Understanding antibiotic use in pig production in Thailand

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Declaration of candidate's roles in the thesis

I, Angkana Lekagul, declare that the thesis presented for the doctoral degree at the Faculty of Infectious and Tropical Diseases, London School of Hygiene and Tropical Medicine, has been solely the result of my own work, except where work which has formed part of jointly authored publications has been included. My contribution and those of the other authors to this work is explicitly indicated below. I confirm that appropriate credit has been given within this thesis where reference has been made to the work of others. I confirm that this thesis has not been submitted in whole or in part for any other degree or professional qualification.

This study course was under the guidance and supervision of Professor Shunmay Yeung (SY) and Professor Anne Mills (AM) from London School of Hygiene and Tropical Medicine, and Professor Jonathan Ruston (JR) from University of Liverpool, and by the advisory committee: Associate Professor Marco Liverani (ML) from London School of Hygiene and Tropical Medicine, and Dr Viroj Tangcharoensathien (VT) from International Health Policy Program, Ministry of Public Health, Thailand.

This thesis is written as a research paper style thesis, in accordance with the guidelines and regulations specified by the London School of Hygiene and Tropical Medicine. There are four papers in this thesis. I, Angkana Lekagul (AL) am the first author of all four papers. The two research papers presented in Chapter 3 have been published in Veterinary and Animal Science as "Patterns of antibiotic use in global pig production: A systematic review" by AL, VT, and SY; and Preventive Veterinary Medicine as "The use of antimicrobials in global pig production: A systematic review of methods for quantification" by AL, VT and SY. Both reviews were conceived by all of the authors. I, VT and SY contributed to the design of the study. I and VT conducted abstract screening and full paper review for eligibility. I assessed the full texts, carried out the analysis and developed the initial draft of the manuscript. All three authors substantively reviewed and revised successive drafts, and approved the final manuscript

The work presented in Chapter 5 has been published in BMJ Global Health as "How antibiotics are used in pig farming: a mixed-methods study of pig farmers, feed mills and veterinarians in Thailand" by AL, VT, AM, JR, and SY. AL, VT and SY contributed to the design of the study. AM and JR provided conceptual and technical support in the study design and data interpretation phases. AL conducted the data collection and analysis and developed the initial draft of the manuscript. AL, VT and SY substantively reviewed and revised successive drafts. All authors approved the final manuscript

I have read and understood the School's definition and policy on the use of third parties (either paid or unpaid) who have contributed to the preparation of this thesis by providing copy editing or proofreading services. I declare that no changes to the intellectual content or substance of this thesis were made as a result of this advice and that I have fully acknowledged all such contributions.

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Back in 2015, before I started my PhD journey, I asked myself why a PhD was worth it. Someone told me that I can be a researcher without a PhD degree, but I can make more of a difference with a PhD.

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I believe that my Phd study has made a difference in me, and that difference has the potential to help our planet.

Abstract

Rising global concern about antimicrobial resistance (AMR) has drawn attention to the use of antibiotics in livestock. Of particular concern is the excessive, sub-therapeutic use of antibiotics for disease prevention, in particular the Critically Important Antimicrobials (CIA), which are reserved as a last resort for the most severe and resistant human infections. Understanding current usage of antibiotics in these animals is essential to design and implement effective interventions that will reduce unnecessary antibiotic use. However, to date few studies have assessed the use of antibiotics for pig production in low- and middle-income countries.

The aim of the thesis is to investigate patterns of antibiotic use and determinants influencing antibiotic use in pig production in Thailand in order to contribute to the development of policies to optimise the use of antibiotics in pig production and control AMR.

Two systematic reviews on antibiotic use in pig production and its associations; and methods and measurements for quantification of the use of antibiotics in pig production were conducted to explore the antibiotic use in pig production globally. Using mixed methods for the empirical research, a survey of pig farmers (n=84), a survey of feed mills (n=31), and interviews with veterinarians (n=5) were undertaken to understand the patterns of antibiotic use. A total of 31 in-depth interviews were conducted with different categories of actors: pig farmers (n=13), drug retailers (n=5), veterinarians (n=7), government officers (n=3) and representatives of animal and human health associations (n=2) to explore determinants influencing antibiotic use in pig production in Thailand.

Evidence revealed several practices associated with antibiotic use in pig production in Thailand, which may contribute to the emergence and threat of AMR to people including a high proportion of pig farmers using antibiotics for disease prevention and using antibiotics in the CIA category; and a large volume of antibiotics being administered in the form of medicated feed. The multi-faceted nature of the views and practices may contribute to misuse or overuse of antibiotics in the study locations, including misconceptions about the nature of antibiotics and AMR (particularly among smallholders), lack of facilities and financial means to establish an antibiotic-free farm, lack of sufficient training on AMR and antibiotic prescribing for veterinarians, the profit motive of pharmaceutical companies and their ties to farm consultants, and lack of sufficient regulatory oversight.

Given the concern on the loss of antibiotic effectiveness through the development of AMR, collective action is required to improve the practices of all actors towards the optimisation of antibiotic use in pig production. For example, farmers need better access to veterinary services and reliable information about animal health needs and antibiotics. Further development of professional training and clinical guidelines, and the establishment of a code of conduct, would help improve antibiotic dispensing practices. In addition, a combination of market access rules by the private sector and control through regulations such as establishing veterinary antibiotic prescriptions monitoring systems and limiting the pharmaceutical industry's influence on the farmers' and veterinarians' decision on the use of antibiotics, could be an effective instrument to govern the use of antibiotic in livestock production.

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AMR	Antimicrobial Resistance
API	Active Pharmaceutical Ingredients
ATCvet	Anatomical Therapeutic Chemical veterinary classification system.
bla NDM-1	New Delhi metallo-beta-lactamase
CIA	Critically Important Antimicrobials
DLD	Department of Livestock Development
FAO	Food and Agriculture Organization of the United Nations
GAP	Good Agricultural Practice
GAP-AMR	Global Action Plan on Antimicrobial Resistance
GDP	Gross Domestic Product
HICs	High-Income Countries
HPSR-AMR	Health Policy and Systems Research on Antimicrobial Resistance
LMICs	Low- and Middle-Income Countries
MCR-1	Plasmid-mediated colistin resistant gene
MDR	Multidrug-resistant
MIA	Medically Important Antimicrobials
MRSA	Methicillin-resistant *Staphylococcus aureus*
OIE	World Organisation for Animal Health
PCU	Population Correction Unit
Thai-FDA	Thai-Food and Drug Administration
Thailand SAC	Thailand Surveillance of Antimicrobial Consumption in humans and animals
WHO	World Health Organization

SECTION A: BACKGROUND

Chapter 1 Introduction

Summary

In this chapter, I set out the background to Antimicrobial Resistance (AMR) and its significance for global health, and I explain the mechanism of AMR emergence and its drivers including the use of antibiotics. Antibiotics are used widely in farming and animal food production around the world. In this chapter, I describe the use of antibiotics in pig production, which is the focus of the research on antibiotic use and AMR presented in this thesis. I address the contribution of agricultural to AMR role of agriculture and antibiotic use in animal production before describing global policy on AMR.

Following this, I provide background information about pig production, the AMR and antibiotic use in pig production, antibiotic distribution and control of antibiotic in Thailand. The chapter concludes with a presentation of the rationale of the thesis, the aim and objectives of the thesis and the structure of the thesis.

1.1 Antimicrobial resistance: a threat to global health

Antimicrobial resistance (AMR) is a serious threat to global health. It has become a growing concern that creates serious implications for human health which leading to increased death rates and health care spending. It is estimated that AMR will claim 10 million deaths annually and cost the world up to US$ 100 trillion, equivalent to 2% to 3.5% of Gross Domestic Product (GDP) by 2050 (1).

The discovery of antimicrobials in the 1940s transformed the therapeutic paradigm in health care. Since then, antimicrobials have been a vital tool to fight infectious diseases and are one of the most important medical interventions in modern medicine. However, the efficacy of antimicrobials in health care is increasingly under threat worldwide as a result of the emergence and spread of untreatable infections with common bacterial pathogens. The situation is worsened by the lack of discovery of any new classes of antimicrobials to treat bacterial infection since the 1980s; meanwhile the resistance rate is increasing (2). The World Health Organization (WHO) says that, "Without urgent action, we are heading for a 'post-antibiotic era', in which common infections and minor injuries can once again kill." (3).

Resistant microbes do not respect international borders. Due to the increase in international travel, the vulnerability of any country to disease is arising faster than ever before in human history. An example of globalisation driving AMR transmission is seen in the spread of the novel carbapenem resistance mechanism of New Delhi metallo-beta-lactamase (bla NDM-1) in Enterobacteriaceae. The bla NDM-1 gene was first reported in 2009 in a *Klebsiella pneumonia* isolated in a Swedish hospital from a patient previously admitted to a hospital in India. Later, the isolation of bacterial species carrying the bla NDM-1 gene was reported in several countries worldwide, mostly from patients who had travelled to and from the Indian subcontinent (4). This example shows that no one single country can protect the health of its population against AMR. International collective action is therefore essential.

The problem of resistant bacteria is not only a public health challenge for the human health sector. AMR has extended far beyond humans because resistant pathogens can spread across humans, animals, food and the environment. The drivers of AMR include the use of antimicrobials in both humans and livestock. Most classes of antimicrobials used to treat bacterial infections in humans are also used in animals. A report in 2015 described the discovery of a plasmid-mediated colistin resistant gene (MCR-1) in commensal *Escherichia coli* from pigs, pork products and humans in China. This raised global concerns due to the fact that colistin is a last-resort antimicrobial used to treat severe infections caused by multidrug-resistant (MDR) pathogens in hospitals (5). Given the important and interdependent human, animal, and environmental dimensions of AMR, this highlights the need for a holistic and multi-sectoral approach or a 'One health' approach. This means the collaboration of multiple disciplines working locally, nationally, and globally to attain optimal health for people, animals and our environment (6). The One Health concept also recognises that both a cause and solution of AMR encompasses interactions among humans, animals and the environment.

1.2 Mechanisms of the development of AMR

Antimicrobials are medicinal products that kill or stop the growth of living microorganisms. Most antimicrobial drugs are produced naturally by living organisms including plants, animals or microorganisms such as environmental fungi and saprophytic bacteria; only few of them are entirely synthetic (for example, fluoroquinolones) (7,8). Antimicrobials are classified based on the microorganisms they act primarily against, including:

- Antibacterials[1] (active against bacterial infections, often called antibiotics)
- Antimycobacterial drugs (antibacterials specifically active against tuberculosis and other mycobacterial infections)
- Antivirals (active against viral infections)
- Antifungals (active against fungal infections)
- Antiparasital drugs (active against malaria and other infections due to parasites).

AMR is a natural process where microbes evolve to resist the action of antimicrobials (9,10). Some microorganisms are naturally resistant to certain antimicrobials. For example, some bacteria have an innate ability to resist the action of some antimicrobials via inherently structural or functional characteristics such as the absence of a susceptible target of a specific antibiotic, which is called intrinsic resistance (11).

[1] In general, this thesis focuses on "antibiotic" which refers to antibacterial. The term "antimicrobials" is used when referring to standard terminology such as antimicrobial resistance.

Microorganisms can also resist the effects of an antimicrobial to which they were once sensitive in other ways, known as acquired AMR. Acquired AMR is driven by several mechanisms. Firstly, resistance can occur via a reduction in the intracellular concentration of antibiotics by a reduction in antibiotic permeability and efflux. Secondly, bacteria may inactivate the antibiotic by modification or degradation of the antibiotic molecule. Thirdly, bacteria can modify the antibiotic target sites by modification or protection of the target, and change of target expression (10,12,13). Figure 1.1 depicts resistance mechanisms including reduced permeability, antimicrobial efflux expression changes, antimicrobial modification, target protection, and target modification. Responses to antibiotics in susceptible organisms are represented on the left and resistant organisms are represented on the right. Furthermore, certain bacteria have evolved resistance through an acquired mechanism, particularly by horizontal gene transfer from other resistant organisms in the environment (13,14). AMR genes in environmental and commensal bacteria are recognised as a potential reservoir of pathogens to humans and animals (15).

