


Labelling and quality of antimicrobial products used in chicken flocks in the Mekong Delta of Vietnam

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Abstract

Background: The Mekong Delta of Vietnam is a hotspot of antimicrobial use (AMU), but there is no information on the quality of the labelling and strength of antimicrobial products used in poultry production.

Methods: Based on a large random sample of farms, we identified the 20 most used antimicrobial products in the area, and investigated their antimicrobial active ingredient (AAI) content by UPLC-MS/MS (91 analytical tests).

Results: Only 17/59 (28.8%) batches contained all AAIs within 10% of the declared strength. Worryingly, 65.0% products provided in their label preparation guidelines for both therapeutic and prophylactic use. Withdrawal times for both meat and eggs were stated in 8/20 (40%) products.

Conclusion: Results highlight deficiencies in quality and labelling contents that undermine authorities' efforts to discourage inappropriate use of antimicrobials.

KEYWORDS

animal production, antimicrobials, poultry, veterinary, Vietnam

1 | INTRODUCTION

Antimicrobials are widely used in animal production, both to prevent and to treat diseases. In some countries, antimicrobials are also added to commercial feed formulations to promote rapid growth (Page & Gautier, 2012). It has been estimated that in African countries about 50% of antimicrobials available in the market correspond to non-standard and non-registered veterinary medicines (Clifford et al., 2018). There is a concern that inadequate formulation of

these products may lead to exposure to sub-therapeutic levels of antimicrobials, therefore promoting resistance among bacterial populations (Nwokike, Clark, & Nguyen, 2018). Recent studies on the quality of antimicrobial products used in shrimp and catfish farming in Vietnam indicated that only ~8% and ~29% products contained an AAI within $\pm 10\%$ (accepted level of variation) (Phu, Phuong, Scippo, & Dalsgaard, 2015; Tran, Tran, Phan, & Dalsgaard, 2018). Globally, the quantity of antimicrobials used in chicken production is estimated at 138.0 doses/1,000 animal-days [inter quartile range (IQR)

[†]Correction added on 11 September 2019, after first online publication: the first name and surname for the third author were interchanged in the original publication; this has now been corrected to Nguyen Van Cuong.

TABLE 1 Characteristics of 20 antimicrobial products investigated, sorted by the number of flocks where they were used

| Product code | No. flocks used (%) | Company | Package content | Target species | Declared strength (%g/100 g product) | Indication | Product description | Withdrawal time indicated (meat, eggs) |
|--------------|---------------------|---------|-----------------|----------------------------------|--------------------------------------|---------------------------|----------------------------------------------------------|----------------------------------------|
| AP01 | 34.5 | A | 100 g | Chickens, ducks | OTC 1.5%; COL 0.07% | Prophylactic, therapeutic | Antimicrobial mixed with vitamins | Meat |
| AP02 | 14.8 | F | 20 g | Poultry, ruminants, pigs, horses | AMX 10%; COL 2% | Therapeutic | Antimicrobial only | Meat, eggs |
| AP03 | 14.8 | A | 100 g | Poultry | OTC 10%; STR 5% | Therapeutic | Antimicrobial only | Meat |
| AP04 | 11.8 | G | 50 g | Poultry | OTC 4%; COL 2% | Prophylactic, therapeutic | Antimicrobial mixed with vitamins | No |
| AP05 | 11.8 | G | 100 g | Poultry, ruminants, pigs | TAP 6%; SMZ 5% | Prophylactic, therapeutic | Antimicrobial only | Meat |
| AP06 | 10.8 | D | 100 g | Poultry, ruminants, pigs | OTC 5%; COL 0.017% | Prophylactic, therapeutic | Antimicrobial mixed with vitamins | Meat, eggs |
| AP07 | 8.4 | B | 100 g | Poultry, pigs | OTC 7%; COL 0.98% | Prophylactic, therapeutic | Antimicrobial only | Meat, eggs |
| AP08 | 8.4 | G | 100 g | Poultry, ruminants, pigs | TYL 7%; GEN 3.5% | Prophylactic, therapeutic | Antimicrobial mixed with minerals | Meat, eggs |
| AP09 | 7.4 | H | 100 g | Poultry, ruminants, pigs | DOX 20%; TYL 10% | Prophylactic, therapeutic | Antimicrobial only | Meat, eggs |
| AP10 | 5.9 | G | 100 g | Poultry | ERY 6%; SMZ 10% | Prophylactic, therapeutic | Antimicrobial only | Meat |
| AP11 | 5.4 | C | 50 g | All animal species | GEN 6%; COL 2.44% | Therapeutic | Antimicrobial mixed with vitamins, anti-inflammatory | Meat, eggs |
| AP12 | 5.4 | G | 100 mL | Poultry, ruminants, pigs | TIL 25% | Prophylactic, therapeutic | Antimicrobial only | Meat |
| AP13 | 5.4 | H | 100 g | Poultry, ruminants, pigs | ENR 5% | Prophylactic, therapeutic | Antimicrobial mixed with expectorant, analgesic | Meat |
| AP14 | 4.9 | I | 100 g | Ducks, Muscovy ducks | ENR 5% | Prophylactic, therapeutic | Antimicrobial only | Meat |
| AP15 | 4.4 | I | 100 g | Poultry | AMX 10%; TYL 10% | Prophylactic, therapeutic | Antimicrobial mixed with expectorant, analgesic | Meat |
| AP16 | 3.9 | A | 100 g | Poultry, ruminants, pigs | OTC 1% | Not explicit | Antimicrobial mixed with vitamin, analgesic, antipyretic | Meat, eggs |
| AP17 | 3.9 | I | 100 g | Poultry, ruminants, pigs | NEO 6%; COL 1.46% | Therapeutic | Antimicrobial only | Meat |

