Practices of antimicrobial usage and associated resistance emergence in smallholder beef cattle production systems in Northern Nigeria: Drivers and One Health challenge

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Abstract

Increased animal intensification has led to increased antimicrobial usage (AMU) with consequent antimicrobial resistance (AMR) development. This study assess farmers' practices regarding AMU in beef cattle farms, explore pathways for AMR dissemination, establish risk status of AMU, and determine residues presence. We hypothesized socio-economic factors not to drive antimicrobial misuse and resistance emergence in beef production systems. Cross-sectional study was conducted on randomly selected beef farms in Northern Nigeria between 2018 and 2019. Traffic Light model was used to assess farms' AMU risk status. Disc Diffusion Test was performed to detect residues in cattle urine. Descriptive and multivariable logistic regressions analyses were performed at 95% confidence level. Of 660 beef cattle farmers selected, 92.1% (n=608) participated in the study. About 78.9% intensive and 76.6% semi-intensive farmers do not followed instructions on antimicrobial dosage. Also, 72.4% of intensive and 83.9.6% semi-intensive farmers do not observed withdrawal period after AMU on animals. Majorities of intensive (71.5%) and semi-intensive (53.2%) farmers used antimicrobials as growth promoters on beef production. Significantly used antimicrobials on beef cattle were: tetracyclines, sulfonamides, and penicillin. Pathways for AMR spread from beef animals were: consumption of contaminated meat ($p=0.007$); contacts with contaminated animals and fomites ($p<0.001$); and contaminated manure and aerosols in environment ($p=0.003$) Factors that significantly drive antimicrobials misuse and resistance emergence were: inappropriate AMU (OR=2.72; 95% CI:1.93-3.83), non-enforcement of laws (OR=2.98; 95% CI:2.11-4.21), low education and expertise (OR=1.52; 95% CI:1.09-2.12), and management system (OR=10.24; 95% CI:6.75-15.54). Traffic Light model has shown 63.6% intensive and 57.63% semi-intensive farms to be in Class 3 (Red risk) status. Antimicrobial residues were in 48.4% intensively managed and 34.4% semi-intensive farms. The study revealed low practices towards AMU in beef cattle productions. Adequate sanitation and biosecurity, and application of 'One Health' will mitigate AMR at animal-human-environment interface.

1 INTRODUCTION

Livestock is very important to the poor smallholder farmers, especially those in the rural areas of the sub-Saharan Africa because it generates income, serves as source of wealth, provides food and nutrition, and increase social status of the farmers (Randolph et al., 2007; Herrero et al., 2013; Oosting et al., 2014). These indicate that it can be linked to some of the United Nations Sustainable Development Goals (UN, 2015). Livestock production is, therefore, very important to poverty reduction in low-and-middle income countries (LMICs) (Pradere, 2014). Productivity of food animals in smallholder farms is often met with health challenges that invariably require the use of antimicrobials for management (Kruse et al., 2019).

Beef production is the third largest meat industry globally, with annual meat output of about 65 million tonnes (FAO, 2015). The global meat production was projected to increase from 218 to 376 million tonnes between 1999 and 2030, respectively (FAO, 2018). Beef production is complex and involves multiple stages that include calving, growing, slaughtering, and processing under intensive management with maximum use of pasture, forages, and protein and mineral supplements (Peel 2003; Cameron & McAllister, 2016). Intensification of beef cattle production facilitates antimicrobial usage (AMU) for the unavoidable infections treatment, prophylaxis, metaphylaxis, and growth promotion (Cameron & McAllister, 2016). From the general farm animal welfare perspective, AMU improves the general animal health and farm environment (Hao et al., 2014). However, confined animal feeding operations also promotes development and dissemination of antimicrobial resistant pathogens and associated antimicrobial resistance genes, especially in the environment (Agga et al., 2016).