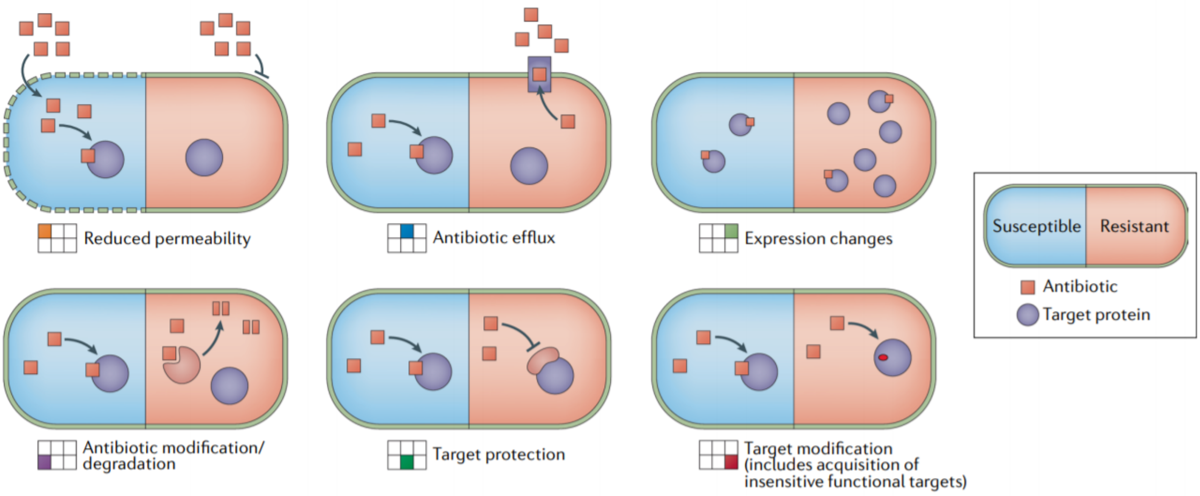

Figure 1.1 Potential resistance mechanisms in micro-organisms

Source: Boolchandani, *et.al* (12)

1.3 Drivers of AMR

The exposure of bacteria to antibiotics creates a selection pressure which favours the survival and growth of resistant bacteria in populations, contributing to the emergence of AMR. Through a range of resistant mechanisms, antibiotics kill the susceptible bacteria while resistant bacteria are selected to survive in the presence of the antibiotics and possibly continue to grow and multiply. Potential drivers of the emergence of AMR are interlinked factors in the context of the health care system and community, including agriculture and the environment.

Antibiotic use is one of the main drivers of AMR. In the human health sector, the high volume of antibiotic prescriptions and poor patient adherence to treatment are related to the development of AMR. For example, antibiotics are often wrongly prescribed to treat flu or common cold symptoms (16). A recent study in the United State (US) showed that nearly 25% of antibiotic prescriptions were inappropriate[2] (17). Moreover, antibiotic self-medication is also common in many countries, particularly in low- and middle-income countries (LMICs) where antibiotics are sold over the counter (18,19). The risk of AMR increases when people do not complete the course or take an insufficient dose, take antibiotics for the wrong indications such as for viral infections, or share antibiotics with their friends or family (18).

In my previous research, I identified the complex determinants of the inappropriate use of antibiotics in both human health and agricultural sectors (20). The supply and demand of antibiotics is the major factor driving the use of antibiotics. The supply side for antibiotics that causes problems includes retail sector, health-care sector and agricultural sector. On the demand side of antibiotics, people, including farmers, lack knowledge and perceive AMR to be a low risk. In some countries, farmers can access active pharmaceutical ingredients for direct use on their animals. In addition, inappropriate use of antibiotics is exacerbated by

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[2] Different terminology has been used to capture a concept regarding the use of antibiotics. Terms have included 'rational/irrational', 'appropriate/inappropriate' or 'prudent/non-prudent', but these all depend on the perspective and there is a lack of a universal standard (137,139,182). In this thesis, the word 'appropriate' has been chosen to mean the rational/correct/proper use of antibiotics according to the selection, dose, duration which is suitable for clinical needs, and is dispensed correctly and taken properly.

loose regulatory systems such as a lack of requirements for prescriptions to obtain and use antibiotics in both humans and animals. (Figure 1.2).

Furthermore, the poor quality of antibiotics, including from substandard and falsified drugs, also contributes to AMR. Poor quality antibiotics create the conditions for similar consequences to the sub-therapeutic level of antibiotic use, both of which promote the development of AMR (21). However, there is currently no conclusive evidence on the impact of the use of antibiotics of poor quality on AMR(22).

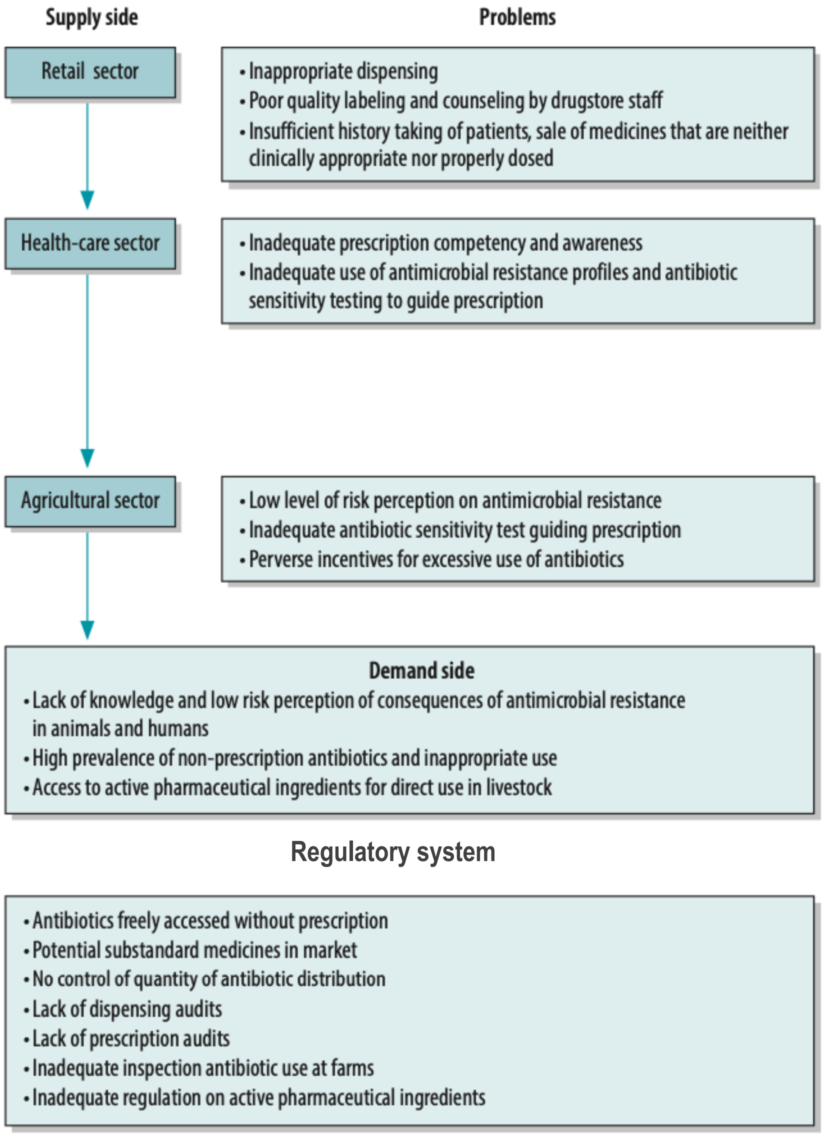

Figure 1.2 Complex determinants of the inappropriate use of antibiotics in both human health and agricultural sectors

Source: Tangcharoensathien (20)

1.4 Contribution of agriculture to AMR

Resistant bacteria can be transmitted to people (both consumers and farmers) when they consume AMR-contaminated animal products such as inadequately cooked food or when they have direct contact with animals and their environment such as through contaminated soil and water (23). One of the main routes of AMR contamination to the environment is through untreated animal waste from farms. Antibiotics including un-metabolised compounds can also reach the environment through medical waste, improper drug disposal from hospitals or medicated feed from animal farms. This contributes to resistance in environmental bacteria and as a result, soils and surface waters in agricultural areas are contaminated by AMR bacteria and AMR genes (24).

AMR bacteria have been detected in food animals, in carcasses and in food products (25–29). AMR bacteria and genes can be also found in manure and in general environments such as soil, water, and the air surrounding animal farms (24,30–34). Among the bacteria found, AMR zoonotic pathogens included *Escherichia coli*, *Campylobacter* spp., *Salmonella* spp. and *Staphylococcus aureus*.

The use of antibiotics in food animal production has been recognised as one of the main drivers of the emergence of drug-resistant bacteria. In a recent study in seven countries in Europe, the level of use of specific antibiotics significantly correlates to the level of resistance to certain antibiotics such as fluoroquinolones, sulphonamides, aminopenicillins, and tetracycline in commensal *E. coli* isolates in pigs, poultry and cattle (35). However, demonstrating concrete evidence of the link between antibiotic use in livestock and transmission to humans is difficult due to a complex causal association. Analysis requires identification of AMR in animal products exposed to antibiotics in the production process, detecting the association between AMR in animals emerging from the use of antibiotics in animal production process, confirming the transmission of the AMR pathogens to humans, and diagnosing the cause of disease in humans by the AMR pathogens (36).

Despite the challenges in demonstrating the association between antibiotic use in livestock and AMR in humans, several studies have shown the presence of AMR in foods of livestock origin throughout the world and evidence of human infection from AMR in animals (37–40) . Previous studies have demonstrated possible transmission of Methicillin-resistant

Staphylococcus aureus (MRSA) between animals and humans (37,38), and MRSA is considered to be a major cause of healthcare-, community- and livestock-associated infections. One study investigated 22 MRSA cases in humans in New Zealand: 4 of them reported contact with cattle and sheep and 2 lived on farms with livestock with mecC-carrying MRSA and some genetic patterns with the human isolates (38). Another study showed that the phylogenetic analysis of mecC-MRSA isolated from humans and from livestock on the farm were identical. The findings support the premise of zoonotic transmission (23).

The current approach to assessing the association is to examine the level of AMR in bacteria in livestock products at the slaughter stage. In European countries, AMR surveillance systems have been established to monitor indicator bacteria in livestock including poultry, pigs and cattle. In 2017, resistance in zoonotic *Salmonella* and *Campylobacter*, and *Escherichia coli*, as well as methicillin-resistant *Staphylococcus aureus*, were found in livestock and meat products (41). In *Salmonella* isolates, high proportions of isolates were resistant to ampicillin (54.9%); sulphonamides (59.1%) and tetracycline (60.8%) in fattening pigs. Some countries reported the occurrence of MRSA in livestock and products. Resistance to colistin was observed at low levels in *Salmonella* and *E. coli* from fattening pigs, calves and meat. Evidence of resistance was also associated with resistant bacteria isolates in humans in the same report.

1.5 Antibiotic use and AMR in animal production

Penicillin, the first antibiotic, was discovered in the 1940s. Since then, antibiotics have changed the treatment of bacterial infections for both humans and animals. The different mechanisms of antibiotics have an impact in the host's intestinal flora, intestinal physiology, and immune system. Mechanisms include reducing the colonization of intestinal bacteria, inhibiting the growth of pathogenic microorganisms, and decreasing the thickness of mucus membrane, leading to more absorption of nutrients and reduced fermentation, and neutralising the host's immune response (42,43).

Antibiotics have been widely used in livestock production since the 1940s (44,45). The efficiency of antibiotics to improve animal productivity and enhance animal growth was unintentionally discovered. It was first reported in 1946 when chickens were fed streptomycin, and this use of antibiotics enhanced growth and feed efficiency, and reduced mortality (46). After this discovery, within a few years, antibiotic use had become common practice for animal growth promotion in many countries in Europe and the US, and helped meet the demands of a post-war policy to increase livestock production (44,47,48). Since 1960, the use of antibiotics has spread widely throughout global food production, mostly in poultry and pigs, with the aim of keeping animals healthy and increasing productivity. Livestock production has also changed, driven in part by an increase in the human population globally and greater demand for livestock products, as people became wealthier. Worldwide, compared with other meat, pork is one of the most highly-consumed meat at approximately 35-40 percent of global meat production and is of critical importance in many countries (49). Global pork consumption has increased from 23.1 kg per capita in 1961 to 42.2 kg per capita in 2011 (50) . The rapid increase in pork production has in part been achieved through supply changes with a shift from household farming to intensive commercial industrial systems. These new systems often have a high density of animals which can exacerbate the risk of infectious diseases and their rapid spread. The area of concern for AMR is that farmers have responded in part to these risks by using antibiotics in their pig production systems, and given the link between antibiotic use and AMR it becomes critical to understand the reasons for this use.

