Sveriges lantbruksuniversitet
Swedish University of Agricultural Sciences

Faculty of Veterinary Medicine and Animal Science

Antimicrobial drugstore supply for Cambodian livestock farmers

A survey study on retailers' influence and knowledge of antimicrobial resistance

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Uppsala
2020

Degree Project 30 credits within the Veterinary Medicine Programme

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Degree Project in Veterinary Medicine

***Credits**: 30*
***Level**: Second cycle, A2E*
***Course code**: EX0869*
***Course coordinating department:** Department of Clinical Sciences*

***Place of publication**: Uppsala*
***Year of publication**: 2020*
***Online publication**: https://stud.epsilon.slu.se*

***Key words**: antimicrobial resistance, livestock, drugstores, knowledge, attitude, Cambodia*

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SUMMARY

Antimicrobial resistance (AMR) has evolved into one of our time's greatest threats to public health. Antimicrobials are widely used, especially in livestock production where they are also used as growth promoters and for prophylactic purposes. Several countries have begun the process of restricting the use of antimicrobials, but in many places and particularly in low-and middle-income countries (LMICs) the antimicrobial market is poorly regulated, and knowledge about the negative effects of antimicrobial misuse is limited. Antimicrobials are often sold over the counter without the need for prescription, and a low price makes them widely used in all types of animal production. In Cambodia, a consequence of this is a high prevalence of a wide range of resistant bacteria, posing health risks for both people and animals. Another matter to address is the occurrence of falsified and substandard (FS) antimicrobials, leading to treatments with subtherapeutic doses, resulting in treatment failure and further development of AMR. To control the emergence of AMR it is of interest to map the antimicrobial network, in order to identify important stakeholders and suitable points of intervention. In this study interviews were held with retailers at drugstores selling antimicrobials for livestock, namely pigs and poultry. The objective was to obtain information on the retailers' knowledge about antimicrobials and AMR, and to assess to what extent they are involved in the treatment choice for animals. Antimicrobial samples were also purchased and analysed with mass-spectrophotometry, to verify the content of active pharmaceutical ingredient (API). The results show that retailers take an active part in choosing what antimicrobial to use, and that the general knowledge of antimicrobials and AMR is low. A wide range of antimicrobials are used to treat poultry and pigs, with amoxicillin and enrofloxacin most frequently stated to be among the most sold ones. Many of the substances used are classified by the World Health Organization (WHO) as critically important antimicrobials for human medicine, and the products most often contained at least two different substances. This broadens the product's treatment spectrum, and can be viewed in light of the current recommendation by WHO to use narrow-spectrum antimicrobials, and whenever possible avoid the use of critically important antimicrobials in livestock. Possible interventions to slow down the development of AMR in Cambodia by reducing and changing the use of antimicrobials, could be by means of education along with strong enforcement of stricter legislation. This survey suggests that retailers at animal drugstores could be a suitable target group for awareness about AMR, since they seem to be influential actors in the antimicrobial network. However, more research is needed to assess the cost-effectiveness of different interventions, especially in LMICs, in order to design measures that are appropriate in the local context.

CONTENT

ABBREVIATIONS

AMR	Antimicrobial resistance
API	Active pharmaceutical ingredient
ESBL	Extended-spectrum beta-lactamases
FS	Falsified or substandard
GDP	Gross domestic product
GMP	Good manufacturing practice
LDC	Livestock Development for Community Livelihood Organization
LMIC	Low- and middle-income countries
MRSA	Methicillin-resistant *Staphylococcus aureus*
NGO	Non-governmental organisation
SLU	Swedish University of Agricultural Sciences
SVA	Swedish National Veterinary Institute
VAHW	Village animal health worker
WHO	World Health Organization

BACKGROUND

Antimicrobial resistance

A global public health threat

Antimicrobial resistance (AMR) is the pathogen's ability to develop resistance to medicines that previously had therapeutic effect on the disease caused by the pathogen. It is found both among bacteria, virus, parasites and fungi, and is now considered to be one of the major threats to global public health (O'Neill, 2016). According to a report by the World Health Organization (WHO, 2001), 85 per cent of the mortality caused by infectious diseases in the world are deaths due to acute respiratory infections, diarrhoeal diseases, measles, AIDS, malaria and tuberculosis (*ibid*.). Among the pathogens causing these diseases, resistance can be found ranging between zero to almost 100 per cent. It is not a new phenomenon, but with an excessive use of antimicrobials globally, combined with the fact that the previous frequent stream of newly discovered substances has waned, AMR has evolved into a fast growing concern (WHO, 2012). Antimicrobials are one of the most prescribed medicines in the world, and how they are used is of great importance in an AMR perspective. Problematic factors are both overuse, where uncomplicated or viral infections are treated with antimicrobials, but also inadequate treatments where the treatment time or dose is not sufficient to cure the infection but still has an impact on the AMR development. This misuse or underuse due to lack of treatment compliance, financial constraints or substandard antimicrobials, also needs to be addressed in order to control the development of AMR (*ibid*.). Additional driving factors for development of AMR are excessive use of antimicrobials for livestock, where the use is not limited to treatment of disease but also for preventive purposes and to promote growth.

AMR in animal production

Antimicrobials are an extensively used pharmaceutical category in animal production, with livestock sector in high-income countries standing for 50-80 per cent of the total amount consumed (Cully, 2014). Globally the livestock sector uses 70 per cent of all antimicrobials consumed (O'Neill, 2015), and the use is projected to rise by 67 per cent by 2030 (van Boeckel *et al*., 2015). As a consequence of this, AMR is an ever-present and growing issue, which does not constitute an isolated problem in animal production but may also affect public health. This is taken into account when using a One Health approach, where both animal and human aspects are addressed in fighting AMR. There are many reports of the interconnection between production animal health and public health, both concerning disease transmission and spread of resistance, however the magnitude is yet to be fully assessed (Tang *et al*., 2019). Zoonoses such as Salmonella can easily spread from animals to humans if biosecurity is lacking, and people working in the livestock industry are at high risk of infection, as well as of getting affected by the antimicrobials the animals are treated with. Pigs and farmers have been shown to share the same MRSA genotypes (Parisi *et al*., 2019), and a clear correlation has been demonstrated between treatment with antimicrobials and presence of MRSA among pigs and farm workers (Smith *et al*., 2013).