Increased global animal protein demand and animal production intensification have led to increase in AMU on food animals and consequent antimicrobial resistance (AMR) occurrence, a worldwide health threat. Global AMU on food animals was estimated to be 63,151 tonnes in 2010 and projected to increase to 105,596 tonnes by 2030 (Van Boeckel et al., 2015), because it is expected that the majority of food animals will be herd via intensive farming by 2030. Five countries: Myanmar, Indonesia, Nigeria, Peru, and Vietnam are expected to have highest percentage increases in AMU in food animals of 205%, 202%, 163%, 160%, and 157%, respectively by 2030 (Van Boeckel et al., 2015). Globally, it was estimated that 45 mg of antimicrobials are consumed from each kilogram of harvested beef and this was projected to increase by 67% between 2010 and 2030 in the LMICs, due to increased demand for animal protein (Van Boeckel et al., 2015). Worldwide, 73% of antimicrobials purchased are used in food animals, which have led to high resistance development in livestock, with highest resistance seen against tetracycline, sulfonamide and penicillin (Van Boeckel et al., 2019).

Globally, AMU in food animals has been associated with AMR development, a situation that has led to decrease in antimicrobials effectiveness (Holmes et al., 2015). AMR has emerged as a major silent global public health pandemic, already causing 700,000 deaths annually and could lead to as many as ten million deaths annually by 2050, with most of these deaths occurring in developing countries (O'Neill, 2014). If uncontrolled, its economic impact could cost more than US$ 1 trillion annually after 2030 (World Bank, 2017). AMR also threatens achievement of United Nations Sustainable Development Goals 2030 and African Union Agenda 2063 (The Africa We Want) Goal 3 of good health and food security. As consumption of animal protein is forecast to increase markedly over coming years in LMICs, identification of practice gaps on AMU and resistance mitigation are imperative and can only be achieved through surveillance and research.

The study objectives were: to assess farmers' practices regarding AMU in beef cattle farms, explore risk pathways for AMR dissemination from farms, establish risk status of AMU in beef cattle production systems, and determine presence of antimicrobials residues. Our Null hypothesis was that socio-economic factors cannot drive antimicrobial misuse and resistance emergence in smallholder beef cattle production systems in Nigeria. Outcomes of the research are expected to provide background information for policy makers and feed back to beef cattle farmers through extension service delivery in developing countries.

2 MATERIALS AND METHODS

2.1 Study design, study area and target population

Cross-sectional study was conducted on randomly selected smallholder beef cattle farms in Northern Nigeria between June 2018 and June 2019. Nigeria has the fifth largest cattle population in Africa, following Ethiopia, Sudan, Chad and Tanzania, and 99% of them are indigenous breeds concentrated in the northern part of the country (NASS 2011). The cattle population in Nigeria was projected to increase between 20.7 million and 53.6 million heads from 2012 to 2050, respectively while beef production was projected to increase from 392,000 tonnes in 2012 to 13,061,000 tonnes in 2050, with annual growth rate of 3.5% (FAOSTAT, 2018).

These projections can be seriously undermined by antimicrobial misuse and resistance emergence in beef cattle production systems.

Target populations were the intensive and semi-intensive beef cattle farmers and their animals domiciled in the area during the survey period. Study eligibility was based on a farmer mainly herding cattle for beef production. For the purpose of this research, an intensive beef cattle farm was defined as a herd that kept mainly cattle for the purpose of beef production, with a permanent homestead, usually on zero grazing. A semi-intensive beef farm was defined as a semi-settled herd that kept mainly cattle for the purpose of beef production, cultivating few crops and having limited movements on low range grazing within the environment.

2.2 Sample size and sampling procedure

The sample size was determined with a software, the Open Source Epidemiologic Statistics for Public Health (OpenEpi) 2.3 (Dean et al., 2009), with power was at 50% and 4% margin of error at 95% confidence level, while a design effect of one was used. A sample size of 600 beef farmers was obtained. A 10% contingency was added to take care of non-response, and 660 farmers were enrolled into the survey. For the laboratory based study, sample size was computed with the same software and power set at 50%, 5% absolute precision at 95% confidence level. A sample size of 384 cattle was determined.

A two-step cluster sampling procedure was adopted. It involved first, randomly selecting cattle fattening farms settlements in the northern area of the country, followed by stratification of farms based on type: intensive and semi-intensive (clusters). Secondly, systematic random sampling of the farms was conducted with a selection probability proportional to the farm size. Questionnaires were administered on the farm owners or their managers. A two-stage sampling method was also conducted for selection of animals. However, urine samples were collected from at least one cattle per farm. Voided urine was collected from 384 animals for antimicrobial residues screening.