To understand the use of antibiotics in pig production, the next section explains three key areas of antibiotics use which are: the purpose of the use; route of administration and pharmaceutical forms; and antibiotic use and common diseases in pigs.

1.5.1 Purpose of the use of antibiotics

Antibiotics, since their discovery to be effective in animals, have been used routinely in livestock. Apart from therapeutic use to treat disease, it is common practice to use sub-therapeutic doses of antibiotics in food-animals to control and prevent the spread of infection or disease. In many countries, antibiotics are used to promote growth.

There is a lack of a standard definition on the use of antibiotics. The World Health Organization defines ‘therapeutic use’ as the use of antibiotics for treating animals with a clinically diagnosed infectious disease (51), while elsewhere the US Food and Drug Administration defines ‘therapeutic use’ to include treatment, control (metaphylaxis), and prevention (prophylaxis) of disease (52). In this thesis, the definitions of antibiotic use are according to the WHO recommendations.

Therapeutic use of antibiotics is targeted at animals infected by disease. When the disease is diagnosed, the most appropriate antibiotic is selected and applied to animals.

Sub-therapeutic doses of antibiotics are applied to a group of animals after the diagnosis of disease in one of the animals, with the purpose of controlling the spread of infection to animals in close contact (metaphylaxis); and preventing disease at points of high-disease risk, particularly when animals are under stress (prophylaxis).

The use of antibiotics for controlling the disease of an individual animal which have already infected or may be sub-clinically infected but is in close contact with others, helps to reduce the risk of the infection becoming clinically apparent, spreading to other tissues or organs, or being transmitted to other animals (metaphylaxis). On a population basis, control refers to the use of antibiotics to reduce the incidence of infectious diseases in a group of animals.

Antibiotic use for disease prevention (prophylaxis) is sometimes used on animals where there is no evidence of disease or infection. It is applied based on history, clinical judgment, or epidemiological information. In livestock production, there are many points of high-disease risk, particularly when animals are under stress including post-vaccination, when moving pens or changing feed. The preventive administration of an antibiotic to either an individual animal or a group of animals aims to mitigate the risk of acquiring disease or infection.

Non-therapeutic use of antibiotics is to enhance growth and feed efficiency as an antibiotic growth promoter. The term antibiotic growth promoter is used to describe any medicine that is administered at a low and sub-therapeutic dose to help growing animals digest their food more efficiently, get the maximum benefit from it and allow them to develop into strong and healthy animals (53). However, the mechanisms of growth promotion are still not exactly known. Possible mechanisms could be improving the digestibility of nutrients, absorption of nutrients, and the structure of intestinal flora (54). Table 1.1 summarises the definitions of antibiotic use according to indications and animal status.

Table 1.1 Definitions of antibiotic use in livestock (51)

Antibiotic use	Indications	Animal status
A. Therapeutic use (antibiotic treatment of disease)	Treatment is the administration of an antibiotic as a remedy for an individual animal or within the group with evidence of infectious disease.	Sick animals
B. Sub-therapeutic doses of antibiotics		
- Antibiotic control of disease (synonym: metaphylaxis)	Control is the administration of an antibiotic to an individual animal in close contact who may be sub-clinically infected. It helps to reduce the risk of the infection becoming clinically apparent, spreading to other tissues or organs, or being transmitted to other individuals. On a population basis, control is the use of antimicrobials to reduce the incidence of infectious diseases in a group of animals.	Healthy animals (subclinical infected animals)
- Antibiotic prevention of disease (synonym: prophylaxis)	Prevention is the administration of an antibiotic to animals, none of which has evidence of disease or infection based on history, clinical judgment, or epidemiological information. In livestock production, there are many points of high-disease risk, particularly when animals are under stress including post-vaccination, moving pen or changing feed. The administration of an antibiotic to an individual animal and a group of animals aims to mitigate the risk of acquiring disease or infection.	Healthy animals
C. Non-therapeutic use	- Enhance growth and feed efficiency	Healthy animals

1.5.2 Route of administration and pharmaceutical forms

Routes of administration are categorised by application location. Enteral administration refers to the uptake of medicine through the gastrointestinal tract, mostly through oral administration. It also includes administration through the rectum. Parenteral route refers to any route of administration apart from the enteral route, and usually refers to injection. The main issues determining the selection of the route are the desired effect of the medicine, and animal management including for example, animal handling or age of pigs (55,56). Unlike in humans, administration of medication by tablets, capsules or liquid formulations is uncommon. Antibiotics are commonly applied to the entire group of pigs through the addition of antibiotics to their feed (in medicated premix) or water because individual animal treatment is impractical. Therefore, oral administration of antibiotics is the most common route for a group application in pigs. Injectable administration is a highly effective route for administration to treat sick pigs experiencing difficulties with eating or drinking.

- An oral solution is commonly used in piglets which can be handled individually for medical administration. The solution is usually available for the treatment of colibacillosis in piglets (57).
- Oral powder through water medication (additives to drinking water) allows for the treatment of groups of pigs that may have poor appetite but are still drinking. However, it is essential to ensure that the water facilities and systems, including water flow rates, are sufficient to deliver to all pigs and that there is no leakage of medicated water. In addition, the water intake of pigs must be checked to ensure they receive the proper dose of antibiotics and it is vital to check water quality. Some substances in water can inactivate some antibiotics. For example, oxytetracycline is inactivated by high levels of calcium, iron, and magnesium (56).
- Medicated feed is the main route of antibiotic administration in many countries, particularly for preventing and controlling disease in a whole group of pigs. This route may not be the most efficient route for administration in sick animals, as sick animals may have less appetite or be unable to feed. Medicated feed is produced by either feed mills or by a farmer who produces their own feed on the farm (home mixed) by mixing medicated premix into feed. However, mixing medicated feed in farms can

result in a lack of quality control for ensuring consistent distribution of antibiotics in the feed (58).

1.5.3 Common diseases and antibiotic use in pigs

A wide range of common diseases are caused by viruses and bacteria in pigs. Age-specific diseases and common pathogens are related to antibiotics use. For example, bacterial infections causing diarrhoea are commonly found in suckling pigs and nursery pigs, therefore antibiotics were commonly used in these pigs for disease prevention (59).

Some of the pathogens in pigs can be also found in humans such as *Escherichia coli, Staphylococcus aureus*, and *Salmonella* spp. Moreover, many bacterial pathogens can be transmitted between animals and humans, so-called zoonosis (60). Table 1.2 presents common bacterial diseases and pathogens in different pig stages.

Table 1.2 Type of farm by phases of pig production, common diseases and pathogens by stage of production

	Common diseases and pathogens
Sow	• Mastitis, metritis, agalactia syndrome (*E. coli*) • Necrotic enteritis (*Clostridium perfringrens* type C) [E] • Progressive atrophic rhinitis (*Pasteurella multocida*) [R]
Suckling and nursery pig	• Neonatal and piglet diarrhoea (*E. coli*) [E] • Post weaning diarrhoea (*E. coli*, *C.perfringrens* type A, *Salmonella* spp.) [E] • Septicemia, endocarditis, arthritis, and pneumonia (*Actinobacillus suis*) * [R] • Meningitis and arthritis (*Streptococcus suis*) * • Glasser disease (*Haemophilus parasuis*) * • Polyserositis, arthritis, low-grade pneumonia (*Mycoplasma hyorhinis*) * [R]
Fattener pig	• Diarrhoea (*Salmonella* spp.) [E] • Porcine haemorrhagic enteropathy (*Lawsonia intracellulalis*) [E] • Swine dysentery (*Bachyspira hyodysentary*) [E] • Enzootic pneumonia (*Mycoplama hyopnuemoniae*) [R] • Mycoplasma induced respiratory disease (*Pasturella multocida*) [R] • Pleuropnuemonia (*Actinobacillus pleuropnueumoniae*) [R] • Mycoplasma arthritis (*Mycopplasma hyosynoviae*) • Erysipelas (*Erysipelas rhusiopathiae*)

[E]= enteric infection, [R]=respiratory infection

*both nursery and finisher phases

Source: Adapted from Sneeringer (36)

Due to the possible association between antibiotic use in livestock and AMR in humans, there are concerns that their level of use is unnecessarily high especially for sub-therapeutic use for growth promotion and disease prevention, and particularly for the use of those antibiotics highly important for humans.

High levels of antibiotic use in livestock

Many reports show a larger proportion of antibiotics used in food-producing animals than used in humans. In Europe, it was estimated that 70% of all antibiotics consumption in 30 European countries was in the animal sector (8,927/12,720 tonnes) (61). Moreover, based on the predicted continued rise in global demand for livestock products, global antibiotics consumption by livestock is predicted to increase by two thirds over the next ten years (62).

Sub-therapeutic use for growth promotion and disease prevention

Many organisations suggest that farmers and the food industry should stop the routine use of antibiotics for the prevention of disease and promotion of growth in healthy animals. For example, the 2015 European Commission Guidelines for the Prudent Use of Antibiotics in Veterinary Medicine state that the routine use of antibiotics for disease prevention should be avoided and antibiotics reserved for exceptional case-specific indications (63). The World Health Organization (WHO) strongly recommends a restriction of the routine use of Medically Important Antibiotics (MIA) for disease prevention and complete restriction of all antibiotics for growth promotion in food-producing animals (51). Many countries have recently banned the use of growth-promoting antibiotics (64). However, antibiotics are still used as growth promoters in some countries. Indeed, 22% (35/153) of World Organisation for Animal Health (OIE) member countries reported the use of antibiotic growth promoters in 2018 (65).

Use of antibiotics in the same class as humans, particularly the Critically Important Antimicrobials (CIA)

The WHO classifies MIA based on their importance to human medicine including: 1) the volume of antibiotic use in humans (high proportion of use in patients and high frequency of use in human medicine); 2) antimicrobials for treatment of transmission of AMR; 3) antimicrobials with limited alternatives for treatment of serious bacterial infections in humans; and 4) antimicrobials for treatment of infections in humans caused by bacteria that may be transmitted to humans from non-human sources, or bacteria that may acquire resistant genes from non-human sources (66). There are three groups of MIA:

1. Critically important antimicrobials (CIA)-highest priority and high priority (Lists of CIA are in Appendix 8);
2. Highly important antimicrobials;
3. Important antimicrobials.

Antibiotics used in animals are often the same or in the same class as those used in humans. Of particular concern has been the use of CIA which are last-resort antibiotics normally reserved for the most severe infections in humans.

Group treatment

In livestock, antibiotics are commonly applied to whole groups through medicated feed or medicated drinking water (67–71). However, the European Commission recommends that administering medication to an entire herd or flock should be avoided whenever possible. Sick animals should be isolated and treated individually (for example, by parenteral administration) (63).

1.6 Global policy on AMR

To tackle AMR, international organizations recommend several implementation strategies for both human health and agriculture. The Global Action Plan on Antimicrobial Resistance (GAP-AMR) was adopted in 2015 by all countries through decisions taken at the World Health Assembly, the Food and Agricultural Organization Governing Conference and the World Assembly of World Organisation for Animal Health Delegates (72). Box 1 describes the strategic objectives of the GAP-AMR.

Box 1.1 Five strategic objectives of the Global Action Plan on AMR

1. To improve awareness and understanding of antimicrobial resistance through effective communication, education and training;
2. To strengthen the knowledge and evidence base through surveillance and research;
3. To reduce the incidence of infection through effective sanitation, hygiene and infection prevention measures;
4. To optimize the use of antimicrobial medicines in human and animal health; and
5. To develop the economic case for sustainable investment that takes account of the needs of all countries, and increase investment in new medicines, diagnostic tools, vaccines and other interventions.

In 2016, the political commitment to AMR was made at the United Nations General Assembly High-Level Meeting (73). Member States committed to develop multi-sectorial national action plans on AMR in line with the GAP-AMR and endorsed a concerted 'One Health' approach which links various sectors and actors in defence of human, animal and environmental health. In addition, all Member States agreed to mobilize adequate and sustained resources to implement activities tackling AMR and pledged to raise awareness of AMR. This is the first time that heads of state committed to collectively solve the AMR problem and only the fourth time in the history of the United Nations that a health issue was discussed at the United Nations General Assembly.

In response to the GAP-AMR, each country is required to develop a national action plan. Based on the global database for AMR country self-assessment in 2018, only a few countries have not yet developed a national action plan on AMR (74,75).

1.7 Pig production in Thailand

Thailand is an upper-middle-income country with a population of approximately 69 million. In 2018, the average income, measured as GDP per person, was about US$ 7,273[3] (76). Thailand's economy has been growing steadily over the last few decades. In 2000, Thailand's GDP per person was one third lower than in 2018. However, although GDP has increased over time, the contribution of the agricultural sector to GDP has declined over the past decade from 12% in 2011 to 8% in 2018 (US$ 42,400 million) (77).