Resistant pathogens can also be transmitted in the food chain, both by means of contamination of other foodstuffs and also by intake of insufficiently cooked meat. It has been shown that

meat as well as vegetables purchased in supermarkets can contain resistant bacteria (Ha Thai & Yamaguchi, 2012; Boonyasiri *et al.*, 2014; Manson *et al*., 2019).

The case of Cambodia

Antimicrobials in Cambodian livestock production

Cambodia is a fast growing economy with economic growth steadily around seven per cent annually over the last ten years, with the agricultural sector serving as an important contributing factor (World Bank, 2019). In 2018 the agricultural sector accounted for 22 per cent of GDP (*ibid*.). With growing demands for animal source foods, livestock production rate and intensity have increased over the last years (Nith & Ly, 2018). A fast growing population has led to an increased pressure on livestock keepers to meet the demand for animal source foods, primarily in the poultry and pork markets. Smallholders still make up the majority of producers, and keeping animals on a small scale can increase a family's income significantly (Poulsen *et al*., 2015). Even though most of the producers are working on a small-scale basis, the larger part of the slaughter pigs come from big commercial companies, located near and around the capital Phnom Penh (Huynh *et al*., 2007). Poultry production has also increased over the last decades, with big commercial companies entering the market in late nineties, although small-scale poultry producers still constitute the vast majority (People in Need, 2015).

In the Cambodian context of intensifying animal production with poor biosecurity conditions, antimicrobials are viewed as a more or less indisputable part of the production system (Om & McLaws, 2016; Ponndara *et al*., 2019). The control of antimicrobials on the market is very low, with over the desk supply for both human and animal use, making it a highly available treatment option for producers (*ibid*.). Recently a study was conducted by Ponndara *et al*. (2019) to map the distribution network of antimicrobials and to investigate the knowledge and attitude on antimicrobials and AMR among pig producers and other stakeholders. The majority of the pig farmers were found to have low knowledge of antimicrobials and AMR, and many of them were in favour of antimicrobial use for preventive purposes and to promote growth (*ibid*.). Generally antimicrobials are the first hand option when confronted with sick animals, and it is common with antimicrobial additives in animal feed (Om & McLaws, 2016). The production system and existing data on the subject of AMR in Cambodia, suggest that further investigation is needed to better understand the complexity of the antimicrobial landscape, and to identify suitable points of intervention (Ström, 2018).

AMR in Cambodia

The number of studies covering the subject of AMR in Cambodia has increased over the last decade although the coverage on AMR in animals and the environment is still poor (Reed *et al*., 2019). A review study by Reed *et al*. (2019) showed that even though many of the findings harmonise with low-and middle-income countries (LMICs) in other parts of the world such as Africa, there are certain resistance patterns that seem to distinguish South-East Asia and Cambodia in this case. One example is *Salmonella typhi*, with resistance to fluoroquinolones ranging from 88.0−95.7 per cent in studies conducted in Cambodia, while in Africa this particular bacterium seems to show high sensitivity to the same family of antimicrobials. According to Reed *et al*. (2019) this highlights the importance of addressing AMR in South East Asia, where antimicrobials such as fluoroquinolones are highly available to the public and often serves as the

first hand choice of treatment of uncomplicated enteric fever in humans. This overuse and misuse will inevitably lead to increased resistance, difficulties in curing infections and a rising proportion of carriers.

In the animal production industry of Cambodia, the problem of AMR is highly present. Strains of *E. coli* resistant to a multitude of antimicrobials have been found in chicken meat, live pigs and organs (Rithy *et al*., 2018; Ström *et al*., 2018; Atterby *et al*., 2019), as well as *Salmonella* spp. with concerning resistance patterns, and particularly in conventionally raised chicken (Por *et al*., 2018). Resistant bacteria can be found not only in animals and animal products, but also in the farm environment (Sokneng *et al*., 2018) and study results indicate that it is common for humans to carry resistant ESBL producing *E. coli* (Rortana *et al*., 2018; Atterby *et al*., 2019). Complicating the matter of disease and resistance transmission in countries such as Cambodia, is the common practice of keeping animals in relatively close contact with people living in the household. Risk behaviours concerning zoonotic diseases are frequent, pinpointing the need for education and intervention in order to improve public and animal health and encourage a sound use of antimicrobials (Osbjer, 2016).

Falsified and substandard antimicrobials

Definition

Falsified or substandard (FS) medicines such as antimicrobials are a major concern in LMICs, both for the individual in a short perspective and for the public health over time (WHOa, 2017). It can cause death to people and animals due to lack of effective treatment, as well as leading to treatment with subtherapeutical levels of active substance, which serves as a driving factor in AMR (*ibid*.). The definition of falsified antimicrobials is an antimicrobial product were the contents, identity or source is deliberately misleading or false (WHOb, 2017). The active pharmaceutical ingredient (API) can be of a lower concentration than presented, ingredients may have been switched to less efficient ones, or medicines that are out of date may have been repacked in new containers. Substandard antimicrobials are products that fail to live up to their given specification or the manufacturer's quality standards, or both. This can be due to lack of good manufacturing practice (GMP) in the production chain, or be a result of improper storage (*ibid*.).