2.3 Data collection with questionnaire

A structured questionnaire was designed and contained mostly close-ended questions to improve response precision, ease data processing, and minimize variation (Thrusfield, 2009). The questions elicited farmers' socio-demographic characteristics; farm information; practices of AMU on cattle; and risk pathways for antimicrobial residues and resistance dissemination; and drivers of antimicrobial misuse. Enumerators were recruited and trained for interviewer-administer questionnaire conduct, with each farm exercise lasting for about an hour.

Respondents were verbally informed about the study objectives and their informed consent also obtained verbally before commencement of each farm exercise. In accordance with the World Medical Association Declaration of Helsinki (WMADH, 2001), participants were informed of their responses confidentiality and withdrawal opportunity without prejudice. Advocacy visits were made to the farmers few days prior to each proposed interview segment and necessary permission obtained.

2.4 Risk status assessment

The Traffic Light model (Grabkowsky, 2009; Alhaji et al., 2018) was used to assess risk status of AMU in beef cattle farms. The model works on the premise of three risk levels: High risk (Class 3) represented by red; Medium risk (Class 2) by yellow; and Low risk (Class 1) by green. The assessment was based on the following assumptions: proportions of farms in which antimicrobials were used "without" veterinarians' consultations were considered to be in Class 3 (Red or High risk) status; while proportions of farms in which antimicrobials were used "with irregular" veterinarians' consultations were considered to be in Class 2 (Yellow or Medium risk) status. However, proportions of farms in which antimicrobials were used always with veterinarians' consultations were in Class 3 (Green or Low risk) status. All proportions were determined at 95% confidence level.

2.5 Samples collection and antimicrobial screening

Urine samples were aseptically collected from at least a cattle that voided urine during the visits to the farms. Collections were done with sterile sample collection bottles and transported to the laboratory in cool icebox at 4 °C. Approximately, each urine sample collected weighted 4 ml.

Disc Diffusion Test was used for the screening. It was performed using Mueller-Hinton Agar (MHA), a medium for susceptibility tests. It has low sulfonamide, trimethoprim, and tetracycline inhibitors, and good reproducibility with satisfactory growth of most pathogens (www.eucast.org). Lyophilised cultures of*Bacillus subtilis* and MHA (Merck, Darmstadt, Germany) were used. Pour plates of MHA were prepared and 1 ml of *B. subtilis* broth culture was inoculated into each agar plate. A 1 cm diameter sterile Whatman filter paper discs were dipped into each urine sample for 15 min. It was then taken out and excess fluid removed by expressing against inner side of the sample container, and placed on the MHA plate. The plate was incubated at 37 °C for 24 hours. Thereafter, it was examined for inhibition zone of *B. subtilis* growth around the discs in the plate. Antimicrobial susceptibility was assessed by measuring the diameter of inhibition zones around the paper disks with scientific ruler. An inhibition zone [?] 2mm was considered positive, while that less than 2 mm was considered negative (Shahbazi et al., 2015).

2.6 Data management and statistical analysis

Data were managed in Microsoft Excel 2007 version spreadsheets (Microsoft Corporation, Redmond, WA, USA). Analytic and descriptive statistics were used for data analysis in Epi Info 7 version 10. Associations between the drivers for antimicrobial misuse in farms and outcome responses were first subjected to univariable analysis using Chi-square tests (Dohoo et al., 2009). Factors found to be significant statistically at this stage were then fitted to likelihood stepwise backward multivariable logistic regression models to control for confounders and test for effect modifiers. The Goodness of Fit of the final model was assessed with Hosmer and Lemeshow test and found to be good. In all analyses, $p<0.05$ was considered statistically significant. Frequencies and proportions were the outputs of this study's descriptive analysis. Relationships of both occupational farmers' response proportions on practices and risk pathways were determined by Pearson's Chi-square test or Fischer's exact test, as appropriate.

3 RESULTS

3.1 Socio-demographic characteristics of beef farmers

Of the 660 beef cattle farmers selected for the study, 92.1% (n=608) participated. Majority of them (27.0%, n=164) were in age group 50–59 years (Figure 1). Most of the participants (72.4%, n=440) were males, and 71.7% (n=436) were married. Stratified by occupation, 37.5% (n=228) were intensive beef cattle farmers, while the majority (62.5%, n=380) were semi-intensive farmers. The majority (36.7%, n=223) of participants did not possess formal education and only few (17.4%, n=106) had tertiary education.

