Antibiotic use and resistance patterns in *Escherichia coli* isolates from rabbit farms in Korhogo, Côte d'Ivoire

.

ABSTRACT

Backround: The use of antimicrobials in rabbit farming is essential for treating sick animals, controlling disease outbreaks, preventing illness, and promoting growth. However, their overuse and improper application contribute to the development and spread of resistant bacteria, posing a significant public health threat. This study aimed to assess antibiotic use and resistance patterns in *Escherichia coli* isolates from rabbit farms in Korhogo, Côte d'Ivoire**.**

Methodology: Questionnaire was sent to 48 farmers, followed by the collection of fresh rabbit droppings from 25 farms. *Escherichia coli* was detected by inoculating droppings on chromogenic medium, followed by identification on the basis of biochemical characteristics. Resistance was studied using the Müeller-Hinton agar disc-diffusion method using12 antibiotics.

Results: Less than one-third of farmers (29.2%) used antibiotics, with oxytetracycline being the most commonly used. Antibiotics were primarily administered for digestive, skin, and respiratory diseases. The 56 *E. coli* isolates were highly resistant to colistin (82.1%), tetracycline (53.6%), amikacin (37.5%) and trimethoprim-sulfamethoxazole (32.1%). Resistance rate to cefotaxime, ceftriaxone, aztreonam, nalidixic acid and ciprofloxacin were very low (< 4%). However, all isolates were sensitive to amoxicillin + clavulanic acid and imipenem. The prevalence of ESBL *E. coli* was 3.6%. A significant number of *E. coli* isolate had a MAR index > 0.2.

Conclusion: This study highlights the poor use of antibiotics on rabbit farms in Korhogo, with high levels of resistance to certain antibiotics of critical importance in human medicine. Hence the need to intensify awareness-raising and training of farmers in the rational use of antibiotics, in order to reduce the risk of dissemination of resistant bacteria within the population.

Keywords:*Rabbits, antibiotics, antimicrobial resistance, farmers practices, Escherichia coli*

1. INTRODUCTION

Antimicrobial resistance (AMR) poses a worldwide public health concern that undermines the provision of effective treatments, leading to limited and more harmful therapeutic options and increased risk of death [1]. There were an estimated 4,95 million deaths associated with bacterial AMR in 2019, including 1.27 million deaths attributable to bacterial AMR. Without preventative measures, it is estimated that by 2050, AMR could potentially become the world's primary cause of death mainly in sub-Saharan Africa, which is considered excepted to be one of the regions with the highest AMR-related mortality rates across all ages [2].

E. coli is a bacterium naturally present in the intestinal tract of rabbits and other warm-blooded animals. It can cause extra-intestinal infections (such as urinary tract infections or septicemia). Antimicrobials are applied in livestock farming for number purposes such as therapeutic (treating sick animals), meta phylaxis (control treatment of whole herd in case of disease outbreak), prophylaxis (preventive treatment), and growth promotion. Therefore,the selection pressure of multi-resistant bacteria due to massive use of antibioticsin farming is high. Thefecal flora of animals contains a relatively high proportion of resistant bacteria making treatment difficult and causing a worldwide public health issue [3 ; 4].Also, although commensal bacteria are normally harmless, they may constitute a reservoir of resistance genes that may be transmitted to pathogenic bacteria [5].

In Africa, the use and control of antimicrobials, remains largely unregulated [6].Some African studies focused on the antimicrobial usage in livestock indicate that there is an irrational use due to the unregulated access and administration of veterinary drugs [7, 8]. Even though in many African countries it is illegal for any person who is not a registered veterinarian to administer antibiotics, there are no strict control measures, and often farmers purchase and administer a drug without veterinary prescription and supervision [7, 8]. The data of different surveys conducted in Nigeria [7], Zambia [8] and South Africa [9] about the sales of antimicrobials for farm animals indicate that, even considering variations between countries or animal species (mammals or poultry), tetracyclines and beta-lactams (mainly penicillin) are among the first four leading antibiotics commonly employed in livestock animal production. Sulphonamides and macrolides are also frequently consumed antimicrobials, this last group (with reference specifically to tyrosine) has been reported as the most extensively sold in South Africa for treatment and prevention of veterinary diseases and also, at subtherapeutic levels, as a registered growth promoter [9]. To limit the misuse of antibiotics affecting the spread of AMR, it is crucial to understand the factors influencing the knowledge of antibiotics and practices among small-scale farmers

The national plan to combat antimicrobial resistance 2021-2025 of Cote d'Ivoire, emphasizes the need for an effective "One Health" approach, involving the coordination of many national and international sectors and players, including human medicine, veterinary medicine, agriculture, finance, the environment and well-informed consumers. This program includes monitoring antibiotic use in the livestock sector and improving awareness of antibiotic use through educational campaigns. The majority of production in Cote d'Ivoire are taken in at small-scale levels and provide investment opportunities and additional income for families. The latest of the few studies on AMR showed misuse of antibiotics and the presence of multidrug-resistant *E. coli* among cattle [10], pigs [11], and poultry [12]. However, data concerning antibiotic use practices and the level of *E. coli* resistance in rabbit farms are no-existent.