Falsified and substandard antimicrobials and AMR

Every time bacteria are exposed to antimicrobials, there is a risk of development of resistance. This process is natural and inevitable, but shows the need of using antimicrobials prudently. It is unclear to what extent FS antimicrobials contribute to the total development of AMR, but it has been shown that low doses of antimicrobials do select for AMR (Kuile *et al.*, 2016). FS antimicrobials may provide an environment where even susceptible microbes may survive and change in order to cope with higher doses of the substance. FS antimicrobials may contain many times less API than specified by the manufacturer or stated on the label, leading to treatments with subtheurapeutic doses, that may result in therapy failure and resistance development. Even very low concentrations of antimicrobials have been shown to affect the animal's own microbiota (Kim *et al*., 2012; Looft *et al*., 2012). The changes seen are both related to population shifts, meaning that certain bacteria might get survival advantages, as well as to selection for resistance genes (*ibid*.). The genes coding for resistance usually do not give the bacteria any

survival advantages and are therefore not selected for, but in contact with antimicrobials these genes will spread and multiply (Gullberg *et al*., 2014). Concentrations of antimicrobials below minimum inhibitory concentration (MIC) have been shown to select for resistance genes, and if different substances are combined, even lower concentrations are needed to promote the development of AMR (*ibid*.).

Existing data

Very little data exist on FS medicines for veterinary use. More efforts have been made to map the prevalence of FS medicines for human use, and one meta-study concluded that the overall prevalence in LMICs was 13.6 per cent (Ozawa *et al*., 2018). In Asia the percentage was 13.7 and the total per cent of FS antimicrobials was 12.4 per cent. Studies conducted in Cambodia on different types of medicines have shown a prevalence of confirmed substandard medicines ranging from five to fifteen per cent (Khan *et al*., 2010, Yoshida *et al*., 2010). In Cambodia, studies have also been conducted on certain medicines, showing a prevalence of 27.1 per cent FS antimalarial drugs, and another study on aspirins found that only 7.3 per cent passed all quality tests (Yang *et al.*, 2004; Lon *et al*., 2016). Although there are great difficulties in estimating the extent of the problem of FS pharmaceuticals globally, regionally and nationally, these results indicate that its significance should not be neglected.

The above mentioned studies have all focused on medicines for human use, hence the prevalence of FS medicines and antimicrobials for animal use is less studied. One recent study on medicines used for chicken in Vietnam however, showed that more than 70 per cent of the tested antimicrobial products contained a lower concentration of API than stated on the label (Yen *et al*., 2019). Considering the widespread use of antimicrobials in the production animal industry in Cambodia (Ström *et al*., 2018), it is of great relevance to investigate the matter further. The current legislation on pharmaceuticals is weak, and in light of the existing data regarding medicines for human use, one may assume that the situation is similar for medicines for animal use. However, an increase of the national surveillance and measurements against illegal pharmacy outlets has, according to Krech *et al*. (2014), significantly decreased the FS medicines on the market.

INTRODUCTION TO STUDY

Cambodia is a lower middle-income country and one example of a LMICs with a fast growing economy and population, and as an effect of this an increased production rate in the livestock sector (Gilbert *et al*., 2015). In this context and in light of the widespread use of antimicrobials (Ström *et al.*, 2018), it is important to understand the stakeholders' role in the distribution network, to enable informed decision making and intervention for policy makers. Limited data on the quality of antimicrobials for animal use is available, and investigation on this subject is essential. The existence of falsified or substandard products may not only affect livestock health but may also act as a driver for development of AMR (Gullberg *et al*., 2014).

To make the most of policies and regulation, it is crucial with scientifically supported decisions and an understanding of the current political and economic context (Dar *et al*., 2016). Although a considerably enhancement of the antimicrobial use (AMU) and AMR knowledge has been seen over the last few years in the agriculture sector, the current situation in Cambodia is still

characterized by poor knowledge on the subject of antimicrobials and AMR among many stakeholders (Ponndara *et al*., 2019), as well as weak legislation regarding pharmaceutical use and distribution. This creates an arena where actors may take advantage of and exploit the market. By gathering data from the field and mapping the antimicrobials network, the most effective points of intervention may be identified for improving the antimicrobial use in the Cambodian livestock sector.

Objectives

- To investigate the retailers' role in the decision making concerning antimicrobial treatment of animals

- To assess retailers' knowledge on antimicrobial resistance and on antimicrobial products they sell

MATERIAL AND METHODS

Study design

The study was performed in Cambodia in September to October, 2019 and comprised of two parts. In the first part, the objective was to investigate the knowledge among personnel working in drugstores about antimicrobials and AMR, as well as their influence on the use of antimicrobials for livestock in Cambodia. In the second part, antimicrobial samples purchased in drugstores were analysed to verify their specified contents of API. The target group for the survey was thus personnel working in drugstores selling antimicrobials for livestock use. Two different regions were studied; one was the peri-urban region in the capital of Phnom Penh, and the other a rural area in the Takeo province bordering Vietnam (see figure 1). The plan was to visit 25 drugstores in each region.

Researchers from the Livestock Development for Community Livelihood Organization (LDC) assisted in organising transports and identifying available drugstores. Drugstores were included in the study if they sold antimicrobials for livestock, namely pigs and poultry. The sampling was based on official records of existing drugstores, supplemented by scouting in the area, in order to reach the desired number of shops. They were all privately owned.

In Phnom Penh, a veterinary official of Phnom Penh City took part in finding the drugstores and accompanying the team, which apart from him included the author J.H. and a project coordinator/senior researcher from LDC (Mr. Vor Sina).