(Continues)

TABLE 1 (Continued)

| Product code | No. flocks used (%) | Company | Package content | Target species | Declared strength (%=g/100 g product) | Indication | Product description | Withdrawal time indicated (meat, eggs) |
|--------------|---------------------|---------|-----------------|--------------------------|---------------------------------------|---------------------------|----------------------------------|----------------------------------------|
| AP18 | 3.4 | I | 100 g | Poultry, ruminants, pigs | TMP 3%; COL 2% | Therapeutic | Antimicrobial only | Meat, eggs |
| AP19 | 3.0 | E | 100 g | Poultry | DOX 2.5%; TYL 2.5% | Prophylactic, therapeutic | Antimicrobial mixed with vitamin | Meat |
| AP20 | 1.0 | C | 50 g | Poultry, ruminants, pigs | GEN 3%; TYL 5% | Therapeutic | Antimicrobial only | Meat |

Abbreviations: AMX, amoxicillin; COL, colistin; DOX, doxycycline; ENR, enrofloxacin; ERY, erythromycin; GEN, gentamicin; NEO, neomycin; OTC, oxytetracycline; SMZ, sulphamethoxazole; STR, streptomycin; TAP, thiamphenicol; TIL, tilicosin; TYL, tylosin.

91.1–438.3], a higher amount than AMU in the two other major terrestrial food animal species (pig and cattle) (Cuong, Padungtod, Thwaites, & Carrique-Mas, 2019). Previous studies have reported exceptionally high levels of antimicrobial use (AMU) in chicken farms in the Mekong Delta region of Vietnam (Carrique-Mas et al., 2015; Carrique-Mas et al., 2019; Cuong et al., 2019; Nguyen et al., 2016). However, there are currently no published data on the quality of antimicrobial products used in these farming systems. We investigated the labelling and strength of AAls of the most commonly used products in representative chicken farms in the Mekong Delta of Vietnam.

Antimicrobial products were identified from a survey of 102 randomly selected farms raising meat chickens in Dong Thap province from November 2016 to March 2018. A total of 203 flocks raised in those farms with a completed full cycle of production were included in the study (Carrique-Mas & Rushton, 2017; Cuong et al., 2019). All flocks consisted of native breed chickens raised over a median period of 18 [Interquartile Range 16–20] weeks, with birds typically raised using all-in-all-out system. At the beginning of the project, farmers were given purposefully designed diaries to record their AMU, as well as containers where farmers were asked to store all packages of antimicrobials. A team of trained animal health workers visited each farm four times during each production cycle to review the collected data. The 20 most frequently used antimicrobial products were identified. Three different batches of each product were purchased from veterinary drug shops within the province of Dong Thap. The 20 most commonly used antimicrobial-containing products (defined as the proportion of flocks using) were identified, and information on strength on AAls, species target, prophylactic/therapeutic indication, and withdrawal times for meat and egg productions was compiled. The products' contents were tested (single blinded) for the presence and strength of the AAls declared in the label at an accredited laboratory (Center for Analysis Service of Experiment, Ho Chi Minh City, ISO 9001:2008 accredited) using Ultra High Performance Liquid Chromatography coupled to tandem Mass Spectrometry (UPLC-MS/MS). Three aminoglycoside antimicrobials (gentamicin, neomycin and streptomycin) were not investigated. For colistin, the number of International Units (IU) indicated in the label was converted to milligrams. Results were expressed as a percent of the declared strength indicated in the label (percent content). The inter-batch variability (in relation to the overall variability) was investigated by fitting a null random effects model with product fitted as a random effect and percent content as the outcome using lme4 package and R software.