Therefore, this study assessed the antibiotic use and practices among rabbit farmers in the Korhogo area. Fecal samples were collected from rabbit farms, and E. coli strains were isolated and analyzed for antibiotic resistance to provide valuable insights for promoting the rational use of antibiotics

2. MATERIAL AND METHODS

2.1 Study area

This study was conducted from November 2022 to May 2023 in Korhogo (Figure 1). This town is located in the Northenpartof Cote d'Ivoire, at 9° 27' 41'' N, 5° 38' 19'' W, witha total town area of 12,500 km^2. Korhogo is part of the Savanes region, bordering Mali and Burkina

Faso. Korhogo is 635 km from Abidjan, the country's economic capital and largest city, and 331 km from Yamoussoukro, the political capital.

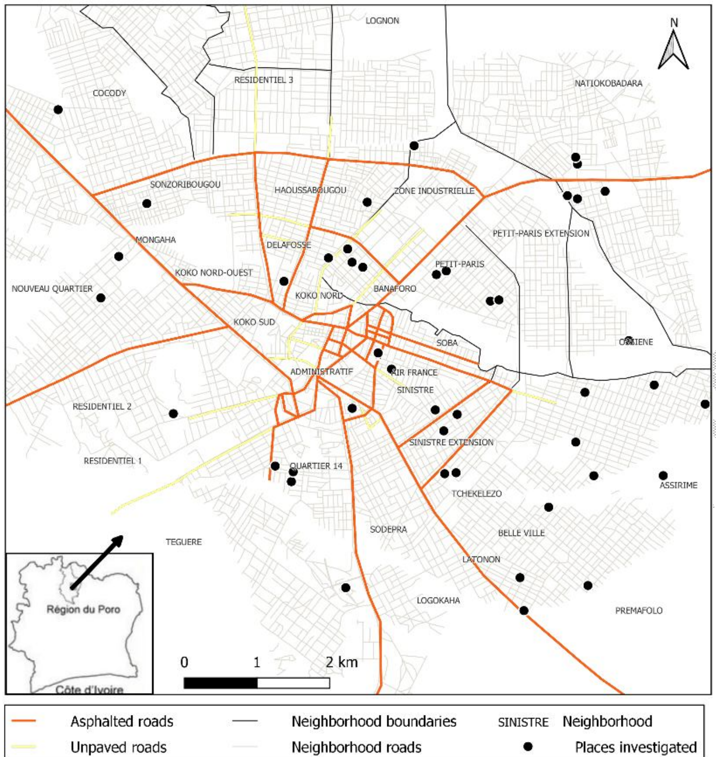

Figure 1. Study area

2.2 Study design and data collection

The first stage was the census and contact phase with the various farmers, followed by the second stage, which involved the survey and collection of rabbit feces. The questionnaire consisted of a brief introduction, which explained the purpose of the questionnaire, the importance of the respondent's participation and a statement guaranteeing confidentially.

A semi structured questionnaire with five different sections. In the first section demographic information such as the gender of farmer, age, (in year), matrimonial status, level of education, experience in farmer, main of occupation. In the second section, consisted of questions related to attitudes and practices. The third section the respondents were asked about types of antibiotics commonly used, the last session consisted of questions related to attitudes and practices. All questions were closed-ended as respondents were given options to select.

A pool of three-day-old fresh droppings was randomly collected from 3 different cages on each rabbit farm. with a sterile plastic spatula, from each selected farm and put in a 30 mL sterile container. The sample were carefully labeled and transported to the University Peleforo GON COULIBALY within 1-6h in a cooler containing cold accumulators, and stored at -20°C in a freezer before microbiological analysis. Because not all farmers accepted, only 25 samples were obtained. Because the sampling process did not harm the animals, ethical approval was not required for the study.

