

Antimicrobials in chicken commercial feeds in Vietnam: a three-year longitudinal study before a nationwide ban of growth promoters

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Abstract

Background

Antimicrobial growth promoters (AGPs) are included in commercial animal feed rations in many low- and middle-income countries (LMICs). We measured antimicrobial use (AMU) in commercial feed products consumed by 338 small-scale chicken flocks in the Mekong Delta of Vietnam, before a nation-wide ban on AGPs which is to be introduced over the coming three years. We reviewed the labels of commercial feeds and calculated amounts of antimicrobial active ingredients (AAs) given to flocks. We framed these results in the context of overall AMU in chicken production, and highlighted those products that did not comply with Government regulations.

Results

Thirty five of 99 different antimicrobial-containing feed products (35.3%) included at least one AA. Eight different AAs (avilamycin, bacitracin, chlortetracycline, colistin, enramycin, flavomycin, oxytetracycline, virginamycin) belonging to 5 classes were identified. Brooding feeds contained antimicrobials the most (51.2%), followed by grower (34.6%) and finisher feeds (12.5%). The average amount of AAs given to flocks per kg of chicken at consumption time was 84.8 (SEM \pm 9.3mg). Quantitatively, chlortetracycline was consumed most (42.2mg/kg SEM \pm 0.34; 50.0% of total use), followed by enramycin (18.4mg SEM \pm 0.03, 21.8%) and bacitracin (16.4mg SEM \pm 0.20, 19.4%). Antimicrobials in commercial feeds were more commonly given to flocks in the earlier part of the production cycle. A total of 10 (9.3%) products were not compliant with existing Vietnamese regulation (06/2016/TT-BNNPTNT) either because they included a non-authorized AA (4), had AAs over the permitted limits (4), or both (2).

Conclusions and recommendation

Some commercial feed formulations examined included colistin (polymyxin E), a critically important antimicrobial of highest priority for human medicine. A tenth of the formulations examined did not comply with Government regulations. We estimated that consumption of AGPs in feed represented ~10% of total AMU in chicken production. We advocate for restrictions on AMU in chicken production that go beyond phased bans on AGPs. Furthermore, these steps could be bolder and implemented without unnecessary delay. Results from this study should help encourage discussion about policies on AGPs in LMICs.

Background

Antimicrobials are used in veterinary medicine. The global annual consumption of antimicrobials intended for animal use has been estimated in ~ 63 thousand tonnes. In European Union (EU) countries, all of which have well-developed antimicrobial use (AMU) surveillance systems, antimicrobials intended for animal use represent about 2/3 of total AMU (1). It is believed that excessive use of antimicrobials in animal production is a major factor contributing to the global rise in AMR (2–3). The total amounts of antimicrobials intended for animal production are expected to increase in coming years due to intensification of livestock production, mostly in low- and middle-income countries (4).

Antimicrobials are used in veterinary medicine to treat and prevent animal disease. In addition, in many countries they are also added to feed rations in sub-therapeutic concentrations in order to increased animal growth and productivity (antimicrobial growth promoters, AGPs). Their mechanism of action is however, poorly understood (5).

Over the last five years, the issue of AMR and excessive AMU has attracted unprecedented attention worldwide. Many policy instruments on AMU/AMR have been recently developed by global organizations such as the World Health Organization (6), the Food and Agriculture Organization of the United Nations (7), and the World Organization for Animal Health (OIE) (8).

AGPs have been the subject of much debate over recent years. Those opposing banning/restrictions of AGPs are often support their views on potential losses in productivity, as well as the likelihood of emergence of certain diseases (i.e. necrotic enteritis in chickens) (9). Positions that favour restrictions often align themselves with the need to protect the efficacy of antimicrobials and human health. In the European Union (EU), mostly as a result of public health pressure, AGPs have been banned since 2006 (10). In recent years, and in line with FAO's recommendations (7), some countries have started implementing bans or restrictions on AGPs in animal feeds, In the USA, voluntary phasing out of certain AGPs commenced in 2013 (1). In the Asia-Pacific region, countries such as Korea (2011), Australia (2013) (12) have implemented bans of AGPs in animal feeds. Countries such as Thailand (2015) (13), China (2016) (14) and India (2019) (15) have also recently adopted policies that restrict AGPs in commercial feeds.

