	Faeces	Double disk test PCR	350	20.57	CTX-M-type (70.8)	NS ^a	Olowe <i>et al.</i> 2015
	Nigeria	2009-2014	Chickens	Faeces/Meat	Double disk test PCR Sequencing	405	1 (ESBLs were only detected in chicken faeces, representing 1.4% of them)	CTX-M-15 (100)	ST10 (3), ST405 (1)	Ojo <i>et al.</i> 2016
	Gabon	2011-2012	Chickens	Meat (imported)	VITEK® 2 Double disk test PCR Sequencing (only CTX-M genes)	60	23.3	CTX-M-14 (35.3), CTX-M-1 (23.5), CTX-M-32 (5.9), SHV-type (41.2), TEM-type (35.3)	NS ^a	Schaumburg <i>et al.</i> 2014
Ghana	NS ^a	Chickens	Meat (local/imported)	Double disk test PCR Sequencing	188	15.4	CTX-M-15 (34.5), CTX-M-1 (3.4), CTX-M-61 (3.4), CTX-M-1 group unknown subtype (10.3), CTX-M-2 group unknown subtype (6.9), blaCIT gene positive (not sequenced) (27.6), unknown ESBL/pAmpC enzyme (13.8)	ST38 (4), ST10 (2), ST354 (2), ST1158 (1), ST2167 (1), ST117 (1), ST4121 (1), ST542 (1), ST2461 (1), ST4120 (1), ST4028 (1), ST642 (1), ST162 (1), ST1304 (1), ST212 (1), ST124 (1), ST1431 (1), ST4122 (1), ST156 (1), ST155 (1), ST205 (1)	Rasmussen <i>et al.</i> 2015	

^a NS: Not specified.

Table 2. Distribution and clonal lineages of ESBL/pAMPc producing *E. coli* in sick husbandry animals in Africa

Country	Study Period	Animal species	Disease	Type of sample	Sample size (number of animals)	ESBL/pAmpC-producing <i>E. coli</i> prevalence (% of total animals/samples/isolates tested)	ESBL/pAmpC enzymes (% in relation with total n° of ESBL/pAmpC)	MLST (number of ESBL/pAmpC-producing <i>E. coli</i> isolates)	Reference
Tunisia	2011-2012	Chickens	Colibacillosis	Faeces	193	4.1	CTX-M-1 (87.5), CTX-M-9 (12.5)	NS ^a	Grami <i>et al.</i> 2013
Tunisia	2010-2011	Chickens	Colibacillosis	Liver	60	0	-	-	Grami <i>et al.</i> 2014
		Cattle	Clinical mastitis	Milk	10	10	CTX-M-15 (100)	ST10 (1)	
Algeria	2006-2011	Chickens	Colibacillosis	Internal organs (spleen, liver, pericardium, ovary)	NS ^a (220 <i>E. coli</i> isolates)	5	CTX-M-15 (100)	NS ^a	Meguenni <i>et al.</i> 2013
Egypt	2008	Cattle	Clinical and sub-clinical mastitis	Milk	86 (99 samples, 42 <i>E. coli</i> isolates)	0 (ESBL were detected among other gram-negative bacteria species)	-	-	Ahmed <i>et al.</i> 2011
Egypt	2011	Chickens	Septicemia	Heart blood	NS ^a (100 samples, 73 APEC isolates)	27.4	CMY-2 (55), CTX-M-15 (30), SHV-2 (15)	O25b-ST131 (3) (PCR assay)	Ahmed <i>et al.</i> 2013
Uganda	2010-2011	Cattle	Clinical mastitis	Milk	97 (97 samples, 12 <i>E. coli</i> isolates)	0	-	-	Kateete <i>et al.</i> 2013

^a NS: Not specified.

Fig.1.