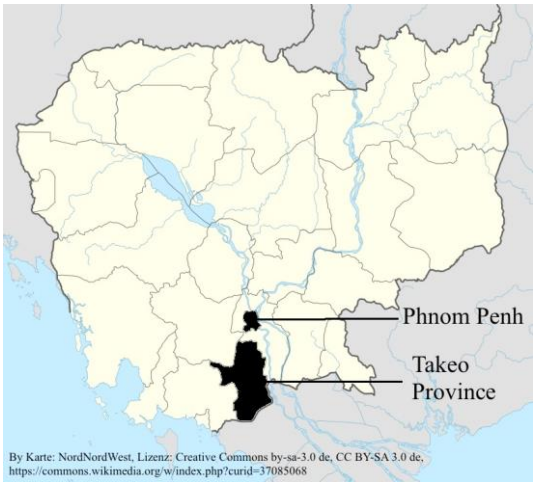

Figure 1. *Map showing Cambodia and the two regions included in the project.*

Questionnaire

A first draft of the questionnaire was developed at SLU and sent to the director of LDC for review. After input from him, the questionnaire was completed and translated to Khmer by the LDC team (see appendix 1). The questionnaire was divided into four parts, where the first part included information about the interviewee's (seller's) educational background as well as experience from working in a drugstore or in the livestock or pharmaceutical sector. The second part contained questions about the seller's role in the choice of treatment for animals, as in to what extent he or she takes an active part in advising on antimicrobials and what his/her recommendations are. Additionally, information was collected about which antimicrobials the retailers stated to be their most sold ones for poultry and pigs respectively. In one question the retailers were instructed to tick boxes indicating if they did or did not sell certain antimicrobials or other pharmaceutical substances. Besides providing information on what medicines they had in stock and were selling, other purposes with this inquiry was to evaluate compliance with the government's banning of certain substances, and also to assess their knowledge of pharmaceutical substances.

The third part of the survey covered AMR, and was based on three questions of true-or-false-type regarding the nature of AMR. The intention was to construct questions that would be fairly easy to answer with very basic knowledge on the subject. Finally, the purpose of the fourth part of the survey was to collect information on the supply chain for each drugstore, and to investigate any possible differences between the two geographical locations. The interviews based on the questionnaires were held in Khmer and translations were made to English after the interviews. All data collected in this survey should be considered as reported data, since the information was not checked against any registers or inventory lists. Comments made by the interviewees during interviews were translated and collected as qualitative data.

Statistical analysis

All recorded data was entered in SPS Statistics 25 (IBM) and analysed with descriptive statistics, and the same software was used to create charts inserted in the thesis.

Analysis of antimicrobial samples

Based on what the respondents reported to be their most sold antibiotic substances, in total fourteen antibiotic samples were purchased from the visited drugstores. The samples were brought to Sweden and analysed at the Swedish National Veterinary Institute (SVA). Mass-spectrophotometry was used to measure the contents of API in each of the samples, and the results were compared with the contents specified on the label.

RESULTS

Questionnaire

A total number of 46 drugstores were visited, with 21 conducted interviews in Phnom Penh including the city's peri-urban region, and 25 in the province of Takeo (see figure 2). Two drugstores in the latter region were situated in a market place on the border between Takeo and another province. Only 21 drugstores were visited in Phnom Penh due to difficulties in finding the desired number during the time available.

Figure 2. *One of the visited drugstores.*

Gender and education

Fifty-seven per cent (26/46) of the respondents were women, and sixty-three per cent (29/46) of all interviewees did have a bachelor degree or had studied two years at the university or a comparable institution. The majority of the bachelors were in Animal Health and Production, a curriculum that has changed during the last decade and now has a more veterinary medicine specific orientation than before, according to researchers at LDC (Weaver *et al*. 2018).

Antimicrobial training

Eighty-five per cent (39/46) claimed to have had specific training on antimicrobial use, although there was a variation in who had provided the training (see table 1). In the city the answers were that training was provided by the university (the majority), private companies or by the city/state authorities. In Takeo province, people got training either from the university (11/19) or from the Village Animal Health Worker (VAHW), usually a person given basic training in animal raising, management and treatment from a non-governmental organisation (NGO) (Weaver *et al*., 2018). In Takeo, forty-two per cent (8/19) of the ones who had received training, had received it from a VAHW, or were themselves a VAHW. In Phnom Penh twenty-for per cent (5/21) declared that they had training from private companies, most often distribution companies they had been working for. Multiple answers were received from several respondents.

Table 1: *Proportion of retailers provided with antibiotic specific training*

Region	Training provided by University	Training provided by Village animal health worker	Training provided by private company	Training provided by city/state authorities	Training provided by city/state authorities and private companies	Training provided by University and private companies	No training
Peri-urban Phnom Penh n=21	9/21	1/21	1/21	5/21	1/21	3/21	1/21
Rural Takeo province n=19	11/19	8/19	0/19	0/19	0/19	0/19	6/19

Recommendations on treatment

Over ninety-five per cent (42/43 and 44/46, respectively) of the respondents said that they always recommend farmers on medication for pigs and poultry. Seventy-six per cent (35/46) said that the animal owners sometimes came back complaining about treatment failure, and twenty-two per cent (10/46) said that this happened very seldom (see table 2).

Table 2. *Retailers' answer to how often farmers complain about treatment inefficiency (n=46)*

		% of cases
Drug inefficiency	Often	2.2%
	Sometimes	76.1%
	Very seldom	21.7%

Around ninety per cent (43/46 and 41/46, respectively) of the retailers said on the question 2.4 (see appendix 1) that possible reasons for an eventual therapy failure were too low dose or too short treatment time (see table 3). During interviews some respondents pointed out that animal owners often do not adhere to treatment recommendations, and tend to use a higher or lower dose than what is instructed. It was also mentioned that animal owners do not follow the recommended treatment time, but use single treatments for economic or other reasons. The most common advise on therapy failure was, in line with the answers to the previous question, to extend the treatment time or increase the dose.

Table 3. *Possible reasons to treatment failure according to retailers based on their discussions with farmers (n=46)*

		% of cases
Possible reasons	Too low dose	93.5%
	Too short treatment	89.1%
	Improper administration	17.4%
	Wrong antibiotic	52.2%
	Resistance	58.7%
	Other	15.2%

Fifteen per cent (7/46) of the retailers said that one of their recommendations in the case of therapy failure was to improve the biosecurity. One of the retailers pointed out that the biosecurity generally in Cambodia is very poor, and that farmers are very hard to influence on that area.