Pork is one of the most common protein sources in Thailand and the majority of pig products were consumed in the domestic market. In 2018, about 10 million pigs were produced by about 180,000 pig farms in Thailand (78). Table 1.3 shows the population census of humans and pigs in Thailand in 2018.

[3] US $1.00 = 31.5 Baht (As of 20 February 2020)

Table 1.3 Key statistics on economic status and pig production in Thailand (2018)

	Thailand profiles
Population census of human	69,428,524[a]
GDP (billion US$)	506,514.0[a]
GDP per capita (US$)	6,592.9[a]
Population census of pig	10,587,303 [b]
- Indigenous pig	647,296 [b]
- Breeder: sow	927,969 [b]
- Breeder: boar	94,225 [b]
- Fattener	8,917,813 [b]
Households raising pigs	184,717 [b]

[a] Source: https://data.worldbank.org/indicator (2018) (76)

[b] Source: http://ict.dld.go.th (2018) (78)

Globally, demand for livestock as a source of food is growing rapidly due to increases in both populations and their incomes. Industrial-scale livestock production has become a major response to rapidly growing consumer demands. Industrial-scale livestock production systems are common in high-income countries (HICs), leading to livestock-derived foods becoming more available, accessible and affordable to all consumers, and contributes to the growth of economies. In low- and middle- income countries (LMICs), the livestock production system plays a vital role in generating income for livestock producers, which benefits a country's economy as a whole and contributes to the production of food.

Since the 1960s, pig production in Thailand has shifted increasingly from smallholder farming for household consumption to intensive large-scale production for commercial use. Pork has become one of the most important sources of animal protein in Thailand, and its production has more than doubled in the last 30 years from around 336 thousand tons (4.6 kilograms/capita) in 1990 to approximately 883 thousand tons (10 kilograms/capita) in 2018 (79). In 2018, the income of the agricultural sector in Thailand accounted for around US$ 42,400 million and pig production generated about 10% of this (77). Along with a rapid increase in pork demand and production, both the number and the size of intensive pig farms have grown significantly.

In the past, smallholder farmers, where pig production is not a major income-generating activity (sometimes referred to as "backyard farms"), fed their pigs from various sources such as leftover food and vegetables. However, feeding pigs with leftover food resulted in poor pork quality and provided a lower return, so farmers turned to commercial feed in response to pork market demands. Now, commercial feed stores are the most common source of feed on smallholder farmers. On commercial farms, farmers either produce their own feed by mixing various ingredients (home mixed) or buy commercial feed from feed companies. Pig farms differ in how they are managed, including their approach to biosecurity. Smallholder farms are often associated with poor hygiene and low biosecurity. By contrast, commercial systems usually have higher hygiene and biosecurity measures than smallholder farms (80).

The majority of pig products (95%) are for domestic consumption (78,81), about 70% of which is distributed to the general market, while 20% is sold through supermarkets (82). In the supply chain, there are many ways to process pork from farms through to markets. Smallholders sell their pigs through middlemen (pig brokers) who contact farmers and slaughterhouses, and then sell pork to retailers (butchers). Some local retailers visit smallholder farms in local communities to buy pigs in small numbers directly. This then becomes fresh pork sales in local markets. However, in the past decade, vertical integration by large companies has become increasingly common. The companies use contract farming with pig farmers for pork production involving pig slaughter, marketing and retail of pork products.

Thailand has experienced fluctuating pig prices due to an oversupply in 2017 and 2018 (83). Many farms, particularly smallholder farms, have closed over the last few years, while commercial farms have expanded with integrated pig production and marketing systems. Consequently, the Thai pig production system is likely to become more dominated by large agro-industrial conglomerates performing integrated operations of animal breeding, feed production, and processing meat products (80). In the integrated business system, contract farming is common where farmers and contracting companies make an agreement in advance on the terms and conditions for the production and the price of products. In general, contracting companies provide inputs such as pigs, feed, medicines, and technical support to contracted farmers, who provide animal housing and labour. The farmers' main obligation is to produce and deliver the products in relation to the contract and the company pays the farmers the agreed price stated in the contract.

In 2018, about 180,000 of Thai farms raised about 10 million pigs with 60% of these farms being commercial farms (more than 51 pigs on a single farm) and raising more than 90% of the pig population[4]. The rest, 40%, were smallholder farms raising indigenous pig breeds comprising 6% of the total pig population (78,81).

1.8 AMR and antimicrobial use in pig production in Thailand

With pig production rates and large commercial farms expanding in Thailand, concerns around antibiotic use and AMR are also growing. Many studies have reported the occurrence of AMR in pathogenic and commensal bacteria isolated from pigs in Thailand. A recent review on AMR in South East Asian countries, including Thailand (84), showed that most of the published work in Thailand relates to non-typhoidal *Salmonella*, *Escherichia coli* (*E. coli*), and *Campylobacter* spp. and MRSA. *Salmonella* isolates were resistant to tetracycline (85,86), streptomycin (85), sulfamethoxazole (85) and nalidixic acid (86). The majority of *E. coli* isolates were resistant to tetracycline (87–89), ampicillin (87–89), streptomycin (88,89) and sulfamethoxazole (89). Multidrug-resistant *Salmonella* and *E. coli isolates* were also reported (86,87,89,90). Two studies reported AMR among *Campylobacter* spp. in pigs in Thailand. The results presented high resistance to nalidixic acid, ciprofloxacin, erythromycin, azithromycin and tetracycline (91,92). Methicillin resistant *Staphylococcus aureus* was found in pig and pork in Thailand (93–96).

A recent study reported the occurrence of the MCR-1 gene on pig farms in Thailand (97). The study examined colistin resistance *E. coli* in healthy fattening pigs (16-24 weeks) in four provinces in Thailand during 2004 -2014. Gene MCR-1 was detected in pigs from three provinces. At Nakhon Pathom, the MCR-1 gene was found at 3.5% of faecal samples from selected farms in 2012 and at 29.5% in 2013. *E. coli* isolated from Ratchaburi and Chonburi were also found in the MCR-1 gene at 3.5% and 20.7%, respectively. No MCR-1 gene was found in Nakhon Ratchasima.

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[4] Based on the number of pigs on the farm, farms were categorised by size according to the Department of Livestock Development (DLD) definition: smallholder farm (less than 50 pigs), and commercial farm subcategorised to small commercial farm (from 51 to 500 pigs), medium commercial farm (from 501 to 5,000 pigs), and large commercial farm (more than 5,001 pigs).

In 2017, the Department of Livestock Development (DLD) established the national surveillance system on AMR in food-producing animals with an aim to monitor the trend of AMR and promote prudent use of antimicrobials in Thailand (98). The Thailand surveillance of AMR includes data on target bacteria such as zoonotic bacteria (*Salmonella* spp. and *Campylobacter jejuni*) and indicator bacteria (*Enterococcus faecium* and *Enterococcus faecalis*, and *E. coli*) collecting from porcine caeca from slaughter houses and pork meat samples from both slaughter houses and retail markets (98). The sample size was calculated according to the OIE guidelines. The tested antimicrobials were included as follows: colistin, ciprofloxacin, cefotaxime and ceftazidime, meropenem, chloramphenicol, sulfamethoxazole and trimethoprim, gentamicin and streptomycin, etc.

In 2018, high levels of resistance in *Salmonella* spp. and *E.coli* were detected against ampicillin, tetracycline, chloramphenicol and trimethoprim/sulfamethoxazole, while low levels of resistance (<10%) against third-generation cephalosporins, ciprofloxacin, and colistin. None of *Salmonella* spp. isolates from all three sources of pigs was resistant against meropenem (Figure 1.3). The prevalence of resistance in *E. faecium* and *E. faecalis* was high against three highest antimicrobials including tetracycline (76.8), erythromycin (75.4%), and streptomycin (54.6%) (99).

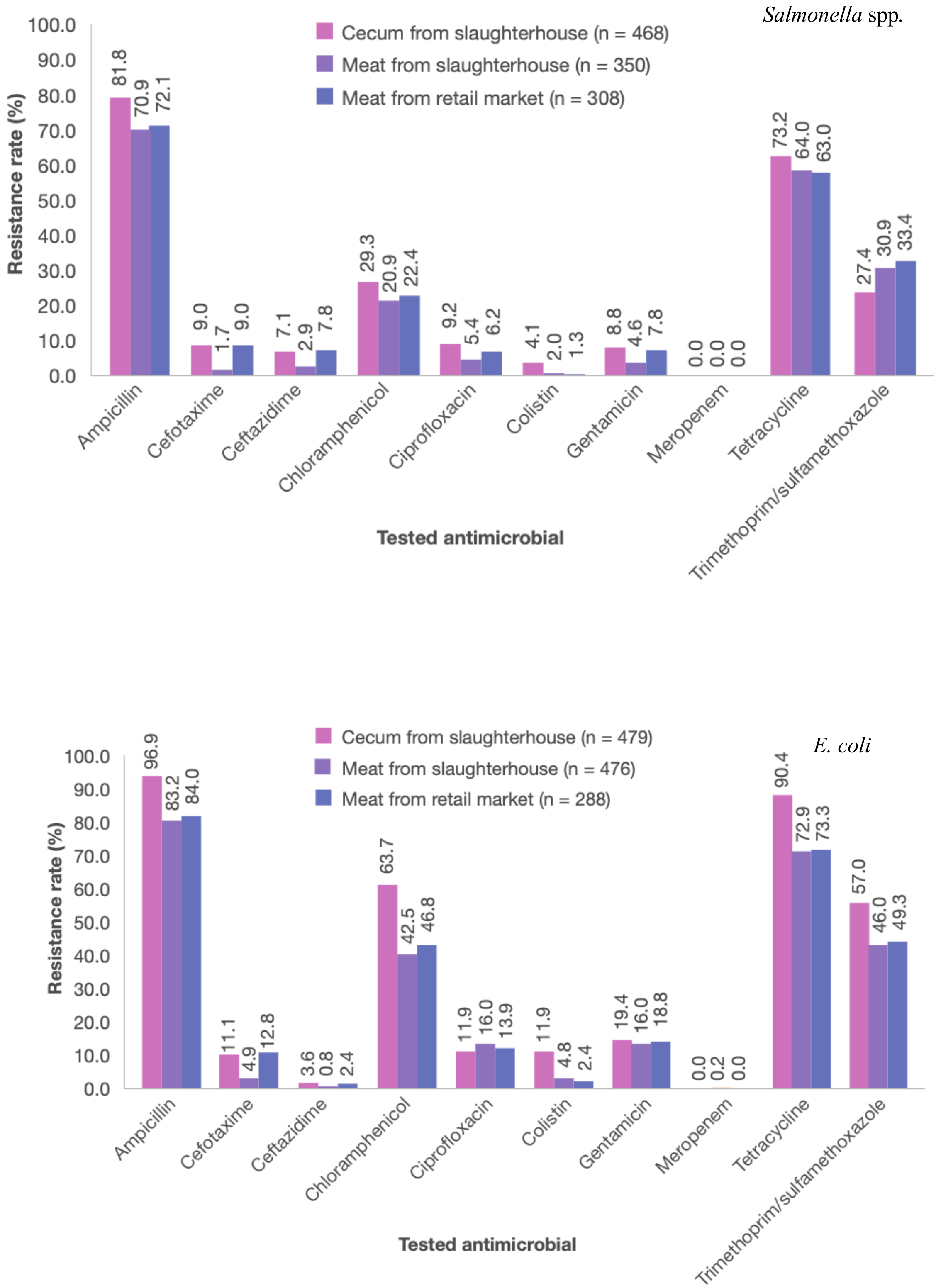

Figure 1.3 Prevalence of resistance in *Salmonella* spp. isolated and *E. coli* isolated from pork samples

Source: Thailand's One Health Report on Antimicrobial Consumption and Antimicrobial Resistance in 2018 (99)

The existing Surveillance of Antimicrobial Consumption in Thailand, called 'Thailand SAC', was developed in 2016 in response to the National Strategic Plan on AMR. Data from an annual report of pharmaceutical operators including importers and manufacturers were used to estimate the total national consumption of antimicrobials in humans and animals.