2.3 Isolation of *E. coli* and antimicrobial susceptibility testing

In the laboratory, 1 g of fecal samples was inoculated into 9 ml of distillated water and incubated at 37° C. for 18 h. Subsequently, the cultures were streaked on RAPID E coli and incubated overnight at 37° C. Tree colonies that showed growth characteristics of E. coli (violet colonies) were randomly selected and subjected to indole and uree tests for identification of E. coli isolates. Confirmed *E. coli* colony per sample was randomly selected for antibiotic sensitivity testing. Selected *E. coli* isolates for sensitivity testing were streaked onto ordinaire agar, incubated overnight and subjected to sensitivity tests the following day.

2.4 AntimicrobialSusceptibility Pattern and ESBL Screening of the Isolated*E. coli*

2.4.1Antimicrobial susceptibility testing

Antimicrobial sensitivity testing was carriedout with the disk diffusion method on Mueller-Hinton agar according to the method reported by the SociétéFrançaise de Microbiologie [13]. Twelve antimicrobial agent disks were selected because they are commonly used to treat bacterial diseases in both humans and animals; these. were amoxicillin-acid-clavulanic (20/10 µg), Ceftazidime (30 µg), Cefotaxime (30 µg), Aztreonam (30 µg), Ceftriaxone (30 µg), Imipenem (10 µg), Ciprofloxacin (5 µg) ; Amikacin (10 µg), Acid nalidixic (30µg), Tetracycline (30 µg), Trimethoprim sulfamethoxazole (1,25/23,75 µg) and Colistin (10 µg). After inoculation by E. coli isolates and antibiotic disks' placement, Muller-Hinton agar plates were incubated at 37 °C for 18 h. After incubation, the inhibition zones were measured using calipers to the nearest milli-meter and interpreted as susceptible, intermediate and resistant [13].

2.4.2Double Disc Synergy Test

To confirm ESBL production, DDST was performed as described elsewhere [14]. Briefly, Amoxicillin-clavulanic acid (AMC, 30 µg) applied with a distance 20 mm center-to-center to that of each antibiotic disc (30-µg) of third-generation cephalosporin (Cefotaxime and Ceftriaxone) and fourth-generation cephalosporins (Ceftazidime) or monobactam '(Aztreonam)on Mueller-Hinton Agar (MHA) plates. Clear extension of the edge of the inhibition zone of cephalosporin toward the AMC disc was interpreted as positive for ESBL production.

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E. coli ATCC 25922 was used as a reference strain for quality control of antibiotic sensitivity testing. The MAR index was calculated following the prescription of Kuperman as number of antibiotics to which isolate is resistant divided by the total number of antibiotics against which isolate was tested.

2.5 Statistical analyses

Data were processed with Microsoft Excel 2019 and analyzed as descriptive statistics.

3. RESULTS

3.1 Farmer's socio-demographics characteristics

The results showed that among the respondents 45 (93.8%) were men, and 3 (6.3%) were women with an average age of 31.9 years. With regard to the level of education, more than half (58.3%, 28/48) had attained higher education, 10 (20.8%) had secondary education, (6.3%) primary education and 7 (14.71%) had no formal education. About experience in rabbit farming, 34 (70.8%) of the farmers have more than 2 years' experience. With regard to training among farmers, the vast majority (72.9%, 35/48) claim not to have undergone any training. Also, farmers were mainly carried out by other than farming (97.9%) (Table 1).

Table 1. Socio-demographic characteristics

Characteristics	n (%)
Gender	
Men	45(93.8)
Women	3(6.3)
Mean age (Median, Mode)	31.90 (29 ;30)
Education level	
Illiterate	7(14.71)
Primary school	3(6.3)
Secondary school	10(20.8)
University school	28(58.3)
Experience in farming (years)	
Less than 1	6(12.5)
1 – 2	8(16.7)
More than 2	34(70.8)
Training	
No	35(72.9)
Yes	13(27.1)
Main occupation	
Rabbits farming	1(2.1)
Other than farming	47(97.9)

3.2 Practices, recent diseases in the farm, antimicrobial used in farms

Practices and use of antibiotics by rabbit farmers are reported in Table 2. About less than one in three of respondents (29.2%) reported to use antibiotics on their rabbits, whereas the rest (70.8%) reported having never used antibiotics on their rabbits. Veterinary pharmacies (92.9%) were the main source of antibiotics for farmers. Among the 14 respondents who used antibiotics, the majority claimed to use antibiotics for infection treatment (71.4%, 10/14). Additionally, antibiotics were mainly administered by injection (57.1%, 8/14), in drinking water (28.6%, 4/14), or both (14. 3%, 2/14). About under half the farms (42.9%,) have a one-week course, 6 (42.9%) have a one-month course and 2 (14.2%) administer the antibiotic when the female has farrowed or if necessary. About under half of farmers (42.9%) say they never estimate the weight of their animals before administering antibiotics. Fewer than one in 3 (28.6%) say they stop administering the antibiotic once the signs of disease have disappeared, 4 (28.6%) take into account the duration of use indicated on the leaflet, and only 1(7.1%) stop treatment only when the antibiotic is finished. The vast majority of farmers (85.7%) claim not to respect the waiting period after applying the drug to rabbits.