Worldwide annual consumption of poultry meat (2013–2015) stands at 110,280 tonnes, second only to pork (117,005 tonnes). By 2025, chicken production is expected to surpass that of pork production (16).

In Vietnam, AGPs are often present both in commercial pig and poultry rations in Vietnam. A study extrapolating AGP consumption from a retail survey of commercial feeds estimated that 77 mg of AGPs are used in the country to produce 1 kg of chicken (17). A study of medium-sized

chicken farms estimated that chickens consumed 57 mg of AGPs per kg of live weight (18). However the study was based on a small sample of 6 farms.

A 2002 Vietnamese government regulation on animal feeds (54/2002/QĐ-BNN) included the ban of 18 chemicals (including chloramphenicol, metronidazole and nitrofurans) (19). Later (2014), new legislation (28/2014/TT-BNNPTNT) expanded the list to include bacitracin, carbadox and olaquidox (20). In May 2016 Vietnam issued Circular 06/2016/TT-BNNPTNT (21) explicitly indicating the list of AAls authorized for inclusion in commercial feed types as AGPs, as well as the maximum levels allowed in each feed type. According to this regulation, the maximum number of different AAls to be included in each feed was limited to two. In 2018, Vietnam introduced a new Animal Husbandry Law (32/2018/QH14) (22) which included a ban on AGPs in commercial feeds. A further decree (13/2020/ND-CP) (23) established the timeframe for its implementation: critically-important AAls still can be used until the end of 2020, highly important AAls until the end of 2021, important AAls until the end of 2022 and all other AAls until the end of 2025.

This study aimed at investigating the types and quantities of AAls in commercial feed in a large representative cohort of small-scale chicken flocks in the Mekong Delta region of Vietnam immediately before the implementation of the new Animal Law. This information complements existing data on antimicrobials administered in water (24), and completes the picture on the scale of total AMU in small-scale chicken flocks in the region. The data on AGP consumption in chicken farming is probably comparable to other LMICs countries that are yet to implement restrictions or bans of AGPs. This knowledge and should form the basis of a informed decisions moving towards with reducing AMU in poultry production.

Results

Description of commercial feed products

A total of 99 different commercial feed products were identified. Those products were produced for usage in chicken (85 products, 85.9%), pig (12, 12.1%), and duck (2, 2.0%). Feed products were classified according to their indication (production stage): brooder (n=40), grower (n=24) and finisher (n=35). A total of 35 (35.3%) contained at least one antimicrobial. All of the 35 antimicrobial-containing feeds were intended for chicken use. The detailed information on these antimicrobial-containing products is available in Supplementary Table 1. Brooder feed products contained AAls the most (51.2%), followed by grower (34.6%) and finisher (12.5%) feeds. All except one product (a brooder feed that contained both chlortetracycline and colistin) contained one AAI. A total of 12 (34%) products had an imprecise (ambiguous) label, indicating they contained one of 2-4 listed AAls. A total of 8 different AAls belonging to 5 classes were listed in the 35 feed products. The most common AAls listed were enramycin (18.8% feeds), followed by bacitracin (16.5% chicken feeds), chlortetracycline (15.3%), avilamycin (5.9%), flavomycin (4.6%), colistin (3.7%), virginamycin (2.4%), and oxytetracycline (1.2%) (Table 1). A total of 10 (9.3%) products were not compliant with Regulation 06/2016/TT-BNNPTNT, either because they included a non-authorized AAI (avilamycin, flavomycin, oxytetracycline) (n=4), AAI/s over the permitted limits (n=4), or for both reasons (n=2).

Table 1. Antimicrobial active ingredients (AAIs) and their concentrations in 85 chicken feed products given to flocks in Dong Thap.