In 2018, the total consumption of antimicrobials in food-producing animals was 3,816.3 tonnes of active pharmaceutical ingredients or 522.1 mg/Population Correction Unit (PCU) Thailand (98). According to the class of antimicrobials, penicillins were consumed most (40.8%, 212.8 mg/$PCU_{Thailand}$), mainly in the form of amoxicillin (210.4 mg/$PCU_{Thailand}$).. The second-ranked consumed antimicrobials belonged to other antibacterials including bambermycin, bacitracin and halquinol, accounting for 18.3%. The third-ranked antimicrobials consumed were tetracyclines (12.1%), of which chlortetracycline and doxycycline were the majority (Figure 1.4). When grouped by pharmaceutical dosage form, more than half of veterinary antimicrobials were in the form of medicated premix (59.1%), followed by oral powder (36.8%) and injection (2.9%).

Regarding the World Health Organization list of Critically Important Antimicrobials (CIA), 55.4% of total veterinary antimicrobials consumed belonged to the CIA. The top-three antimicrobials consumed in the highest priority group were colistin, tilmicosin and tylosin and the top-three in the high priority group were amoxicillin, neomycin and dihydrostreptomycin.

However, the surveillance data were limited. The consumption data were not stratified by animal species or indication, so it was not possible to identify the extent of use in individual species such as pigs.

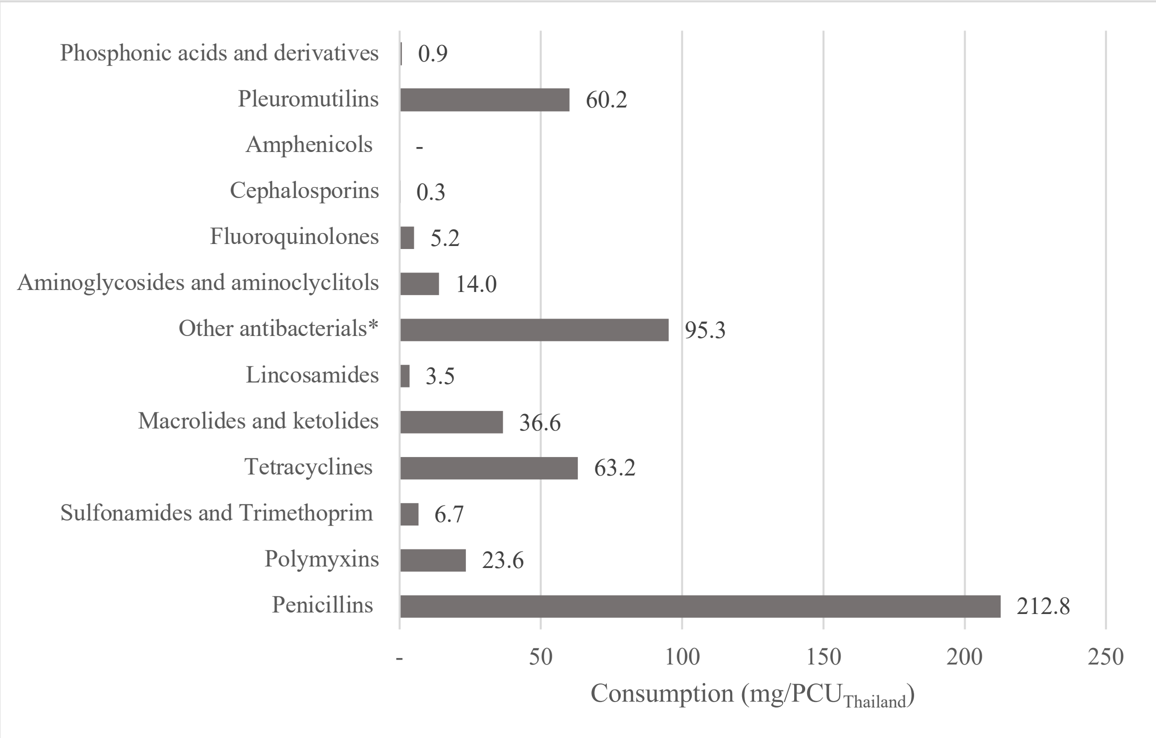

Figure 1.4 Consumption from veterinary antimicrobials classified by drug class in 2018 (mg/$PCU_{Thailand}$)

*Other antibacterials includes bambermycin, bacitracin and halquinol.

1.9 Antibiotic distribution and control of antibiotics in Thailand

Between 2016 and 2017, I led a study in parallel to my PhD research, to analyse how antibiotics are imported, manufactured, distributed and regulated in Thailand. The academic article was published in the Bulletin of the World Health Organization in 2018 (Appendix1) (100). Based on this research, I extracted the following information.

In summary, antibiotic distribution in livestock is a complex array of activities including marketing, distribution, prescription, and use. A number of different public and private stakeholders are involved at different stages of this process, including pharmaceutical companies who import, produce and distribute antibiotics, retail pharmacies, health professionals and farmers. It also includes feed mills which produce and distribute medicated feed to feed stores and farms either directly or through distributor companies. Table 1.4. summarises the process of antibiotic distribution and different key actors.

Table 1.4 Process of antibiotic distribution and key actors

Function	Actor	
	Antibiotic	Medicated feed
Production/ importation	Pharmaceutical companies	Feed mills
Distribution	Pharmaceutical companies, distributor companies	Feed mills, distributor companies
Prescribing	-	Veterinarians
Dispensing/retail sale	Pharmacies, pharmaceutical companies, veterinarians	Feed stores
Consumption	Farmers	

Figure 1.5 illustrates the antibiotic distribution flow in Thailand. Thailand imports Active Pharmaceutical Ingredients (API) for local manufacturing and finished product of antibiotics (including medicated premix for producing medicated feed). Once antibiotics are produced by manufacturers, they are sold to wholesalers, pharmacies (drug stores), feed mills and farms, or distributed through distributors. The wholesalers, distributors and pharmacies need to hold a medicines sale license authorised by the Thai-Food and Drug Administration (Thai-FDA). Feed mills add antibiotics to feed to produce medicated feed and sell it to feed stores and animal farms. Both feed mills and feed stores must hold a license authorised by DLD. Farmers can buy antibiotics through several channels including distributors, wholesalers, pharmacies, and medicated feed from either feed mills or feed stores. By law, Thailand does not allow distributors, wholesalers, pharmacies to sell API to feed mills and farmers, and does not allow feed mills and farmers to add API into medicated feed.

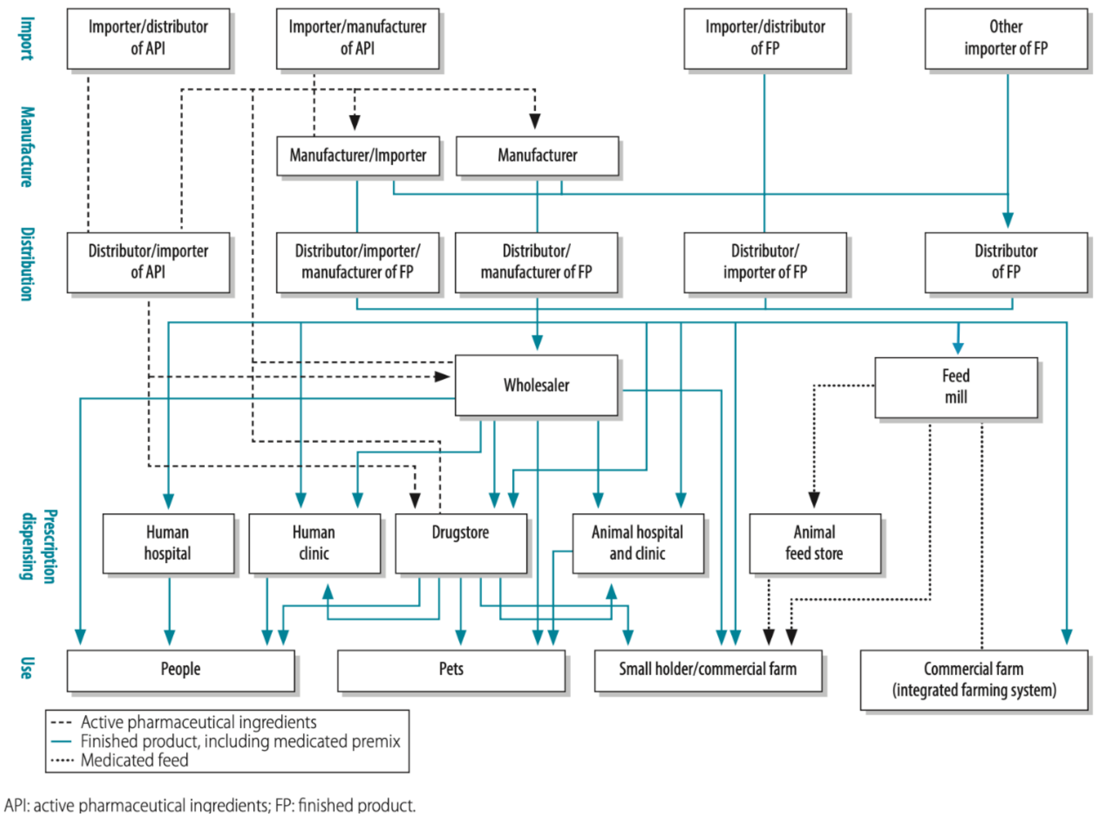

Figure 1.5 Antibiotic distribution in Thailand (100)

The regulation of antibiotics is generally covered through drug regulations where the main aim is to ensure the safety, efficacy, and quality of drugs in both human and animal sectors. The main regulatory functions are broadly categorised as licensing of manufacturers, importers, wholesalers and retailers; issuing marketing authorization; inspecting of licensees; controlling and monitoring the quality of medicines on the market; controlling promotion and advertising of medicines; monitoring adverse reactions to medicines; and providing independent information on medicines to professionals and the public (101).

In developing countries, regulations control antibiotic use through the classification of antibiotics and the restriction of access to highly important antibiotics through the requirement of prescriptions. However, in LMICs, regulatory processes mostly focus on the licensing process of medicines (102). Over-the-counter sale of antibiotics is reportedly common (103).

In Thailand, the relevant regulations regarding antibiotics which are described in more detail in the report "System analysis of antimicrobial utilisation in humans and animals: actors and legal framework" (Appendix 2).There are regulations about antibiotic use in relation to pig production systems (Box 1.2). Two main laws govern the distribution of antibiotics for humans and animals: the 1967 Drug Act under the responsibility of the Thai-FDA; and the 2015 Animal Feed Quality Control Act, under the responsibility of the DLD. In addition, the non-legal norm on the Good Agricultural Practice (GAP) certification established by the government also addresses standard practice on antibiotic use in pig farms.

The Drug Act was first legislated in 1967; it has been amended four times in 1975, 1979, 1984 and 1987 and the current version is the Drug Act (1987). The law aims to assure safety, efficacy and quality of medicines including antibiotics. The Drug Act classifies medicines into four categories and regulates which outlets patients can access. The Drug Act controls pharmaceutical operators through licensing in relation to the distribution process including importation, manufacture and sale of medicines. It is nevertheless noteworthy that no regulation exists to contain the number of medicines distributed through different channels or to end-users.

The Animal Feed Quality Control Act BE 2558 (2015) controls the quality and standard of medicated feed including medicated premix used in medicated feed. The Act covers the process of licensing and inspection of medicated feed's operators covering feed mills, feed stores and livestock farms. Veterinary prescriptions and Good Manufacture Practice certificates are required for feed mills prior to medicated feed production.

The Veterinary council and Pharmaceutical council work in accordance with the Veterinary Profession Act (2002) and Pharmaceutical Profession Act (2015). Both councils have regulatory functions including setting educational standards, licensing, and conducting continuing education of health professionals. However, no standards of practice and professional ethics specific to antibiotic use for veterinarians are established in Thailand.

The GAP certificate for pig farms was introduced as a voluntary standard for food safety to fulfil trade and government regulatory requirements. The National Bureau of Agricultural Commodity and Food Standards is the accreditation body, while the DLD provides implementation functions. Farmers submit their application form and relevant documents to their provincial livestock office which carries out the approval and an annual inspection. The standards range from farm infrastructure, animal feed quality, water quality, farm management, animal health management including the use of antibiotics, animal welfare and the environment.