Table 2. Practices and use of antibiotics

Elements	***n (%)***
Use antibiotics	
No	34(70.8)
Yes	14(29.2)
Source of antibiotics	
From veterinary pharmacy	13(92.9)
From other than veterinary pharmacy	1(7.1)
Purpose	
Treatment	10(71.4)
Prevention (prophylaxis)	3(21.4)
Growth promotion	1(7.2)
Administration route	
Drinking water	4(28.6)
Injection	8(57.1)
Drinking water and injection	2(14.3)
Frequence of administration	
Week	6(42.9)
Month	6(42.9)
After parturition	2(14,2)
Estimated animal weight before antibiotic administration	
Never	6(42.9)
Sometimes	2(14.2)
Always	6(42.9)
Antibiotics discontinuation criteria	
Signs of illness have disappeared	4(28.6)
According to the duration indicated on the package leaflet	5(35.7)
As recommended by veterinarian	4(28.6)
When antibiotic is finished	1(7.1)
Respect for waiting times after treatment	
No	12(85.7)
Yes	2(12.3)

Table 3 reported diseases for which antibiotics are used by farmers. Respiratory diseases (38.71 %), skin disease (30.65%) and digestive diseases (25.81 %) are the main causes of antibiotics used by farmers. In over hand, antibiotics are used too for pain (3,23 %), and post-parturient infection (1.61 %;).

Table 3. Diseases treated with antibiotics on 20 small farms in korhogo, Côte d'Ivoire 2023

Elements	***n (%)***
Diseasestreated(n=62)	
Respiratory disease	24(38.71)
Skin disease	19(30.65)
Digestive disease	16(25.81)
Pain	2(3.23)

Post-parturient infection	1(1,61)

The frequency with which antibiotics used on the various farms were cited is shown in **Table4**. The main antibiotics were oxytetracycline (52.94%; 9/17), penicillin (17.65%; 3/17), cefoxitin (11.6%; 2/17), while colistin, sulfadine and tylosin, were each cited by 5.88% (1/17) (Fig. 2).

Table 4. Antibiotics use by farmers

Elements ***Antibiotics (n=17)***	**n (%)**
Cefoxitin	2(11.6)
Colistin	1(5.88)
Oxytetracycline	9(52.94)
Penicillin	3(17.65)
Sulfadine	1(5.88)
Tylosine	1(5.88)

Fig. 2. Antimicrobial use by rabbit's farmers

3.3 Isolation of *E. coli*

From November 2022 to May 2023, a total of 58 isolateswere obtained, from 25 fecal samples received from 25 different rabbit farms. Two strains have been missed so 56 were tested for sensitivity to twelve antibiotics.

3.4 Antimicrobial susceptibility testing

From **table5**, all strains were sensitive to amoxicillin+ clavulanic acid and imipenem. We detected high resistance to colistin (82.1 %), tetracycline (53.6 %), amikacin (37.5 %) and trimethoprim-sulfamethoxazole (32.1 %) and low resistance to cefotaxime (1.8 %) nalidixic acid (1.8%), ceftriaxone (3.6 %), aztreonam (5.4 %), ceftazidime (7.1 %), ciprofloxacin (3.6 %). In more, 2 strains were phenotype ESBL (Fig. 3).