The 20 products identified were marketed by nine different companies, and all except one (a French company selling product AB008) were Vietnamese (Table 1). All products were formulated for oral administration: Nineteen (95%) were powder-based formulations and one (5%) was a liquid solution. Five (25%) products contained a single antimicrobial and 16 (75%) a mixture of two antimicrobials. In order to investigate the inter-batch variability, three batches of 19 products and two batches of one product (AB051) were investigated, making a total of 91 analytical tests (Table 1).

Twelve different AAls were identified in the 20 products, the most common being: colistin (8 products), oxytetracycline (6), gentamicin (2), tylosin (2), doxycycline (2), amoxicillin (2) and enrofloxacin (2). Other AAls (trimethoprim, streptomycin, tilmicosin, erythromycin and neomycin) were contained in one product each. Six of those AAls (colistin, gentamicin, tylosin, erythromycin, tilmicosin and neomycin) are considered to be critically important antimicrobials according to the World Health Organization (Anon 2017).

In six (30.0%) products the label provided an explicit indication for therapeutic administration only, 13 (65.0%) products provided an indication for both therapeutic and prophylactic use, and one (5.0%) did not include any indication. Withdrawal times for both egg and meat production were provided in the labels of eight (40.0%) products; in 11 (55.0%) products withdrawal times were indicated only for meat (but not for eggs); one product contained no indications with respect to withdrawal time. A total of 11 (55.0%) products contained only one AAI, and the remaining had other substances (including vitamins, mineral supplements and expectorants and analgesic substances). Twenty-eight (30.8%) samples tested were within 10% of the strength declared in the label. Thirty-four (37.4%) contained AAls above the declared upper limit, and 27 (29.7%) below the declared lower limit. Two extreme values were observed for two

AAls: one (Product AP16) contained oxytetracycline with strength ranging from 10.3% to 11.9% and another (AB09) product had doxycycline strength ranging from 141.5% to 165.0% of the stated value (Figure 1).

In 27/91 (29.7%) of the tests conducted the AAls had a strength below the acceptable lower limit (-10%). Unexpectedly, 34/91 (37.4%) had AAls with strength higher than that indicated in the label. Of the 59 individual product batches investigated, only 17 (28.8%) had all their AAls within the $\pm 10\%$ acceptable range. Only 3 of the 20 (15.0%) products had all batches and all their AAls within the $\pm 10\%$ range. A total of 24.5% of the variance was attributed to between-batch variation, the remainder being due to between-product variation.

Since our study is based on a random sample of farms, we are confident that these results are representative of antimicrobial products most commonly used by poultry farmers in the Mekong Delta of Vietnam. Currently there are >10,000 licensed veterinary products in the country, of which about $\sim 50\%$ consist of antibacterial antimicrobial formulations (Anon 2016). This makes quality control monitoring extremely challenging, particularly in a limited-resource setting such as Vietnam.

Quality testing of AAls is very costly, and there is a lack of unbiased information about this issue in animal production in most countries. It has been previously estimated that one in 10 medicinal products in low- and middle-income countries is substandard or falsified (Nwokike et al., 2018). Given that the identity of antimicrobials declared in the label was confirmed in all cases, we do not believe that outright falsification is a major issue here. Furthermore, 'legal' antimicrobials are currently very affordable in Vietnam, and two-thirds of the products investigated had an indication for 'prophylactic use' in the label (normally followed by a list of bacterial diseases). This labelling openly conflicts with the animal health authorities' efforts to discourage routine use of antimicrobials for preventing disease (Aidara-Kane et al., 2018; Anon 2013) and sends a 'wrong' message to farmers (the end users), who will not be able to discern in the few instances that medication may be required in the absence of disease. This is particularly relevant in the context of small-scale farmers in many low- and middle-income countries. Farmers in these settings often do not have access to veterinary services capable of providing them with unbiased advice on AMU.