	Class	Products (n=85) (%)	AAI mean concentration (range in mg/kg feed) (No. products)			**Permitted concentration (range in mg/kg feed)
			Brooder	Grower	Finisher	
			n	Polipeptides	16 (18.8)	
n	Polipeptides	14 (16.5)	[51.1- 63.1] (8)	[125- 125] (1)	[50-60] (5)	[4-50]
acycline	Tetracyclines	13 (15.3)	[52.7- 61.1] (9)	[40-50] (4)	-	[10-50]
in	Orthosomycin	5 (5.9)	[12.5- 12.5] (2)	[15-15] (1)	[10-10] (2)	NA
in	Other [‡]	5 (5.9)	[6-6] (2)	[2-2] (1)	[10-10] (2)	NA
	Polipeptides	4 (4.7)	[70-136.6] (3)	-	[60-160] (1)	[2-20]
ycin	Streptogramin A	2 (2.4)	[5-15] (1)	-	[5-5] (1)	[5-15]
ycline	Tetracyclines	1 (1.2)	[50-50] (1)	-	-	NA

*Critically important antimicrobial class according to WHO. **AAI permitted in chicken feeds from 1 to 28 day old birds (brooder and grower feeds) (2). NA = Not allowed. [‡]Antibiotic complex of obtained from *Streptomyces bambergiensis* and *Streptomyces ghanaensis*.

Flock consumption of AMUs through commercial feed

All flocks used commercial chicken feed. In addition, pig and duck feeds were given to 12.1% and 0.6% flocks, respectively. Each flock had been given a median of 2 [IQR 2-3] different commercial feed products. Flocks received a median of 1 [IQR 1-1] antimicrobial-containing products. Chickens were fed a mean of 84.8 (SEM \pm 9.3 mg) [range 71.4-98.2] of AAI/kg over their production cycle. Chickens raised in Thap Muoi and Cao Lanh districts were given 87.7 (Standard Error of the mean, SEM \pm 14.8 mg/kg) [range 76.1-99.3] and 81.7 (SEM \pm 11.0 mg/kg) [range 66.3-97.1], respectively. Overall, the highest magnitude of AMU corresponded to chlortetracycline (42.2mg SEM \pm 0.34), followed by enramycin (18.4mg SEM \pm 0.03) and bacitracin (16.4mg SEM \pm 0.20) (Table 2).

Table 2. AMU in commercial feed among 338 small-scale chicken flocks over 6,041 observation weeks.

AAIs	No. flocks (n=338) (%)	Probability of AMU by week (mean \pm SEM) [lowest-highest]	Total AMU over the production cycle mg/kg chicken (mean \pm SEM) [lowest-highest] (%)
Enramycin	152 (45.4)	0.319 (\pm 0.004) [0.306-0.333]	18.4 (\pm 0.03) [17.3-19.5] (21.8)
Chlortetracycline	73 (22.5)	0.134 (\pm 0.002) [0.134-0.135]	42.2 (\pm 0.34) [40.6-43.9] (50.0)
Bacitracin	103 (30.5)	0.095 (\pm 0.01) [0.080-0.111]	16.4 (\pm 0.20) [10.5-22.3] (19.4)
Virginamycin	8 (2.9)	0.010 (\pm 0.03) [0.005-0.014]	0.5 (\pm 0.17) [0.1-0.8] (0.6)
Colistin*	7 (2.0)	0.005 (\pm 0.03) [0.003-0.008]	6.4 (\pm 4.21) [2.6-10.3] (7.6)
Avilamycin	8 (2.3)	0.005 (\pm NC) [0.0-0.010]	0.3 (\pm 0.08) [0.0-0.6] (0.4)
Flavomycin	8 (2.3)	0.005 (\pm NC) [0.0-0.010]	0.2 (\pm 0.11) [0.0-0.4] (0.2)
Oxytetracycline	4 (1.1)	0.0 (\pm NC) [0.0-0.001]	0.07 (\pm 0.73) [0.0-0.15] (0.1)
Total	297 (87.8)	0.575 (\pm 0.02) [0.529-0.624]	84.8 (\pm 9.4) [71.4-98.2] (100)

NC = Not calculated. *Critically-important antimicrobial class according to the World Health Organization.

Commercial feed rations were given to flocks in at total of 5,655 of 6,041 (93.6%) observed weeks. The probability of AMU in flocks decreased with the age of the flock (Figure 1a). On average, flocks were given AGPs in feed on 57.5% (95% CI 54.5-

60.5%) weeks. Interestingly, a relatively high fraction of brooder products were used in later stages, while some finisher products were also used more in the growing period. Enramycin was used dominantly throughout the production cycle, while colistin was found only in later stages (Figure 1).