Table 5. Susceptibility of *E. coli* to antibiotics (S: susceptible; I: intermediate; R: resistant)

N°	Antibiotics	Number of *E.coli* (%)		
		R	**I**	**S**
1	Amoxicillin/clavulanic	0(0)	0(0)	56(100)
2	Aztreonam	3(5.4)	0(0)	53(94.6)
3	Cefotaxime	1(1.8)	0(0)	55(98.2)
4	Ceftazidime	4(7.1)	0(0)	52(92.9)
5	Ceftriaxone	2(3.6)	0(0)	54(96.4)
6	Imipenem	0(0)	0(0)	56(100)
7	Niladic acid	1(1.8)	0(0)	55(98.2)
8	Ciprofloxacin	2(3.6)	0(0)	54(96.4)
9	Tetracycline	30(53.6)	2(3,6)	24(42.9)
10	Amikacin	21(37.5)	0(0)	35(62.5)
11	Trimetoprime+Sulfametoxazole	18(32.1)	1(1.8)	37(66.1)
12	Colistin	46(82.1)	8(14.3)	2(3.6)
2 missing				

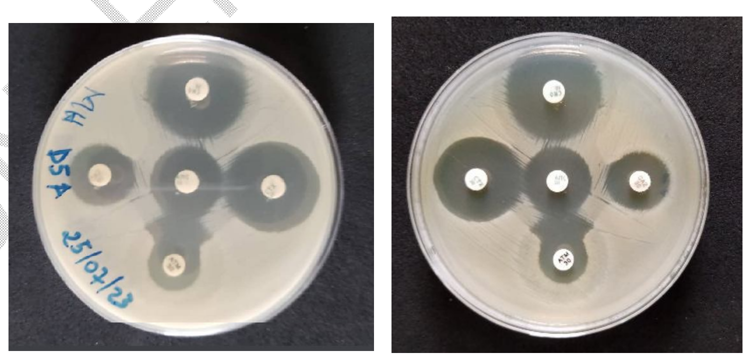

Fig3.*E. coli* ESLB isolates

When the MAR indices of the isolates was calculated, 53.6% were found to have an index ≤ 0.2 while none had an index of 1.0, being resistant to all antibiotics it was tested against (**Table6**).

Table 6. Multiple Antibiotic Resistance index of *E. coli* isolates

MAR index	Number of *E.coli* (%)
0.1	8 (14.3)
0.2	22(39.3)
0.3	19(35.8)
0.4	1(1.8)
0.5	1(1.8)
0.6	1(1.8)

3.5 Discussion

This study was conducted to assess *E. coli* resistance levels on rabbit farms in Korhogo, Côte d'Ivoire. To this end, a questionnaire was administered to rabbit breeders to collect data on their knowledge, attitudes and practices regarding antibiotics. Subsequently, samples of rabbit droppings were analyzed for *E. coli* bacteria.

In this study, the common diseases faced by livestock farmers were mainly, respiratory diseases (38.71 %), skin disease (30,65%) and digestive diseases (25.81 %). In comparison, data from the network monitoring antibiotic resistance of animal pathogenic bacteria diseases indicated respiratory infections (29%), followed by a similar incidence of digestive infections (21%), septicemia (16%), skin and soft tissue infections (13%) [15]. In this study, it was found that a large proportion of these diseases required the use of antibiotics by farmers. These data are similar to a study carried out in Italy, [16] where a large majority of rabbit breeders (76%) use antibiotics on their farms. The low use of antibiotics on rabbit farms, in contrast to other sectors such as cattle [10], poultry [12], could be explained by the fact that farmers have a high level of education and are certainly aware of the effects of antibiotic misuse on human health.

Cattle farmers claim to use antibiotics, some of which are classified by the World Health Organization (WHO) as critically important for human medicine: oxytetracycline, penicillin, cefoxitin, colistin, sulfadine and tylosin[17]. In Côte d'Ivoire, the use of antibiotic groups such as tetracycline, sulfonamide and penicillin, colistin in cattle [10], and poultry [12] has been reported. The irrational use of these broad-spectrum antibiotics of importance in human and animal health may contribute to the selection of resistant bacteria in rabbit farms, and in the long term pose a threat to public health.

Just under half of the farmers said they never estimated the weight of their animals before administering antibiotics, and in some cases, the time limits for antibiotic use were not respected. Some farmers said they did not respect the waiting period after administering the drug to rabbits. The vast majority of farmers purchased antibiotics from veterinary pharmacies. The majority of farmers claimed to use antibiotics for curative purposes. Antibiotics were mainly administered by injection or in drinking water. In view of the above, we can affirm that farmers use antibiotics inappropriately, yet inappropriate use of antimicrobials is always a determining factor in the development of antimicrobial resistance [18].