Box 1.2 Regulations and standards in relation to antibiotics in pigs

Drug Act (1987)

- Aim: to ensure the safety, efficacy and quality of drugs, which contribute to the health protection of consumers.
- Regulated by Thai-FDA, Ministry of Public Health
- Five regulatory functions include market authorisation, licensing, inspection, quality control and pharmacovigilance

Animal Feed Quality Control Act (2015)

- Aim: controls the quality and standard of animal feed including medicated feed
- Regulated by DLD, Ministry of Agriculture
- Regulatory functions include licensing, inspection, registration, quality control, and post-marketing surveillance

Professional standards (Veterinary Profession Act (2002) and Pharmaceutical Profession Act (2015))

- Functions:
  - Setting educational standards
  - Licensing
  - Continuing education of health professionals

GAP for livestock certificate

- Voluntary standards for food safety and good production
- National Bureau of Agricultural Commodity and Food Standards is the accreditation body.
- DLD provides implementation functions.
- The standards range from farm infrastructure, animal feed quality, water quality, farm management, animal health management including the use of antibiotics, animal welfare and the environment.

Regulations previously described show cross-regulations at different levels. Table 1.5 maps regulations according to settings, functions, regulator and tools for enforcement. The Drug Act controls the production, importation, distribution, and the sale of antibiotics of pharmaceutical companies and pharmacies. The Animal Feed Quality Control Act regulates the production of medicated feed, use of antibiotics, veterinary prescriptions at feed mills and animal farms, and the sale of medicated feed at the animal feed store. On farms, practices for antibiotic use are controlled under the GAP standard of farm management. The Veterinary Profession Act and Pharmaceutical Profession Act controls the dispensing and prescription of antibiotics in veterinarians and pharmacists.

As mandated by the Drug Act (1987), Thai-FDA classified most human and veterinary antibiotics as “dangerous drugs”. They do not legally require a prescription but must be dispensed by a licensed pharmacist or veterinarians in licensed pharmacies or pharmaceutical companies. Recently, in 2019, a number of restrictions were introduced on the veterinary use of certain reserved groups of antibiotics. A prescription is now needed for the sale of quinolones, cephalosporins, macrolides and polymyxin by pharmacies and pharmaceutical companies, and also for the sale of all medicated premix (antibiotic mixed in feed) (104). In addition, some CIA including polymyxin, penicillins, fluoroquinolones, fosfomycin and cephalosporins are not allowed to use for disease prevention through medicated feed (105). Yet implementation is still at an early stage and compliance has to be monitored closely. The introduction of laws and regulations does not always result in the desired outcomes unless there is robust institutional capacity for regulatory enforcement. The ineffective functioning of the regulatory system has been well documented, including the lack of inspections of the supply chain (106). In South East Asia, only a few countries have the capacity to ensure the implementation of antibiotic use regulation (107). However, there is no study on regulatory capacity to control the use of antibiotics in Thailand. The appropriate prescribing and dispensing of medicines are the responsibility of health professionals, yet neither prescription monitoring nor auditing systems are in place.

Table 1.5 Regulations and regulators of antibiotic use in relation to pig production systems

Settings	Function	Regulation	Regulator	Tool for enforcement
Pharmaceutical manufacturers	Production of antibiotic	Drug Act (1987)	FDA	Pharmaceutical manufacture license, Inspection (1-2 times/year)
Pharmaceutical companies	Importation, distribution, sale of antibiotic	Drug Act (1987)	FDA	Pharmaceutical import license, pharmaceutical sale license
Feed mill	Production of medicated feed	Animal Feed Quality Control Act (2015)	DLD, Provincial Livestock Office	Animal feed manufacturer license (with GAP), Inspection (1-2 times/year)
Pharmacy	Sale of antibiotic	Drug Act (1987)	Thai-FDA, Provincial Health Office	Pharmaceutical sale license, Annual inspection
Farm	Use of antibiotic	GAP for livestock certificate (voluntary)	DLD, Provincial Livestock Office	Audit, licensing and relicensing (q 3 years)
	Production of medicated feed, use of antibiotic, veterinary prescription	Animal Feed Quality Control Act (2015)	DLD, Provincial Livestock Office	Inspection (1-2 times/year)
Feed store	Sale of medicated feed	Animal Feed Quality Control Act (2015)	DLD, Provincial Livestock Office	Animal feed sale license, Inspection (1-2 times/year)
Veterinarian	Dispensing and prescription of antibiotic	Veterinary Profession Act (2002)	Veterinary council	Licensing, continuing education, response to complain
Pharmacist	Prescription of antibiotic	Pharmaceutical Profession Act (2015)	Pharmacy council	Licensing, continuing education, response to complain

1.10 Structure of the thesis

This PhD thesis is structured in a research paper style along with introductory and supplementary materials, in accordance with the guidelines and regulations specified by the London School of Hygiene and Tropical Medicine. There are four research papers: two in the literature review section and two in the results section. Three out of four of these research papers have been published in peer-reviewed journals (one is currently under consideration with a journal). The thesis comprises three main sections and 8 chapters (see Figure 1.6).

In Section A, Chapter 2 indicates aim and objectives of the thesis. Chapter 3 provides a description of materials and methods including the study design and the methodological considerations for data collection and analysis. Chapter 4 presents a literature review on antibiotic use in pig production globally. It covers two published systematic reviews on antibiotic use in pig production and its associations, and methods and measurements for quantification of the use of antibiotics in pig production. Following this, potential factors influencing the use of antibiotics are addressed.

Section B comprises Chapters 5 and 6, with results presented as two research papers from empirical research. The results of the study of the patterns of antibiotic use in pig farms and the total amount of antibiotics used in pig production in Thailand from an analysis of the mixed-methods study are reported in Chapter 5. Chapter 6 presents the factors contributing to the use of antibiotics in pigs in Thailand from the qualitative study.

Section C includes the conclusion and reflections in Chapter 7 on research findings in relation to the aim and objectives of the thesis. Chapter 8 presents key implications of the study, including policy recommendations, recommendations for research priorities. Finally, additional information is provided in the Appendices.

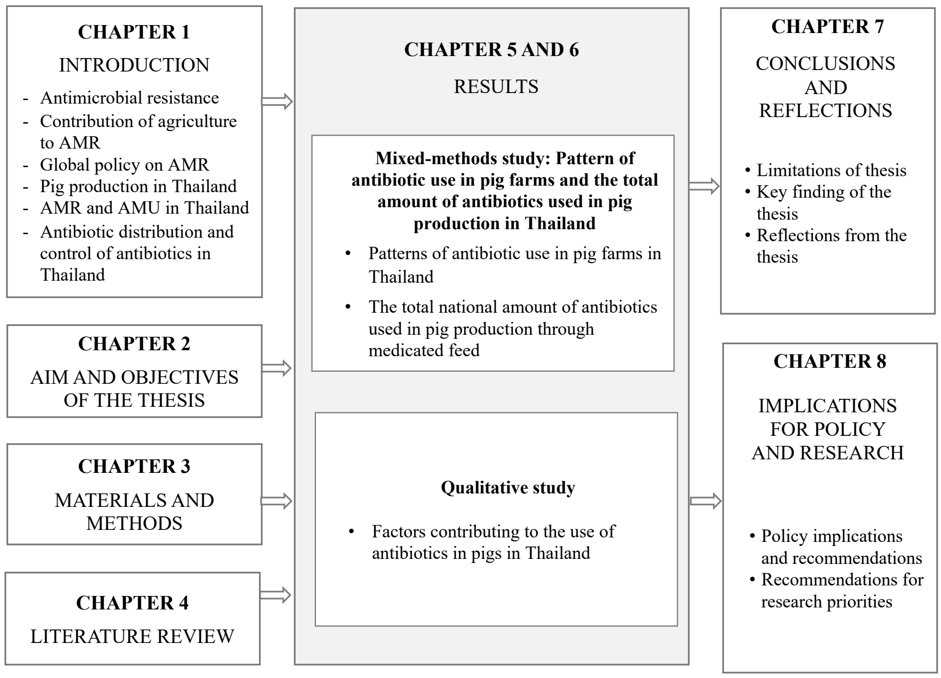

Figure 1.6 Mapping eight chapters in the thesis

Chapter 2 Aim and objectives

Summary

This chapter presents the overall approach, design and methods. It begins with the thesis aim and objectives in section 1. Subsection 2 addresses the study frameworks.

2.1 Aim and objectives

The overarching aim of the thesis is to investigate patterns of antibiotic use and determinants influencing antibiotic use in pig production in Thailand in order to contribute to the development of policies aimed at optimising the use of antibiotics in pig production.
The specific objectives are:

2. To critically review the literature on the use of antibiotics in pigs and to identify the methods and measurements used to quantify antibiotic use in pigs;
3. To describe patterns of antibiotic use and estimate the total amount of antibiotics used in pig production in Thailand;
4. To explore the practices and views of pig farmers and other stakeholders about determinants influencing antibiotic use in pig production in Thailand;
5. To identify potentially effective policy options to optimise the use of antibiotics in pig production.

2.2 Study framework

The study framework is presented in Table 2.1. It includes the relationship between the thesis objectives, research questions and methodology. The systematic reviews were conducted to explore on how antibiotics are used in global pig production and what methods and measurements are used to quantify the use of antibiotics in pigs? The empirical research comprises of two sub-studies based on study objectives and primary data collection. In the rest of the thesis, the term 'the study' means the empirical research.

The 1st sub-study was a mixed-method study to describe the patterns of antibiotic use and estimate the total amount of antibiotics used in pig production in Thailand, in order to address objective 2. A mixed-methods approach was applied to gain a comprehensive understanding by comparing and synthesising both qualitative and qualitative data. A questionnaire survey with farmers was conducted to collect data on the patterns of antibiotic use in pigs in selected pig farms in a single province. The amount of antibiotics is estimated through secondary analysis of a 2017 national survey of feed mills conducted by the International Health Policy Program, Ministry of Public Health. Data obtained from feed mills was supplemented by interviews with veterinarians working in the feed mill industry to gain a deeper understanding of the use of medicated feed.

The 2nd sub-study was a qualitative study which involved interviews with farmers and other stakeholders in line with observations on selected pig farms, in order to address objective 3. The purpose was to explore the practices and views of pig farmers and other stakeholders about determinants influencing antibiotic use in pig production.

Evidence generated from the above was synthesised to discuss and identify relevant policy and interventions to enhance the rational use of antibiotics in pig production in Thailand, in order to address objective 4.

Table 2.1 Relationship between thesis objectives, research questions and methodology

Objectives	Research questions	Methodology
Objective 1: To critically review the literature on the use of antibiotics in pigs and to identify the methods and measurements used to quantify antibiotic use in pigs;	- What is known about how antibiotics are used and which factors are associated with the use of antibiotics in global pig production? - What methods and measurements are used to quantify the use of antimicrobials in pigs?	Systematic reviews
Objective 2: To describe the patterns of antibiotic use and estimate the total amount of antibiotics used in pig production in Thailand.	- How are antibiotics used in terms of types, routes, and purposes in pig production? - Which farm and farmer characteristics are associated with the use of antibiotics? - What volume of antibiotics is used in pig production?	A mixed-methods study - Questionnaire survey of pig farmers and feed mills - Interviews with veterinarians in the feed industry
Objective 3: To explore the practices and views of pig farmers and other stakeholders about determinants influencing antibiotic use in pig production in Thailand.	- What determinants influence the use of antibiotics in pig production?	A qualitative study - Interviews with farmers and other stakeholders including animal drug retailers, veterinarians, government officers - Observation in selected pig farms
Objective 4: To identify potentially effective policy options to optimise the use of antibiotics in pig production in Thailand.	- What are effective policy options to optimise the use of antibiotics in pig production in Thailand?	Synthesis of evidence generated from the above

The study is concerned with exploring how and why antibiotics are used in pig production in Thailand. Figure 2.1 summarises the conceptual framework about antibiotic use in pig production and factors influencing the use of antibiotics. At the bottom of the figure, patterns of antibiotic use in pig production are categorised by type of antibiotics, route of administration, purpose of antibiotic use and volume of antibiotic use. The determinants influencing the use of antibiotics in pig production involve different levels. The following section describes the conceptual framework in detail.