Discussion

There are very few published data describing and quantifying consumption of AAs (AGPs) in commercial feeds in poultry farming systems in low-and middle income countries (LMICs) (4). Our findings complement existing data on antimicrobials administered to chicken flocks (mainly through water) (~792 mg/kg) in the Mekong Delta region of Vietnam (24). Consumption of in-feed antimicrobials over the life of the flock (~85 mg/kg), therefore represents ~10% of total chicken AMU. These figures are consistent with previous estimates (77-95 mg/kg) (17, 18).

This study is based on data from a large cohort study aiming at reducing AMU in chicken production in the Mekong Delta of Vietnam (25). The study is representative since the selection of farms was random. Even though our data came from an intervention study, our advice to farmers was focused on reducing AMU as medicine (both prophylaxis and therapeutic), and did not include any advice on feed. We did not find any difference between flocks allocated to the intervention compared with the baseline phase (data not shown).

A major concern is the relatively high number of products that did not comply with Vietnamese regulations. Bacitracin, banned in feed rations in Vietnam since May 2016 (21), was the second most common AA found. More worryingly, 6/35 (17%) antimicrobial-containing feeds included AAs in concentrations above those permitted by the Vietnamese authorities. For example, the colistin concentration in all feed products examined was 3-5 times greater than that permitted by the Government. Non-authorized antimicrobials (avilamycin, flavomycin, oxytetracycline) were also found in some chicken feeds. This raises concerns regarding compliance of commercial feed mills with regulations, and casts doubts over the effective enforcement of the planned bans (23). An additional challenge is the ambiguous labelling with regards to AA in about a third of the rations investigated.

Recent studies have reported a high prevalence of colistin resistance encoded by *mcr-1* in chicken flocks in the area (18, 26). This antimicrobial, classified as highly critically important by WHO (27), was listed in 5% feeds examined (brooder feeds) and it was estimated that on average, flocks consumed 5mg/kg (about 3% of total in feed AMU). This is a modest amount compared with the reported magnitude of AMU through water administration (42mg/kg). However it is of concern that in our study cohort farms tended to use these feeds towards the end of the production cycle with high drug concentration. This resulted in long elimination profile of antimicrobials, therefore posing a risk of residues in poultry meat (28).

Quantitatively, chlortetracycline, bacitracin and enramycin were the AAs most consumed through commercial feeds. These results are not dissimilar to previous extrapolations from a retail survey (17). Tetracyclines were also the most consumed antimicrobial consumed by flocks through water (24). Tetracyclines is also the antimicrobial class against which resistance among *Escherichia coli* and non-typhoidal *Salmonella* strains in the Mekong Delta is highest (29, 30, 31, 32). Bacitracin use has been shown to promote resistance among *Clostridium perfringens* isolates from chickens (33-35). With regards to enramycin, there is little information on its impact on AMR. A Japanese study that investigated *Enterococcus faecium* isolates from chicken flocks found no evidence of resistance against enramycin (36), although the study presented no enramycin use data.

The inclusion of AGPs in animal feeds and its impact on human health have been the subject of intense debate since the ban of AGP in animal production in Europe (37, 38). A major concern prior to the ban on AGPs in Europe was the widespread inclusion of avoparcin (a glycopeptide) in animal feeds, which was identified as a source of vancomycin resistance among zoonotic *Enterococcus faecium* bacteria (39). In contrast, other studies have indicated that the use of enramycin and bacitracin as AGPs involves no risk to human health (40, 41). The association between AGPs in animal feeds and human health is beyond the scope of this study.

The finding that AAs in feed were consumed in some of our study flocks during the latter weeks of the production cycle is of concern given the potential for residues in chicken meat. A recent survey showed that 8.4% of chicken meat samples in Vietnam contained antimicrobials residues, with tetracyclines being the most common residue detected (42).

Much of the debate on AMU in animals has often been framed around the issue AGPs. Unfortunately, accurate data on total amounts of AGPs consumed globally are lacking. In Great Britain, in 2001 (5 years before the 2006 EU ban), growth promoters represented only 11.6% of 371 tonnes of antimicrobial active ingredients used in animal production (43). We believe that AGPs still represent a considerable fraction of total AMU globally, although the quantities have been decreasing over recent years, since more and more countries have phased out their use. A recent OIE survey reports that AGPs were used in 23% countries surveyed in 2018, compared with 51% countries in 2012 (44, 45). A review of the data of the impact of AGP from 1950 to 2010 on farm productivity indicate that productivity gains due to AGP in feeds decreased over the years, suggesting that any potential positive effects are of greater magnitude in low-biosecurity production systems (46). Indeed, recent studies in industrial broiler production systems have identified that AGPs had an overall negative impact on flock productivity (47, 48). In the non-industrial chicken production systems included in this study, AGPs in feeds represented a small fraction of total AMU. It is conceivable that even if APGs

resulted in marginal productivity gains, these would be offset by the high mortality rates due to disease observed in the area (49). However, data from Vietnam suggest that consumption of AGPs in pig production is of considerable greater magnitude than in chickens (17), and therefore the outcomes of AGPs reductions in this species are more uncertain.