3.2 Practices of antimicrobial usage on beef cattle farms

The significant (p <0.05) practice levels by the beef cattle farmers are presented in Table 1. On personnel that prescribed antimicrobials, more than half (54.0%, n=123/228) of the intensive farmers and over two-third (86.3%, n=328/380) of the semi-intensive farmers engaged in self-prescription of antimicrobials used on beef cattle production. Majorities of the intensive farmers (48.6%, n=111/228) purchased antimicrobials used on the animals from the veterinary drug shops, while 48.7% (n=185/380) of the semi-intensive farmers patronized the animal drug hawkers. In addition, majorities of the intensive farmers (68.4%, n=156/228) and semi-intensive farmers (58.2%, n=221/380) practiced self administering of antimicrobials on animals without technical knowledge of drug administration. More than two-thirds of the intensive (78.9%, n=180/228) and semi-intensive (76.6%, n=291/380) farmers do not followed instructions on antimicrobial dosage before usage. Also, more than two-thirds of the intensive (72.4%, n=165/228) and semi-intensive (83.9.6%, n=319/380) farmers do not observed withdrawal period after AMU on the animals. Regarding purpose for AMU in beef farms, more than two-third of the intensive farmers (71.5%, n=163/228) and over half of the semi-intensive farmers (53.2%, n=202/380) used the drugs for growth promotion on beef cattle (Table 1).

3.3 Frequently used antimicrobials on beef cattle farms

Beef farmers recounted usage of a range of different antimicrobials on beef production. Most frequently and significantly ($p<0.05$) used antimicrobials in beef farms were: tetracyclines (97.8% by intensive farmers and 93.2% by semi-intensive farmers), sulfonamides (96.5% by intensive farmers and 89.7% by semi-intensive farmers), and penicillin (93.2% by intensive farmers and 93.2% by semi-intensive farmers). Other significantly used antimicrobials were gentamicin (85.1% by intensive farmers and 78.2% by semi-intensive farmers), and ciprofloxacin (75.0% by intensive farmers and 53.3% by semi-intensive farmers) (Table 2).

3.4 Risk pathways for AMR and residues dissemination from farms

Significant dissemination routes for AMR and residues from beef animals to humans were: consumption of contaminated meat and meat products (p=0.007); contacts with contaminated animals, beef, and fomites ($p<0.001$); and contaminated manure and urine, contaminated flies and rodents at farm site, and contaminated aerosols in farm environment (p=0.003) (Table 3, Figure 2).

3.5 Drivers for antimicrobial misuse and resistance emergence

Logistic regression models have shown from multivariable analysis a significant correlation relating to influence of the socio-economic drivers on antimicrobial misuse and resistance emergence in beef farms (Table 4). The models indicated that inappropriate AMU was significantly more likely (OR=2.72; 95% CI:1.93-3.83) to drive misuse of antimicrobials and emergence of AMR in beef production systems, Also, non-enforcement of laws regulating AMU was more likely (OR=2.98; 95% CI:2.11-4.21) to drive misuse of antimicrobials and resistance in the farms. Weak economic status of the farmers as well as their low education and expertise were more likely [(OR=2.12; CI:1.49-3.01), and (OR=1.52; 95% CI:1.09-2.12), respectively] to influence misuse of antimicrobials and resistance in beef farms. Furthermore, intensive management system, and poor sanitation and biosecurity at farm sites were more likely [(OR=10.24; 95% CI:6.75-15.54), and (OR=1.67; 95% CI:1.18-2.37), respectively] respectively] to drive antimicrobial misuse and resistance emergence in beef farms (Table 4).

3.6 Risk status of AMU on beef cattle farms

The Traffic Light model indicated that 63.6% (n=145/228) of the intensive beef farms and 57.63% (n=219/380) of semi-intensive farms were in Class 3 (Red risk) status of AMU. Also, more than one-quarters of the intensive farms (30.3%, n=69/228) and semi-intensive farms (29.5%, n=112/380) were in Class 2 (Yellow risk) status. However, less than one-quarters of the intensive farms (6.1%, n=14/228) and semi-intensive farms (12.9%, n=49/380) were in Class 1 (Green risk) status, indicating that all antimicrobials used on them were carried out with veterinarians' consultations (Figure 3).