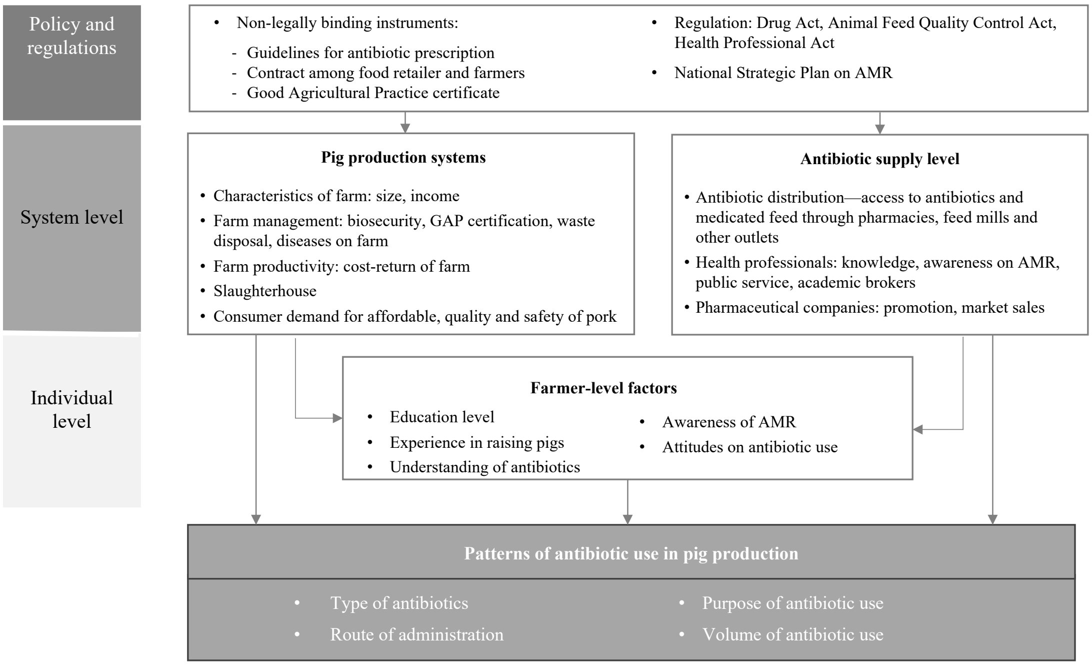

Figure 2.1 Conceptual framework describing the use of antibiotics in pig production and factors influencing antibiotic use

Firstly, the question of how antibiotics are used in pig production is addressed through a study of pig farms that aims to identify patterns of antibiotic use, focusing on the types of antibiotics, the volume of the different types of antibiotics, their intended purpose and routes of administration. The types of antibiotic are described in terms of active ingredients according to the anatomical therapeutic chemical veterinary (ATCvet) classification system. The types also relate to the WHO CIA list for human medicine (66). The volume is calculated in kilograms. The routes of administration include injection, oral medication, and medicated feed. The purposes of the use include for treatment, for control and prevention of disease and for growth promotion.

Secondly, as the determinants influencing the use of antibiotics in pig production can be considered at different levels as illustrated in the conceptual framework. This study considered the determinants influencing antibiotic use at three levels: farmer level, systems level and policy level.

At the farmer-level, factors that have been considered include educational level; experience in raising pigs; understanding of antibiotics; awareness of AMR; attitudes on antibiotic use.

At the system level, two systems were considered at the system level, the pig production systems and antibiotic supply systems. Factors attributable to pig production systems cover farm characteristics, farm management, health status of pigs on farms, farm productivity, slaughterhouse, and the role of consumers and food retailers that can stimulate the reduction of antibiotic use in pig production. Factors attributable to antibiotic supply systems (production, distribution, prescription, sale and use of antibiotics) focuses on access and availability of antibiotics, and roles of relevant stakeholders involved in the systems such as veterinarians and the pharmaceutical industry.

Policy and regulations include the drivers associated with the government, regulations and policies concerning the use of antibiotics in pig farms. The regulations cover formal legal restrictions, enforced by a government authority, to non-legal norms or enforced self-regulation through professional bodies. To control antibiotic distribution, the Drug Act, Animal Feed Control Act and Health Professional Act play a vital role as common legal mechanisms. Guidelines for antibiotic prescription and use leads to optimal use of antibiotics for both health professionals and farmers. Through the National Strategic Plan on AMR, several interventions aim to optimize use of antibiotics at pig farms. At farm level, the government promotes the good practice of farm management including increased farm biosecurity and rational use of antibiotics.

Chapter 3 Material and methods

In order to achieve the stated aim and objectives, a wide range of methods was used. This chapter describes the study design and outlines a brief description of the methodological considerations. Systematic review was used to describe the pattern of antibiotic use in pigs, and methods and measurement to quantify antibiotic use in pigs. For the empirical research, a mixed-methods study was conducted to explore the use of antibiotics and estimate the total amount of antibiotics used in pig production in Thailand. In addition, a qualitative approach was used to explore the practices and views of the various key actors associated with the use of antibiotics for pig farming in Thailand. Full details of the methodology are presented in each results chapter in the form of an academic article.

3.1 Systematic reviews

I conducted two systematic reviews. The studies included in the review focus on antibiotic use in global pig production, involving pigs of any age and type of production, with a focus or clear explanation of the methodology in pigs or other food producing animals including pigs. The studies were reviews, clinical research, pharmacokinetic, biopharmaceutical studies and laboratory studies were excluded.

The operational definitions of the terms used in the reviews are as follows.

Term	Definition
Antimicrobials	According to World Organisation for Animal Health (OIE) definition, an antimicrobial is considered as a naturally occurring, semi-synthetic or synthetic substance that exhibits antimicrobial activity (it kills or inhibits the growth of micro-organisms) at concentrations attainable in vivo. Anti-helminthic and substances classed as disinfectants or antiseptics are excluded from this definition (108).
Pig	The term refers to all stages of swine production including breeding and gestation, farrowing (from birth to weaning), nursery and feeding and finishing.
Use and consumption	WHO defines consumption data as quantitative data (amounts of antimicrobial) and qualitative data (description of antimicrobial class, indication, route of administration, etc.) collected from several sources such as import data, wholesale data or aggregated health insurance data. Use data refers to estimates derived from patient-level data. It may focus on how and why antimicrobials are being used by health care providers and patients. Usually, data on consumption is reported when information on antimicrobial use in patients is not available. Consumption data provides a proxy estimate of the use of antimicrobials (109). However, in this study, for simplicity the term "use" is applied to refer to both use at farm level and consumption at aggregate national or sub-national level.

The online electronic database through LSHTM databases: MEDLINE (http://ovidsp.tx.ovid.com; 1946 until present), Scopus (http://www.scopus.com; 1823 until present) and Web of Science (http://apps.webofknowledge.com; 1970 until present) were searched with restriction of the date of publication between 2000 and 2017 to capture up-to-date data, using the following search strategy:

- (antibiotic OR antimicrobial OR antibacterial) AND
- (livestock OR swine OR pig* OR farrow OR weaner OR finisher OR sow) AND
- (use OR utilisation OR consum* OR practice OR administration)

The titles and abstracts were reviewed for relevance to the study question and the full text of articles identified as potentially relevant were examined. The reference lists of final papers included in the review were searched to identify additional relevant papers. Articles were exported into EndNote, de-duplicated and then exported into an excel spreadsheet to permit the selection of articles and data extraction. The Critical Appraisal Skills Programme (CASP) was applied for quality assessment by two independent reviewers. When there were conflicting views, the reviewers will be discussed and seek consensus.

3.2 Study design and methodological considerations for the empirical research

3.2.1 Study design

The study applied a convergent parallel mixed-methods design, in order to compare different perspectives drawn from quantitative and qualitative data on determinants influencing the use of antibiotics. Figure 3.1 summarises the study design and methods used in the study.

First, mixed methods were used to describe the patterns of antibiotic use and estimate the total amount of antibiotics used in pig production in Thailand. The quantitative strand included a survey among farmers describing types, routes, and purpose of antibiotics used in pig farms, and a survey of feed mills presenting the volume of antibiotics used in pigs. The qualitative approach through interviews with veterinarians working in the feed mill industry provided a deeper understanding about antibiotics used in medicated feed in relation to common diseases and pathogens in pigs. Second, the qualitative approach, including interview and observation, was used to explore the practices and views of pig farmers and other stakeholders about determinants influencing antibiotic use in pig production.

Using a mixed methods approach, I was able to compare and integrate findings from questionnaire surveys with farmers with the perspective of other stakeholders concerning determinants influencing the use of antibiotics in pig production.

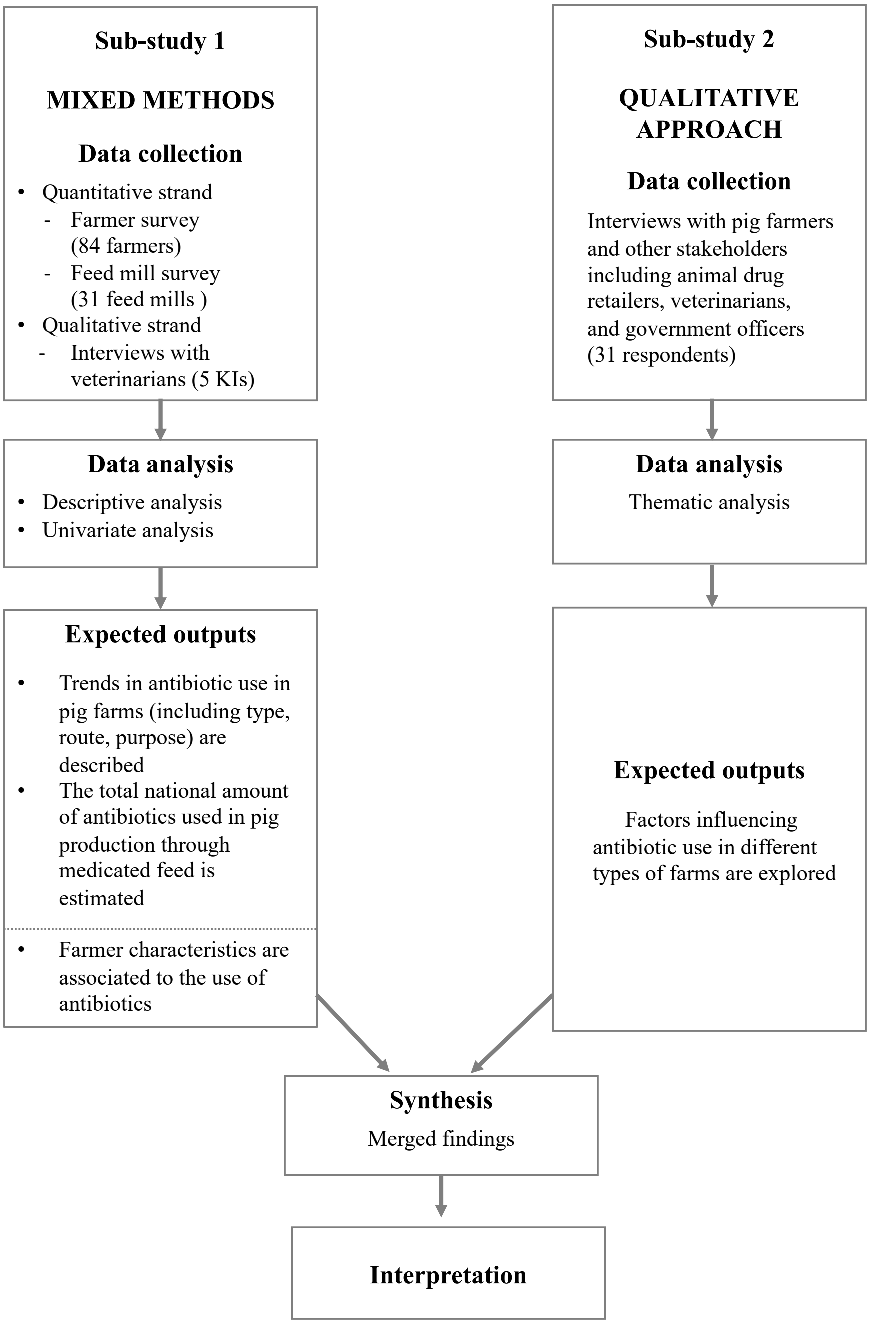

Figure 3.1 Diagram demonstrating the study design using the convergent parallel mixed methods design

3.2.2 Setting

The study was conducted in province A located in the central region of Thailand, which has one of the highest pig populations, accounting for about 20% of total annual Thai pig production (78). The province has an area of about 5,000 square kilometres and around 100,000 inhabitants. It is sub-divided into ten districts, some with a high density of pig and cattle farms, and others with very low density.

Data from the study of antibiotic distribution in 2016 (100) demonstrated that there is a wide range of types of farm management in this province including smallholder farms managed by the individual farmer, smallholder farms managed under a cooperative association and commercial contracting farms. This diverse setting supports a range of situations of interest that will provide greater in-depth understanding antibiotic use in pigs in Thailand.

3.2.3 Methodological considerations

This section gives brief methodology considerations based on the two sub-studies: a mixed-methods study and a qualitative study. The research methodology for each sub-study is explained in full in the next chapters.