Preventive use and group treatments

Twenty-four per cent (11/45) of the retailers said that they did or often did recommend antimicrobials for disease prevention (see table 4). Almost everyone used to recommend antimicrobials for group treatment, something that may be explained by that such practice is common in poultry production. This is in compliance with the data on antimicrobials sold for pigs and poultry respectively, since almost all respondents sold antimicrobials for poultry mainly as water or feed additives. For pigs, all top-selling antimicrobials sold were in injection form.

Table 4. *Per cent of respondents recommending antimicrobials for disease prevention (n=45)*

		% of cases
Antimicrobial disease prevention	Yes, always	4.4%
	Often	20.0%
	Sometimes	31.1%
	No	44.4%

Most sold antimicrobials

Thirty different answers were obtained from the questions on top three antimicrobials sold by the drugstores for poultry and pigs respectively. The ten most frequent answers are shown in table 5 and 6.

Table 5. *Most sold antimicrobials for poultry, based on reports from 46 drugstores on the top three most frequently sold antibiotics*

		% of cases
Antimicrobials	Amoxicillin	26.8%
	Enrofloxacin	19.6%
	Doxycycline	15.9%
	Tetracycline	11.6%
	Lincomycin	3.6%
	Tylosin	3.6%
	Ampicillin	2.9%
	Sulfa	2.2%
	Colistin	2.2%
	Penicillin/streptomycin	0.7%

Table 6. *Most sold antimicrobials for pigs, based on reports from 43 drugstores on the top three most frequently sold antibiotics*

		% of cases
Antimicrobials	Penicillin/streptomycin	17.8%
	Amoxicillin	16.3%
	Tylosin/gentamicin	14.0%
	Enrofloxacin	10.9%
	Streptomycin	7.0%
	Tylosin	6.2%
	Lincomycin	6.2%
	Ampicillin/penicillin	5.4%
	Ampicillin	5.4%
	Tetracycline	3.9%

The answers were often given on separate substances referring to corresponding products, but the products were most often found to contain at least two different antimicrobial substances.

Knowledge of AMR

None of the respondents answered correctly on all three questions concerning AMR, and thirty per cent (14/46) said that AMR does not spread between humans and animals (see figure 3).

Over eighty per cent (38/46) answered correctly that AMR implies that diseases develop resistance against antimicrobials, but the same proportion of respondents also said that AMR means that animals develop resistance against the antimicrobials.

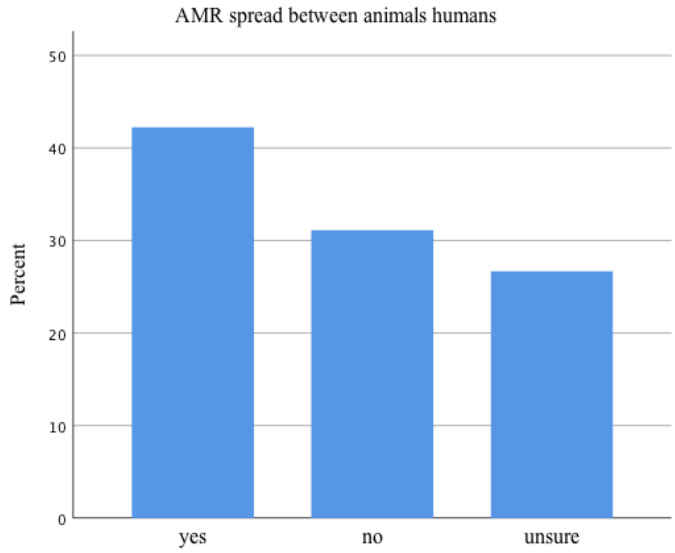

Figure 3. *The retailers' answers to the statement that AMR spread between animals and people (n=45).*

Supply

Eighty-seven per cent (40/46) of the respondents got their antimicrobial supply from companies specialized in distributing pharmaceuticals, and fifty-four per cent (25/46) from other drugstores in the same region. Seven per cent (3/46) got their supply from a neighbouring country, and no one got their supply directly from manufacturing companies or shops in other regions in the country. On this question more than one answer could be chosen.

DISCUSSION

This study indicates that retailers at drugstores retailing antimicrobials for livestock are influential actors in the choice of treatment for animals in Cambodia. The results also point at a knowledge gap regarding antimicrobials and AMR among these retailers, which could affect what treatment they recommend. Our results suggest that retailers might be an appropriate target group in raising awareness and spreading knowledge on AMR, in order to reduce antimicrobial use in general and in particular the critically important antimicrobials for humans. Today, a wide range of different antimicrobials are used to treat livestock in Cambodia, many of them classified as critically important for humans by WHO. Possible interventions to slow down the development of AMR in Cambodia, by reducing and changing the use of antimicrobials, could be by means of education along with strong enforcement of stricter legislation.

Survey results

Influence and education

The large number of respondents claiming that they frequently recommend farmers on what medicines to use, confirms the hypothesis that drugstores could be influential actors in the antimicrobial market. It also agrees with observations in Cambodia made by Ponndara *et al.*

(2019). In their study it was concluded that animal drugstores play an important role in the antimicrobial chain, and affect not just smallholders but also semi-commercial pig producers (farms sized 50-499 pigs). Since retailers often recommend what antimicrobial to use, it could be of interest to assess from where they receive antibiotic training. According to this survey, the university, VAHW and private distribution companies play an important role in providing information about antimicrobials and their use. The same actors were also identified in the stakeholder mapping by Ponndara *et al*. (2019). Most of the retailers who had specific antibiotic training got it from the university, showing the need to include education about AMR in the animal health and production curriculum.

The distribution companies appear to be a key stakeholder, both in the distribution network of antimicrobials, but also in providing information and education on antimicrobial use. The high percentage of drugstores getting their supply from distribution companies indicates that the latter might have a significant impact on the drugstores and what they sell. Additionally, distribution companies offer specific training on antimicrobials, but according to respondents this training is focused on storage and different antimicrobial substance groups rather than on responsible use.