Conclusion

Compared with antimicrobials administered to chicken flocks through water, consumption of AGPs in feed represents a relatively small fraction (10%) of total AMU in Vietnamese chicken production. However, it is of great concern that some feed formulations examined included colistin (polymyxin E), a critically important antimicrobial of highest priority for human medicine. Furthermore, a considerable number of feed formulations did not comply with Government regulations. The Vietnamese Government has adopted an approach based on long-term phasing out AGPs; we advocate for this approach to be bolder and enforced without delay, since any potential small losses in productivity need to be balanced against the undesirability of increasing the risk of AMR. Policy efforts should, however, focus on restricting antimicrobials used for prophylactic purposes which widely available and are sold over the counter. Our results highlight the challenges in effectively enforcing and monitoring such restrictions in Vietnam, this situation is likely to be common to many other LMICs. It is likely that the types and quantities of AGPs in feeds vary by country and production system, therefore more data are needed in order to recommend policy initiatives on AGPs.

Material And Methods

Farm selection

Farm owners in two districts (Cao Lanh, Thap Muoi) within Dong Thap (Mekong Delta, Vietnam) were randomly selected from the official farm census and were contacted by the veterinary authorities. Farmers about to start raising flocks of ≥ 100 meat chickens that practiced all-in-all out management were recruited, and flocks were followed up longitudinally. A total of 115 farms were recruited (59 in Cao Lanh; 66 in Thap Muoi). Selected farms were part of a longitudinal study aimed at reduce AMU in chicken production through the provision of veterinary advice (25). Owners of selected farms were requested to record in detail the types of commercial feed used and to keep the sacs of all feed products used. A field study team visited farms four times over the production cycle to collect data on commercial feed products used by week. A total of 338 flocks raised in these farms were investigated. Of the 115 farms, 44 completed 1 cycle (38.3.4%), 25 (21.7%) 2 cycles, 8 (7.0%) 3 cycles, 11 (9.6%) 4 cycles, 12 (10.4%) 5 cycles, and 15 (13.0%) more than 5 cycles. The median flock size at restocking was 303 [IQR 200-500]. A total of 6,041 weeks of data were collected. The median duration of one production cycle was 19 [IQR 17-21] weeks. All farm visits were conducted from October 2016 to Oct 2019.

AAIs in commercial feed products

All commercial feed products containing an antimicrobial active ingredient (AAI) were singled out after reviewing their label. Ionophores (mostly aimed at controlling coccidial infection) were excluded. AAIs were described by: (1) target species (duck, chicken or pig); (2) indication by stage of production (brooder, grower or finisher); and (3) type of formulation (crumbs, mash or pellets). From each feed product, we described the AAIs contained, its concentration (expressed in mg/kg product). AAIs were classified based on the OIE list of antimicrobial agents (50) and any antimicrobials regarded as critically important by WHO (27) were highlighted. We excluded ionophores since it is thought that these substances, commonly used as coccidiostats, do not have a link with AMR or against antimicrobials commonly used to treat human or animal bacterial disease. We identified those feed products containing antimicrobials at concentrations not permitted under Vietnamese legislation (21).

Data analyses

We calculated AMU consumption in feed by week by relating the amounts of AAI (mg) to the weight of birds at the time of consumption (standard weight of the flock) (kg) (mg/kg live chicken) for all weeks (n) over the flock's life duration (Expression 1).

$$\text{mg/kg chicken at time of consumption} = \sum_{k=1}^n \frac{\text{AAI used (mg) in week } k}{\text{Standard weight of the flock (kg) at week } k}$$

Weekly consumption of AAIs in feed was calculated by multiplying the weekly feed consumption by the AAIs concentration indicated in that feed. The feed consumption was estimated from unpublished data related to native Vietnamese layer pullets, where 443g of feed were consumed by 1 kg of live chicken per week. The denominator (total weight of the flock at week k) was calculated from the number of chickens present in the flock multiplied by an estimated (standard) weight. The latter was

based on weekly data from 10 randomly selected chickens from 11 representative flocks, from week 1 until week 22 of their production cycle (24).