3.7 Antimicrobial residues assessment

The Disc Diffusion Test revealed antimicrobial residues with [?]2 mm diameter on MHA plates in 48.4% (92/192) urine samples of intensively managed beef cattle farms, while 34.4% (n=66/192) urine samples in the semi-intensive cattle farms have antimicrobial residues. The statistical analysis revealed that there was a significant difference between the samples taken from the two production systems ($X^2 = 7.25$, df = 2, p=0.007) (Table 5).

4 DISCUSSION

This survey investigates AMU in comparable beef cattle production systems and associated drivers for misuse and resistance emergence in Nigeria. We found overall low level of practices towards AMU amongst beef farmers. This can predispose MAR emergence. The low levels of practices could be due to lack of sensitization of farmers on the impacts of AMR and consequent public health implications. Antimicrobials sales are supposed to be restricted and sold only by trained animal health authorities. However, we found high practices of over-the-counter purchase of antimicrobials from human pharmacy stores and drug hawkers for use in beef farms. This could be due to lack of stringent government regulations guiding antimicrobials sales for animal use in Nigeria.

The study found high practices of self administration of antimicrobials among intensive beef farmers (68.4%) and semi-intensive farmers (58.2%). This can lead to under-dosing or over-dosing on animals, a characteristic of antimicrobials misuse (Maron et al., 2013). We observed practices of giving only a single dose of antimicrobials once on sick animals. The use of appropriate dose is as important as the completion of the antimicrobial course (Maron et al., 2013). It is noteworthy that a single dose of antimicrobials administered to an animal has the propensity to generate AMR within pathogens populations resident in that animal, and the repeated and continued AMU compounds this risk (Harada & Asai, 2010). Inappropriate AMU on animals exposes the pathogens to sub-inhibitory concentrations of the antimicrobials (Davies & Davies, 2010), which can result as in the development of AMR. High practices of inappropriate dosing could be due to inadequate veterinary services (Garforth, 2015).

We also found non compliance with antimicrobials withdrawal periods among intensive (72.4%) and semi-intensive (83.9%) farmers. Lack of compliance with antimicrobials withdrawal periods could create low therapeutic doses and high concentration of residues in tissues, which in turn, could result in new pathogens with antimicrobial resistant genes emergence (Alhaji & Isola, 2018). Additionally, this identified antimicrobials to be used for therapeutic, prophylaxis and growth promotion purposes in the two beef production systems. The likelihood of AMR emergence from these purposes is dependent factors that are mainly associated with quantity, dosage, frequency and duration of application (McEwen, 2006). The most striking concern was the use by high proportions of intensive and semi-extensive farmers (71.5% and 53.2%, respectively) for promotion of growths in beef farms. AMU for growth promotion and infection prevention in food animals significantly contributes to AMR emergence, an escalating global public health threat (Pokharel et al., 2020). When antimicrobials are used for growth promotion, selective pressure is created among the pathogens, and possibly forcing the exposed pathogens to mutate or acquire DNA pieces to become antimicrobial resistant (Zowawi et al., 2015).

Tetracyclines, sulfonamides and penicillin, amongst others, were observed to be significantly used in very high proportions in the farms. This is consistent with findings that reported high level of AMU, especially tetracycline, aminoglycoside and penicillin in food animals in Africa (Kimera et al., 2020). The high levels usage may be due to poor sanitation and low biosecurity practices. Most of the observed frequently used antimicrobials are considered by WHO to be critically important (neomycin) or highly important (oxytetracycline and sulphonamides) for humans (WHO, 2012). Their residues in beef products can be transferred to humans with consequent reactions.

The study identified risk routes for dissemination of antimicrobial residues and resistance, creating potential One Health challenge. The most probable ways are through: consumption of contaminated beef and beef products; direct or indirect contacts with contaminated beef animals, beef and fomites; and contaminated faeces and urine, aerosols, as well as flies and rodents in farm environment. These are in consonant with reports of a study that found AMR, especially resistant pathogens, to be transmitted from food animals to humans through consumption of food, contacts with contaminated animals and their waste products in the environment (Marshall & Levy, 2011). Most of the farmers in Africa are often in close contacts with animals, which facilitate resistant pathogens transmission (Doyle, 2015). Studies have shown that food animal products contaminated with resistant pathogens are direct pathways to human colonization (Hong et al., 2011; Marti et al., 2013). Food animals have been shown to be most important known pathway for the spread of AMR to humans (Capita and Alonso-Calleja, 2013).