Under dosing is expected to result because of either sub-optimal quality of the manufactured product, or inadequate preparation at the point of administration by the farmer. For most products, the guidelines for product preparation (mixing with water) for prophylaxis were about half the strength required for therapeutic purposes. There is a risk that this may increase the probability of selection of AMR in bacterial populations (Ungemach, Mueller-Bahrdt, & Abraham, 2006). Withdrawal times for egg production were not specified in 60% of the antimicrobial products investigated. This is a concern, since these products are likely to be used both in meat and layer flocks. The observed inter-batch variation in product quality suggests deficiencies in the mixing/packaging process, since in Vietnam most AAls sold in Vietnam are bulk-imported and then mixed, packaged and distributed within the country.

Based on a representative field survey, we identified the most common antimicrobial products used in poultry farming in the

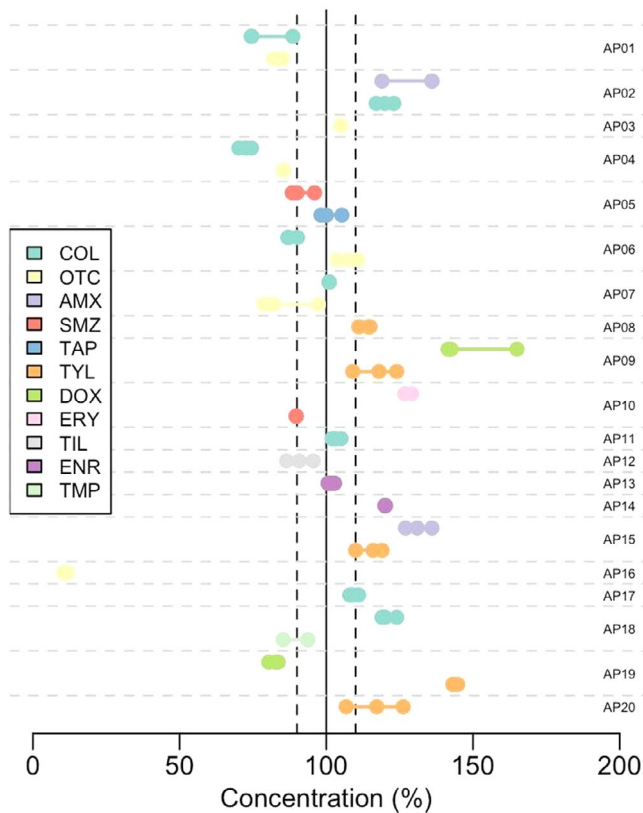


FIGURE 1 Results of the analyses of strength of antimicrobial AAls in the 20 most commonly used products in poultry farms in the Mekong Delta of Vietnam. Products are sorted by decreasing prevalence of use by flock. Each dot across horizontal line corresponds to the results of the concentration of one AAI analysed

Mekong Delta. Results indicate variable quality results, with only 17 (28.8%) product batches containing AAs within the acceptable $\pm 10\%$ range. In addition to improving quality control of veterinary medicine products, we strongly advocate for enhancing regulation and inspection of antimicrobial product labelling, crucially removing the indication for prophylactic use. In all cases, products should indicate withdrawal times for meat, eggs and milk (for products aimed at ruminants). It would be desirable to limit the access to antimicrobials of critical importance for human health for veterinary use, and therefore development of policies aiming at this should be a priority.

CONFLICT OF INTEREST

The authors declare no conflict of interest.

ETHICAL STATEMENT

The authors confirm that the ethical policies of the journal, as noted on the journal's author guidelines page, have been adhered to. No ethical approval was required, as this is a retail study, with no direct implications or impact on any particular subject.