Knowledge of antimicrobials and AMR

Generally there seemed to be a low level of knowledge of what pharmaceutical substances the products in stock contained. The retailers recognised antibiotic substances that were included in the product's name, but had very little awareness of additional substances specified on the labels. On numerous occasions, the retailers claimed not to sell certain antibiotics, although products containing these antibiotics where observed in their stock. Furthermore, on several of the antimicrobial products sold at the drugstores, indications such as "cold" or "inflammatory disease" could be read on the labels (see figure 4). Some of the interviewees also pointed out that many farmers demanded antimicrobials to treat their pigs when the pigs had contracted African swine fever, a viral disease that at the time for the survey was spreading in the country. These observations indicate that antimicrobials may be frequently used to treat viral infections where they have no therapeutic effect.

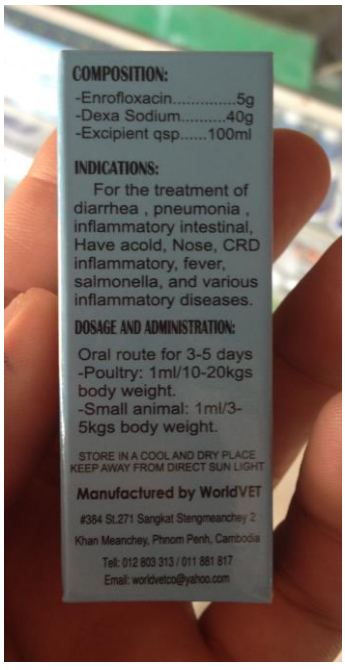

Figure 4. *Product information on a package of enrofloxacin.*

The knowledge about AMR among retailers was found to be low, in line with results from the study by Ponndara *et al*. (2019). Many retailers did not think that AMR can spread between humans and animals, and a high proportion of retailers said that AMR implicates that the animal is resistant to antimicrobials. Surveys carried out in other LMICs have also identified a knowledge gap on the subject of AMR, including among doctors and medical students (García *et al*., 2011; Thriemer *et al*., 2013; Quet *et al*., 2015). García *et al*. (2011) showed in a survey in the neighbouring country Laos that almost 30 per cent of the responding doctors considered unnecessary antimicrobial treatments as harmless. This

highlights the fact that a lack of knowledge regarding AMR is not limited to the public, but widespread also among medical professionals.

Several of the responding retailers pointed out a lack of biosecurity in Cambodian farms, a problem identified by a number of studies (Osbjer, 2016; Ström, 2018). Overuse of antimicrobials will inevitably lead to a rising prevalence of resistant pathogens where further spread to people is facilitated by poor biosafety and biosecurity practices (Osbjer, 2016). The potential transmission routes between animals and people could be an issue to emphasise when providing information on AMR.

Almost sixty per cent of the respondents stated that they regard resistance as a possible reason for treatment failure. This might indicate that there is some awareness of the AMR-issue, although it should be interpreted with caution since it is unclear what their perception of resistance is. A comparison can be made with results from a study by Pearson and Chandler (2019), investigating the knowledge and attitude regarding AMR in different LMICs. They targeted both human and animal healthcare professionals prescribing or selling antimicrobials, and interviews were held in six different countries in Africa and Asia. Their results showed that despite a high awareness of AMR among the professionals, this did not lead to a reduced or changed behaviour regarding prescription or dispensing of antimicrobials. The prescriber's awareness but inability to acknowledge his or her own role in the AMR development, has been identified in other studies as well (García *et al*., 2011; Thriemer *et al*., 2013; Quet *et al*., 2015). Pearson and Chandler (2019) stressed various contributing factors, including poor hygiene practices, lack of information on local resistance patterns and a strong influence from representatives from the pharmaceutical industry. Their findings are consistent with results from the current study, where the distribution companies seem to play an important role in education and supply.

Critically and highly important antimicrobials

The large number of different antimicrobial substances sold at the drugstores is a concern, since many of them are essential in human medicine. It is in line with the results from Ström *et al.*'s study from 2018, where they found at least seventy different antimicrobial brands used by ninety-one surveyed pig farmers. In 2005, WHO held the first expert meeting on critically important antimicrobials for human health (CIA) in Canberra, Australia, where a group of experts developed criteria for antimicrobials to be categorised into different groups of importance (WHO, 2019a). Based on these criteria, a list was formulated. Since the first meeting the list has been revised six times. On the current list, revised in November 2018, five antimicrobial classes are classified as "Critically important antimicrobials" with "Highest priority". These are cephalosporines (3rd, 4th and 5th generation), glycopeptides, macrolides and ketolides, polymyxines and quinolones (WHO, 2019a). At least two of these were sold at the drugstores surveyed in this study, i.e. as the substances colistin (polymyxin) and enrofloxacin (quinolone). The latter was the second most commonly sold antimicrobial for pigs and poultry. Additionally, one shop claimed to sell vancomycin that is a glycopeptide. Among the antimicrobials classified as "Critically important" with "High priority", classes such as aminoglycosides and aminopenicillins are found, these were sold at the drugstores as the substances gentamicin and ampicillin, respectively. Gentamicin in combination with tylosin composed seven per cent of the top selling antimicrobials for poultry and pigs, and ampicillin four per cent. Several more than the above

mentioned substances are also found in this category, and others in the next category of the list, "Highly important antimicrobials".

According to WHO (2019b) quinolones are classified as critically important with highest priority since they are known to select for resistance in *Salmonella* spp. and *E. coli* when used as treatment for animals. Additionally, it is a substance of high priority to treat severe infections caused by these pathogens in people. Glycopeptides and polymyxines are in the same classification group for similar reasons, since development of resistance among other bacteria has been observed when the substances are administered to animals (*ibid*.).