The concentration (strength) of AAI in each feed product was obtained from its label. However information in a number of feed products contained uncertain information in their labels, concerning the identity of the AAI and the amounts included. For feed products with AAI content ambiguously labeled (i.e. indicating inclusion of one of >1 listed AAIs), the amount of each AAIs was calculated by assigning each antimicrobial a probability corresponding being included (probability=1), and not being included (probability=0). For products indicating their AAIs concentration as a range, lowest and highest estimates were calculated for each antimicrobial. The amounts of each AAIs were summarized in each flock by AAI and by week. The total amounts of each AAI were aggregated to calculate total consumption by flock, including the estimation of a lower and upper limit from the above calculations.

Declarations

Ethical approval and consent to participate

This study was granted ethics approval by the Oxford Tropical Research Ethics Committee (OXTREC) (Ref. 5121/16) and by the local authorities (People's Committee of Dong Thap province). All participating farmers consented to the study.

Consent for publication

Not applicable.

Availability of supporting data

All data generated or analysed during this study are included in this published article and in its supplementary information file.

Competing interests

The authors declare no competing interests.

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Authors' contributions

NVC, BVH and JCM conceived and designed the study. BTK, DHP and NVC carried out data collection; NVC, MC and JCM performed data analyses; BTK, BDT contributed to data entry, NVC, BDT, DHP, JCM and GT contributed to writing up and editing. All authors read and approved the final manuscript.

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Figures

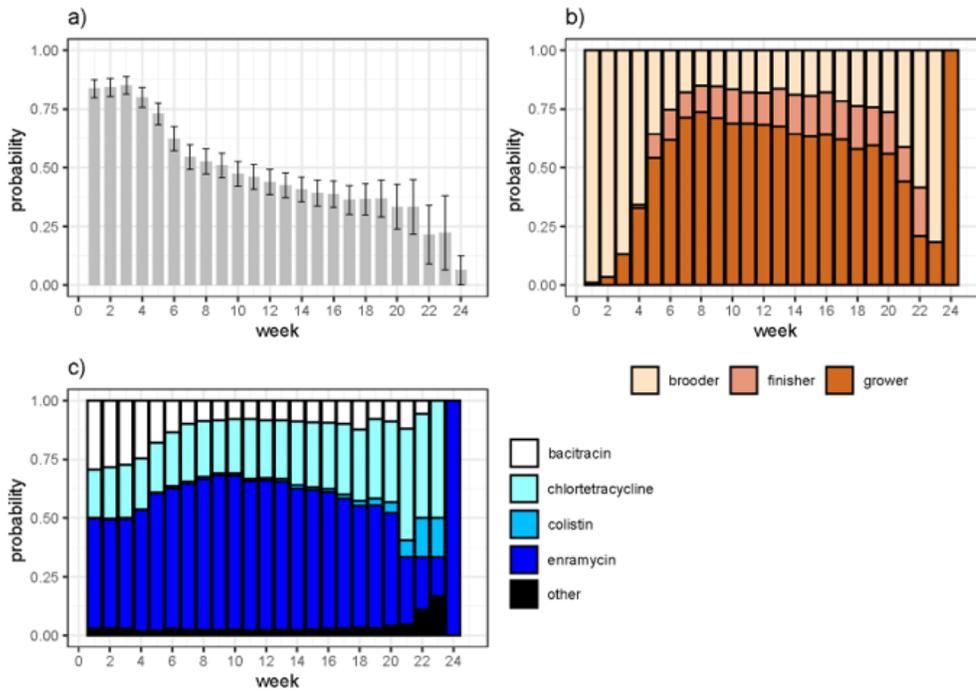


Figure 1
 (a) Probability of consumption of AAIs in chicken feeds by week among study flocks; (b) Weekly distribution of types of feed (production stage) consumed by flocks; (c) Weekly distribution of AAIs consumed by flocks through commercial animal feeds.

Supplementary Files

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