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REFERENCES

- Aidara-Kane, A., Angulo, F. J., Conly, J. M., Minato, Y., Silbergeld, E. K., McEwen, S. A., & Collignon, P. J. (2018). World Health Organization (WHO) guidelines on use of medically important antimicrobials in food-producing animals. *Antimicrobial Resistance & Infection Control*, 7(1), 7.
- Anon. (2013). RUMA seeks to clarify the position on preventive use of antibiotics. *Veterinary Record*, 172, 379.
- Anon. (2016). List of authorized imported antimicrobial products for animal use [in Vietnamese] Department of Animal Health, Vietnam. Available at: https://bientap.vbpl.vn//FileData/TW/Lists/vbpq/Attachments/114545/VanBanGoc_Phu%20luc%201B.%20Dan%20muc%20thuoc%20thuoc%20nhap%20khu%202016.pdf (Accessed 15 Jan 2019).
- Anon. (2017). WHO critically important antimicrobials for human medicine 5th revision World Health Organization, Geneva. Available at: https://www.who.int/foodsafety/areas_work/antimicrobial-resistance/cia/en (Accessed 4 Jan 2019)
- Carrique-Mas, J., & Rushton, J. (2017). Integrated Interventions to Tackle Antimicrobial usage in animal production systems: The ViParc Project in Vietnam. *Frontiers in Microbiology*, 8, 1062.
- Carrique-Mas, J. J., Trung, N. V., Hoa, N. T., Mai, H. H., Thanh, T. H., Campbell, J. I., ... Schultsz, C. (2015). Antimicrobial usage in chicken production in the Mekong Delta of Vietnam. *Zoonoses and Public Health*, 62, 70–78.
- Carrique-Mas, J., Van, N. T. B., Van Cuong, N., Truong, B. D., Kiet, B. T., Thanh, P. T. H., ... Choisy, M. (2019). Mortality, disease and associated antimicrobial use in commercial small-scale chicken flocks in the Mekong Delta of Vietnam. *Preventive Veterinary Medicine*, 165, 15–22.
- Clifford, K., Desai, D., da Costa, C. P., Meyer, H., Klohe, K., Winkler, A. S., ... Zaman, M. H. (2018). Antimicrobial resistance in livestock and poor quality veterinary medicines. *Bulletin of the World Health Organization*, 96(9), 662.
- Cuong, N., Padungtod, P., Thwaites, G., & Carrique-Mas, J. (2019). Antimicrobial usage in animal production: a review of the literature with a focus on low-and middle-income countries. *Antibiotics*, 7(3), 75.
- Cuong, C., Phu, D. H., Van, N. T. B., Truong, B. D., Kiet, B. T., Vo, H. B., ... Carrique-Mas, J. J. (2019). High resolution monitoring of antimicrobial consumption in Vietnamese small-scale chicken farms highlights discrepancies between study metrics. *Frontiers in Veterinary Science*, 6, 174.
- Nguyen, N. T., Nguyen, H. M., Nguyen, C. V., Nguyen, T. V., Nguyen, M. T., & Thai, H. Q. (2016). Use of colistin and other critical antimicrobials on pig and chicken farms in southern Vietnam and its association with resistance in commensal *Escherichia coli* bacteria. *Applied and Environmental Microbiology*, 82, 3727–3735.
- Nwokike, J., Clark, A., & Nguyen, P. P. (2018). Medicines quality assurance to fight antimicrobial resistance. *Bulletin of the World Health Organization*, 96, 135–137.
- Page, S. W., & Gautier, P. (2012). Use of antimicrobial agents in livestock. *Revue Scientifique et Technique (International Office of Epizootics)*, 31, 145–188.
- Phu, T. M., Phuong, N. T., Scippo, M. L., & Dalsgaard, A. (2015). Quality of antimicrobial products used in striped catfish (*Pangasianodon hypophthalmus*) Aquaculture in Vietnam. *PLoS ONE*, 10, e0124267.
- Tran, K. C., Tran, M. P., Phan, T. V., & Dalsgaard, A. (2018). Quality of antimicrobial products used in white leg shrimp (*Litopenaeus vannamei*) aquaculture in Northern Vietnam. *Aquaculture*, 482, 167–175.
- Ungemach, F. R., Mueller-Bahrtd, D., & Abraham, G. (2006). Guidelines for prudent use of antimicrobials and their implications on antibiotic usage in veterinary medicine. *International Journal of Medical Microbiology*, 296, 33–38.

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