In summary, substances widely used in Cambodia to treat livestock, are found both to be highly selective for resistance, and are also key medicines to treat common but severe human infections. Current recommendations encourage the use of antimicrobials with narrow-spectrum to treat uncomplicated infections (Magnusson *et al*., 2019). The fact that most of the products mentioned by the retailers in this survey contained at least two different substances, points at the widespread use of broad-spectrum antimicrobial treatment of livestock in Cambodia. The use of narrow-spectrum antimicrobials should thus be emphasised in future information and awareness campaigns, which has been put forward also in the health sector by Huttner *et al*. 2019. The results from this survey regarding the most selling antimicrobials must be interpreted in light of the fact that they are based on reported data, and have not been checked against selling records or tables of content on the products.

Policy compliance

Thirteen of the respondents said that they did sell chloramphenicol, and enrofloxacin was one of the most frequently sold antimicrobials for poultry, administered as a feed or water additive. Both of these are examples of antimicrobial substances that have been banned as feed additives by the Cambodian government (USDA, 2019). This shows a gap in the stakeholders' compliance with new regulation on pharmaceuticals. Assessments have been made to determine if restricted access to antimicrobials in different countries can lead to a reduction in AMR emergence. The results show that interventions of this kind do reduce the risk of resistance development, except if the restriction is limited to include single antimicrobial classes or antimicrobials (Tang *et al*., 2019). Successful restrictions included antimicrobials used as growth promoters, the ones for non-therapeutic use and total banning of all therapeutic and non-therapeutic use (*ibid*.). In LMICs such as Cambodia these interventions can prove to be challenging to implement due to limited experience in regulating access and use of antimicrobials in addition to limited human and economic resources to enforce new legislation. By targeting broader categories of substances in the regulatory framework rather than single classes or substances, as also suggested by Tang *et al*., Cambodia can achieve a more comprehensive legal framework resulting in ceased resistance development. It cannot be ruled out that the presence of the veterinary official affected the answers regarding prohibited substances in the Phnom Penh group of drugstores.

Possible interventions

In conclusion, this study identifies some areas to address in order to reduce antimicrobial use in livestock, and halt AMR emergence. Retailers at animal drugstores in Cambodia are influential stakeholders in the antimicrobial chain, and could therefore be targeted in raising awareness about AMR. Village Animal Health Workers are often directly involved in the trade of antibiotics, serve as a source of information to farmers (Catley *et al*., 2004) and should therefore be considered also as a suitable target group for educational programs. Information to this group should be focused on better farm management, improved animal husbandry and biosecurity to achieve improved infection prevention and control.

In other countries there has been a reduction in the use of antimicrobials after information campaigns addressed to prescribers outside hospitals, however these projects have been implemented in high-income countries only and focusing on human medicines (Goossens *et al*., 2008; Sabuncu *et al*., 2009; Nathwani *et al*., 2011). Campaigns directed towards the public have also proved to decrease the use of antimicrobials, although these operations have been carried out in high-income countries as well, and would probably need to be modified in order to be successful in an LMIC context (Cross, Tolfree & Kipping, 2017). Conditions also differ between LMICs, and interventions that result in reduction of antimicrobial use in one place, might not yield the same results in a neighbouring country, showing the need to properly adapt interventions to local conditions (Chalker *et al*., 2005). Public awareness campaigns have also been used globally in attempts to raise awareness of AMR and to reduce the use of antimicrobials. Although these initiatives have received great support from countries engaged, the actual outcome regarding its mission has been difficult to assess and in some cases the effect has been proven limited (Dar *et al*., 2016).

Besides education, information and awareness campaigns, legislation is a tool to control AMR emergence (Cox *et al*., 2017). WHO has provided a list of antimicrobials that need to be used restrictively, and new legislation could be designed on the basis of this. Focus should be on feed producers selling feed for healthy animals with antimicrobial contents, as well as on commercial manufacture and distribution companies, as also emphasized by Om & McLaws (2016). Today many retailers get their antimicrobial training from commercial companies, which can prove problematic since incentives to reduce the use of antimicrobials are lacking. Establishing alternative information sources and implementing stricter legislation on the pharmaceutical market could possibly address this. The prohibition of certain feed additives and antimicrobials by the Cambodian government is an attempt to do this, but new regulations such as this need to be well implemented and enforced. Stakeholders must be informed by the government agencies on new legislation, and the information must be comprehensive and easily accessible.

In summary, there is very limited data on cost-effectiveness regarding different interventions, particularly in LMICs. With limited resources it is important that the money invested leads to the greatest possible outcomes in terms of a reduction in antimicrobial use and development of AMR (Okeke *et al*., 2005). More studies on interventions in LMICs are needed in order to design suitable legislative and educational measures.

POPULAR SCIENCE SUMMARY

Antimicrobials are biologically active substances that are used to kill bacteria and other disease-causing microorganisms such as parasites and fungi, also called pathogens. Antimicrobial resistance (AMR) is the concept of microorganisms' response to antimicrobial treatment, which involves development and spread of resistance against certain medicines. Antimicrobials will have little or no effect on diseases caused by pathogens that have developed resistance, which leaves the medicals no choice but to switch to another antimicrobial. When pathogens have developed resistance against many different antimicrobials they are called multi-resistant. Multi-resistance makes it increasingly difficult to treat infections caused by resistant pathogens, and AMR is considered one of our time's greatest challenges for public health.

AMR is a natural evolutionary process, but it is accelerated by a global overuse of antimicrobials, both in human health care and for veterinary use. Every time antimicrobials are used, there is a risk of resistance development, underlining the need to use them wisely and restrictively. In livestock production antimicrobials in low doses are used as growth promoters, and in many low-to-middle-income countries low price, high accessibility and weak legislation make antimicrobials widely used. This has led to a high prevalence of resistant bacteria, with severe consequences for people's health. Adding to the problem is the existence of falsified or substandard antimicrobials on the market, contributing to treatment with insufficient doses and reducing the product's credibility.