In this study, the resistance profile of 56 *E. coli* strains to 12 antibiotics listed as both critically important antimicrobials for human therapy (CIA) and critically important veterinary antibiotics (CVIA), including amoxicillin-clavulanic acid, amikacin, and ciprofloxacin. Four were exclusively in the AIC category: ceftazidime, cefotaxime, aztreonam and imipenem. In addition, a few antibiotics, such as cefoxitin, and trimethoprim-sulfamethoxazole, were included in the WHO list of Very Important Antibiotics (VIA) [17]. Our results reveal high levels of resistance to several critically important antibiotics used in human and veterinary medicine: colistin (82.1%), tetracycline (53.6%), amikacin (37.5%) and trimethoprim-sulfamethoxazole (32.1%). The high rates of resistance of *E. coli* isolated from rabbit droppings to colistin differ from those reported in other studies (10%) [15]. High rates of resistance to tetracycline have already been reported, in Tunisia (95%) [19], in Tai 'an(78.2%)[20], in France (83%) [15], due to the widespread use of tetracyclines to control and prevent rabbit diseases. In Côte d'Ivoire, its frequent use in the veterinary and human health sectors has been cited as a factor contributing to the emergence and spread of tetracycline-resistant bacteria in cattle [10] poultry [12]and pig [11] farms. In this study, the rate of resistance to amikacin (37.5%) was contrary to those of Silva *et al.*[21], (8.3%) and Marinho*et al.*[22], (1.3 3%). With regard to the high level of resistance to trimethoprim-sulfamethoxazole (32.1%) obtained in our study, data are far higherto the level of resistance to trimethoprim-sulfamethoxazole (1.3%) on *E. co*li isolates isolated from wild rabbits on the island of São Jorge, in the Azores archipelago [22]. However, these data are still lower than previous studies, which report much higher resistance to trimethoprim-sulfamethoxazole in *E. coli* isolated from farmed rabbit droppings, notably in Tunisia (60%) [19] and Portugal (75%) [21].Nevertheless, some broad-spectrum beta-lactams (cefotaxime, ceftriaxone, aztreonam) and quinolones (nalidixic acid and ciprofloxacin) have low resistance rates (5.4 %), as do amoxicillin + clavulanic acid and imipenem, for which no resistance has been observed. Low levels of resistance or the absence of resistance to these molecules has already been reported [19, 23]. The low levels of beta-lactam resistance observed in this study may be explained by the fact that beta-lactams are rarely used in rabbits, due to drug-related diarrhea.

In this study, the presence of *E. coli* ESBL was detected in 2 of the 56 strains studied (3.6%). This low rate could be explained by the fact that farmers rarely use beta-lactam antibiotics. Our results are contrary to those reported in many countries such as Portugal [21], China [20] or Italy [16]. ESBL pathogens pose a significant threat as they can cause severe and long-lasting infections, raising the possibility of a global pandemic [24]. Multiple antibiotic resistance index is helpful in analyzing health risk, as well as to check the extent of antibiotic resistance [25]. In this study, a significant number of *E. coli* isolate had a MAR index > 0.2 indicating their source to be from sources where antibiotics are commonly used, or previous exposure of the organism to antimicrobial agents. Which means that isolates were from high-risk sources of antibiotics resistance.

Like all scientific work, this study has its limitations. The first limitation concerns the survey data, in particular antimicrobial use and practices. The results are based on self-reports and are therefore likely to be biased. It is therefore likely that the list of antibiotics and the conditions of their use are not exhaustive. In this context, the data from the current study should be interpreted with caution. The second limitation of the study is the relatively small size of the droppings sample, which was only taken from 25 of the 48 farms surveyed, as some farmers refused to allow samples to be taken. The third limitation concerns the panel of antimicrobial activity tests used. This panel is designed to detect resistance in *E. coli*, so there may be resistance in other bacterial species and to other antimicrobials not tested in this study.

4. CONCLUSION

This survey of small-scale rabbit farmers in Korhogo showed that the majority of breeders claim not to use antibiotics. But when they do, they use them inappropriately. The use of antibiotics, some of which are classified by the WHO as critically important for human medicine, was reported. This is thought to be due to multifactorial causes such as the high prevalence of infectious diseases, low levels of education, easy access to antibiotics and weak biosafety measures. The study also showed high levels of resistance to many critically important antibiotics, such as colistin, tetracycline, amikacin and trimethoprim-sulfamethoxazole. This uncontrolled use of antimicrobials and the presence of resistance bacteria in rabbits may present a substantial source of transmission to farmers, to consumers via contaminated food and also risks of dissemination in the environment, via the use of droppings as organic fertilizer

Disclaimer (Artificial intelligence)

Authorshereby declare that NO generative AI technologies such as Large Language Models (ChatGPT, COPILOT, etc.) and text-to-image generators have been used during the writing or editing of this manuscript.

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