The findings on environmental pathway through contaminated faces and urine, and aerosols are extremely important. It has been reported that antimicrobial residues, resistant genes and pathogens can be disseminated through airborne particulate matter from large cattle feedlots (McEachran et al., 2015). Rapid and ceaseless transportation of people and animals as well as aerosols from one place to another make transmission of resistant pathogens easy, thereby threatening global health, food safety, and food security (Zhao et al., 2010; Hong et al., 2011; Li et al., 2012; Woolridge, 2012; FAO, 2016). This means that there is higher propensity for transboundary spread of resistant pathogens propagated in food animals in the environment via aerosols.

Some factors that include inappropriate dosage of antimicrobials, non enforcement of laws regulating AMU, weak economic status of beef farmers, low education and expertise of the farmers, husbandry management systems, and poor sanitation and biosecurity at farm sites were observed to significantly drive antimicrobials misuse in farms. Excessive use and misuse of antimicrobials are widely identified as major drivers for AMR as a result of the selection pressure imposed on food animal microbiota abd consequent emergence, persistence, and dissemination of resistant pathogens to humans (Morgan et al., 2011; Larissa et al., 2013; Novo et al., 2013; WHO, 2014). Absence of adequate regulations promotes misuse, residues and resistant pathogens emergence and spread (Mtenga et al., 2011). Poverty has been reported to be a major driver of antimicrobial misuse in developing countries (Okeke et al., 2005).

In the present survey, Traffic Light model findings indicate that very high proportions intensive (63.6%) and semi-intensive (57.6%) farms are at Red risk status (Class 3) due to frequent AMU without veterinarians' consultations, a common practice by farmers in developing countries, just to save costs. The predisposition to rely on personal experience without patronizing veterinary services drives farmers to indiscriminately use antimicrobials through unregulated supply chains. They only consult professionals when there are complications after all available options of therapy have been tried with no response, a common practice found in developing countries (Kunin, 1993; Byarugaba, 2004). In many countries such as the Netherlands, Denmark, Norway and Sweden, the use of antimicrobials on food animals are strictly under the veterinarians' supervision (Cogliani et al., 2011), and such practices are very much needed in beef farms in developing countries, especially Nigeria.

Significant antimicrobial residues were identified in the urine of intensively managed farms (48.4%) and semi-intensive herds (34.4%). Food animals are estimated to excrete between 10% and 90% of the antimicrobials ingested, either as bioactive compounds or unchanged, and these can potentiate resistant pathogens emergence in the environment (Li et al., 2018). As food animal production and associated consumption of animal protein is forecast to markedly increase over the years to come in LMICs, systematic surveillance of AMU on animals has become imperative so as to mitigate AMR (Cuong et al., 2018). Best practices of biosecurity measures are also required to control and prevent high level of infectious diseases in farms and avoid frequent use of antimicrobials in farms.

The study was limited by use of relatively small sample size (660) for the farmer when compared to the size of the study area. This might have underestimated the effects of determinants on the outcomes. Lack of full adjustments for clustering in the designed random sampling is a further limitation. Application of central tendency measures, however, was valuable enough to tolerate the likely imperfections in the confidence intervals. Being a cross-sectional study, the survey did not demonstrate causal relationship but does show associations of dependent and independent variables.

5 CONCLUSIONS

The study revealed low practices towards AMU on beef cattle among surveyed farmers. The Traffic Light model has shown risk status of the various production systems. Multiple factors drive misuse of antimicrobials in farms and could predispose to residues and resistance emergence and dissemination to humans, a One Health challenge. To effectively combat menace of AMR and mitigation of these factors, it is imperative to engage in AMR surveillance programmes and research, as well as sensitization of farmers on prudent AMU in beef production. Adequate sanitation, best practices of biosecurity in farms, and application of One Health approach are needed to mitigate antimicrobials misuse and resistance emergence at animal-human-environment interface.

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ETHICS

The research protocol was approved by the Niger State Ministry of Livestock and Fisheries Research Ethics Committee (Ref. No.: NGS/MLF/1022).

CONFLICT OF INTEREST

The authors declare that they have no conflict of interests, and the work was not supported or funded by any pharmaceutical company.

DATA AVA I L A B I LIT Y STATEMENT

Data that support findings of this study are available upon reasonable request from the corresponding author.

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