Cambodia is an interesting country to study in the context of AMR, since it is a fast growing economy, with increasing demands for animal source products. This has led to an intensifying livestock production, with increased use of antimicrobials to maintain the animals' health. Antimicrobials are generally cheap and can be bought over the counter at animal drugstores. In Cambodia, bacteria resistant to a wide range of antimicrobials have been found both in animals, their environment and in people. Studies on falsified and substandard products have focused on human medicines, and data on antimicrobials for veterinary use is lacking.

This study aimed at investigating the people working in animal drugstores, and their role in the antimicrobial network in Cambodia. The hypothesis was that they play a key role in decision making regarding treatment of livestock, and could therefore be targeted in future interventions to decrease the use of antimicrobials. The retailers' knowledge on antimicrobials and AMR was also investigated, and antimicrobial samples were purchased for analysis at a laboratory in Sweden. Interviews with a total number of 46 retailers were performed in September 2019, in the capital of Phnom Penh and in the province of Takeo. The language used during the survey was Khmer, and translations to English were made after every interview.

The results showed that the retailers to a high extent recommend livestock owners on what antimicrobial they should use to treat their animals with. Data obtained also confirmed the knowledge gap on antimicrobials and AMR that other studies on the subject have identified. A wide range of different antimicrobials are used in Cambodia to treat livestock, of which many are classified as critically important for human medicine by the World Health Organization. These substances have been proven to drive resistance development among certain bacteria,

and are often one of few choices when it comes to treating severe infections in people. Therefore, it is of great importance that they are used restrictively, and primarily for humans.

Since people working in animal drugstores seem to exercise influence on livestock owners on how to treat animals, they could be a suitable target group to educate on antimicrobials and AMR. What must be considered is the fact that the retailers in turn, and to a significant extent, are influenced by distribution companies, from where they get both their products and antimicrobial specific training. This puts light on the need for stricter regulations on the pharmaceutical market in Cambodia, possibly by prohibiting groups of substances or by restricting the indications for use of antimicrobials. However, more research is needed on what type of interventions that are most effective, and measures taken must be adapted to Cambodia in terms of its political, economic and cultural context.

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APPENDIX

Questionnaire used for antibiotic supply study

1. **Background data**

1.2. Age: _____ years

1.3. Sex:

☐ male

☐ female

1.4. Highest achieved education level (select one)

☐ No formal education

☐ Primary school

☐ Secondary school

☐ High school

☐ University

1.5 Owner ☐ or employee ☐?

1.6 How long have you been in this business? _____

1.7 Previous experience from livestock sector? (yes☐/no☐)

- If yes, how long? _____

1.8 Previous experience from pharmaceutical/chemical sector? (yes☐/ no☐)

- If yes, how long? _____

1.9 Received specific training on antibiotic use? (yes☐ / no ☐)

- If yes, from whom did you receive the training? _____

2. **Choice of treatment**

2.1 How often do you recommend the farmer which medication to use for pigs? (select one)

☐ Always

☐ Mostly

☐ Sometimes

☐ Very seldom (the farmer knows what to use)

☐ Never

2.2 How often do you recommend the farmer which medication to use for poultry? (select one)

☐ Always

☐ Mostly

☐ Sometimes

☐ Very seldom (the farmer knows what to use)

☐ Never

2.3 Does it happen that the farmer comes back to you, saying/complaining that the drug doesn't work? (select one)

☐ Often

☐ Sometimes

☐ Very seldom

☐ Never

2.4 If the drug doesn't work, what could be the reason? (select one or more)

☐ too low dose

☐ too short treatment time

☐ the animal is not given the medicine properly

☐ wrong antibiotics

☐ poor quality of antibiotics

☐ the disease has developed resistance towards the drug

☐ other (please specify):

2.5 If the drug doesn't work, what do you recommend? (select one or more)

☐ continue with the same drug but higher dose and/or longer time

☐ switch to another antibiotic

☐ recommend a veterinary consultation

☐ other (please specify):

2.6 Do you recommend livestock owners to use antibiotics for preventing diseases? (select one)

☐ Yes

☐ Often

☐ Sometimes

☐ No

2.7 Do you recommend livestock owners to use antibiotics for group treatments? (select one)

☐ Yes

☐ Often

☐ Sometimes

☐ No

2.8 Which three antibiotics do you sell most to poultry producers, and in what administration form (feed/water additive, injection, other)?

- 1: _____ administration form: _____
- 2: _____ administration form: _____
- 3: _____ administration form: _____

2.9 Which three antibiotics do you sell most to pig producers, and in what administration form (feed/water additive, injection, other)?

- 1: _____ administration form: _____
- 2: _____ administration form: _____
- 3: _____ administration form: _____

2.10 Does your shop sell any of the following active ingredients or substances? (select one or more)

☐ Chloramphenicol (yes/no)

☐ Thrimetoprim (yes/no)

☐ Clenbuterol (yes/no)

☐ Ampicillin (yes/no)

☐ Diethylstilbestrol (yes/no)

☐ Amoxicillin (yes/no)

☐ Glycopeptides/Vancomycin (yes/no)

☐ Gentamicin (yes/no)

☐ Fluoroquinolones/Ciprofloxacin (yes/no)

☐ Nitrofuran/Furazolidine/Nitrofurazone (yes/no)

☐ Tetracycline (yes/no)

3. Antimicrobial resistance

3.1 Antimicrobial resistance means that *animals* become resistant to antibiotics and their effect is reduced. (select one)

☐ yes

☐ no

☐ unsure

3.2 Antimicrobial resistance means that *diseases* become resistant to antibiotics and their effect is reduced. (select one)

☐ yes

☐ no

☐ unsure

3.3 Antimicrobial resistance can spread between animals and humans. (select one)

☐ yes

☐ no

☐ unsure

4. Supply

4.1 From where do you get antibiotics to your shop? (select one or more)

☐ from other shop in this region (Takeo or Phnom Penh)

☐ from other shop in another region

☐ drug distribution company

☐ drug manufacturing company

☐ supplier in neighboring country (Specify)

☐ other (please specify):