A mixed-methods study

To describe patterns of antibiotic use in pigs, it is necessary to focus on the active ingredients of antibiotics, the quantity of antibiotics used for different purposes and routes of administration. Based on my systematic literature review, there are four possible approaches to collect antibiotic use data (Table 3.1).

At farm level, data from prescription records can be accurate in terms of indication and doses given to animals. However, it is difficult in countries where no prescription is required for antibiotics. Antibiotic treatment records are available on some farms. In prospective data collection, a researcher might provide a record book to farmers, but these data are likely to be confidential on some farms. In many HICs, data on antibiotic use are available via online platforms including antibiotic application (by farmers) and antibiotic prescription (by veterinarians). It is practical to obtain, verify and use this data for analysis. However, it is only available for a few farms in LMICs. If no standard programme at a national level exists, investment and training is required to develop an online data entering system. In addition, it is challenging in countries where no prescription is required for antibiotics. Data from pharmaceutical companies and pharmacies are likely to be more practical to collect. However, these data cannot capture the number of animals which received antibiotics including doses, indications and duration. This data might also be confidential for the pharmaceutical industry.

Table 3.1 Different approaches for data collection on antibiotic use

Data source	PROS	CONS	Comments
FARM VISIT			
- Antibiotic prescription (a prescription record at farm)	- Accurate data on medicine, indications and doses	- The prescribed antibiotics may not be used by animals	- Difficult in countries where no prescription required for antibiotics
- Antibiotic application (treatment record)	- Indicate the number of animals which received antibiotics - Indicate dose and duration		- Available on some farms. It can be a prospective data collection. Researcher may provide a record book to farmers
- Antibiotic invoice	- Easy to access	- Difficult to capture the number of animals which received antibiotics - Unable to capture indications, dose and duration	- May not be available in all farms
ONLINE PLATFORM			
- Antibiotic prescription (by veterinarians)	- Easy to obtain, verify and use data for analysis		- Available in few farms in LMIC. - If no standard programme at a national level, it requires investment and training to develop the online data entering system - Difficult in countries where no prescription required for antibiotics.

Data source	PROS	CONS	Comments
- Antibiotic application (by farmers)	- Easy to obtain, verify and use data for analysis		- Available in few farms in LMIC - If no standard programme at a national level, it requires investment and training to develop the system
PHARMACEUTICAL COMPANY			
Antibiotic sale	- Practical to collect data	- Unable to capture the number of animals received antibiotics - Unable to capture dose, indications and duration - All antibiotics sold may not apply to animals	- Confidential data for a pharmaceutical company
PHARMACY			
Antibiotic prescription, Antibiotic sale		- Unable to capture the number of animals received antibiotics - Unable to capture dose and duration - All antibiotics sold may not apply to animals	- Confidential data for a pharmacy

Based on the availability of data from different approaches, a questionnaire survey of pig farmers, secondary analysis of data from a survey of feed mill operators, and interviews with veterinarians were applied in the study to determine the patterns and total amount of antibiotic use in pig production in Thailand.

- Survey of pig farmers

Initially, I planned to obtain the sampling frame from national data of the DLD database. The random sampling methodology therefore would be applied to calculate the number of pig farms in the study. The primary sampling is an area (province) and the secondary sampling unit is a farm. However, the absence of complete up-to-date lists of pig farms in 2018 at district level limited the application of a census and random sampling technique for a sample selection of farms (more information is discussed in the strengths and limitations of the study, chapter 7).

Based on the best available data and discussions with each district health office, the three districts with the highest number of pig farms were purposively selected and within each district, the two sub-districts with the highest number of pig farms were selected.

The objective of a questionnaire survey of farmers was to assess the use of antibiotics; the source of antibiotics (including medicated feed); and how much access to information farmers had on animal health management, feed and antibiotic administration.

The questionnaire was developed based on the relevant literature about antibiotic consumption in pig farms (110–112) and modified after the first phase of the interview with a small set of farmers, to ensure suitability to the local context in Thailand. The questions covered the following areas:

- General information on farmer: gender, age, educational level
- Characteristics of farms

    - The size of farm is categorised based on the number of pigs on the farm according to the Department of Livestock Development (DLD) definition: smallholder farm (less than 50 pigs), and commercial farm, subcategorised to small commercial farm (from 51 to 500 pigs), medium commercial farm (from 501 to 5,000 pigs), and large commercial farm (more than 5,001 pigs);

- Good Agricultural Practices for the pig farm are introduced as voluntary standards for food safety and livestock production. The farm standards range from farm infrastructure, animal feed quality, water quality, farm management, and animal health management including the use of antibiotics;
- A contracted farm is classified to be where the contracting company provides pigs, feed, medicines, and technical support to farmers and farmers provide animal housing and labour. A non-contract farmer is independent of contracting companies;
- The type of pig production is grouped into farrow-to-finish (breeder, suckling piglet, nursery pig, fattener), fattening (fattener-only), and breeding (breeder-only) (Figure 3.2).

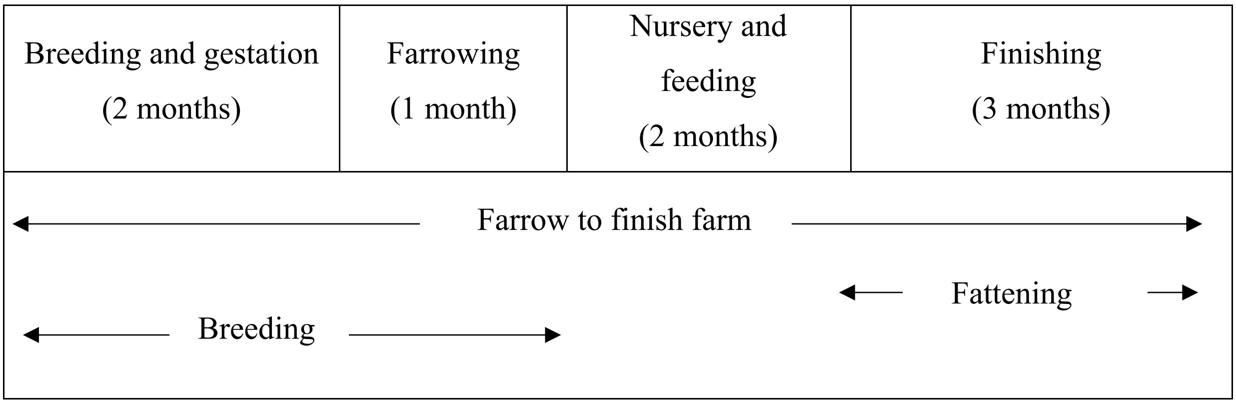

Figure 3.2 Types of pig production

- Destination of pig products: pig broker, pork retailer, consumer, other farms, household own consumption;
- Antibiotics and medicated feed used:
  - The types of antibiotic are described according to the ATCvet classification system;
  - Antibiotics are also categorised by WHO CIA for human medicine;
  - Routes of administration included injection medication, oral solution, oral power through water medication (medicated drinking water) and feed medication (medicated feed);
  - Purposes of antibiotic use are categorised as therapeutic use (treatment of disease), preventive use (sub-therapeutic doses of antibiotics) including for control of disease (metaphylaxis) and prevention of disease (prophylaxis), and non-therapeutic use.
- Sources of antibiotics and medicated feed (pharmaceutical company, pharmacy, internet, feed mill, feed store;
- Knowledge and awareness about antibiotics and AMR;
- Perceptions of the factors regarding the use of antibiotics.

The questionnaire is in Appendix 3.1. Data collection, data management and analysis of farmer survey are explained in full in chapter 5.

- Survey of feed mills

The survey of feed mill operators aimed to collect information about the production of medicated feed at a national level and included information about the type and volume of antibiotics mixed in medicated feeds. In order to determine the total amount of antibiotics used in pig production, the initial plan was to collect data through records of antibiotic administration on farms. However, it became clear that this would not be adequate. First, farmers had no recording system on the use of medicated feed. Second, there was a potential recall bias by farmers during interview. Third, there were no labels with the antibiotics' names and concentration levels on the feed package (although there were feed codes on the feed packages, these codes were not specific to antibiotic contents). Fourth, farmers were not willing to disclose information in relation to the use of antibiotics. Limitations in estimating the volume of antibiotics use is described in Figure 3.3.

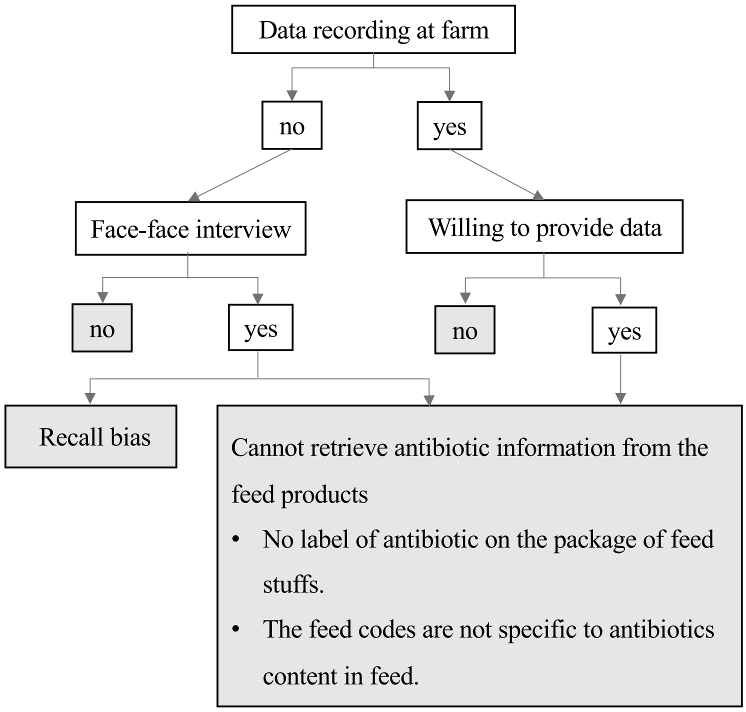

Figure 3.3 Limitations of estimating the volume of antibiotics in feed on farm

Given these limitations, data from a national survey of feed mill operators for feed production in 2017 were used for the secondary data analysis. The national survey of feed mills was conducted by the International Health Policy Program as part of the Thailand Surveillance of Antimicrobial Consumption in humans and animals (Thailand SAC) (81). Thailand SAC was developed in 2017 in response to the National Strategic Plan on AMR. Data from an annual report of pharmaceutical operators including importers and manufacturers were used to estimate the total national consumption of antimicrobials in humans and animals. Given the limitations of Thailand SAC, data are not available to disaggregate by animal species. In 2017, the working group decided to collect data of antibiotics used in medicated feed (medicated premix) because about half of antimicrobials used in food-producing animals was in the form of medicated premix (81).

Data extracted for the analysis from the survey forms included the following variables:

- Name of the antibiotic (medicated premix) according to the anatomical therapeutic chemical veterinary (ATCvet) classification system;
- Thailand FDA market authorization identification number;
- Type and amount of antibiotic added to the feed;
- Unit of measurement: kilograms;
- Stage of pig production: breeding pigs (sows), pigs less than 25 kg (suckling and nursery pigs) and fatteners.

A full explanation of the sample population, data collection and data management and analysis of feed mill survey is in chapter 5.

- Interviews with veterinarians in the feed industry

The interview with veterinarians in the feed industry was conducted to understand the use of medicated feed in pig farms. The Thai Feed Mill Association was asked to propose a list of veterinarians working at the feed mills, who were members of the Thai Feed Mill Association, to participate in the study. All of the interviews were conducted face-to-face in Thai through semi-structured interviews. A full description of data collection, data management and analysis is in chapter 5.

A qualitative study

A qualitative approach was used to explore determinants influencing antibiotics use. The interviews were conducted with pig farmers and other stakeholders including animal drug detailers, food animal industry veterinarians and government officers concerning antibiotic control to explore their views about the practices of antibiotic use, and its drivers in pig production.

Interviews were used with open questions to reconstruct meanings of antibiotic use through actors' practices, perceptions, attitudes and motivations (113). There was little information about the use of antibiotics in pigs in Thailand; therefore, data from the key-informants supplemented the interview questionnaire to try to obtain information about potential factors influencing the use of antibiotics.

To design the interview guide, interviews were conducted with a small set of farmers, such as a representative of a pig farmer association or a representative of a pig cooperative association. Based on the study framework and the first phase of interviews, the interview guide covers the potential factors contributing to antibiotic use:

- Animal health and farm management;
- Pig production and market demand;
- Relationship with other farmers
- Regulation and policy on antibiotic use.

Farmers respondents in the farmer survey of antibiotic usage were asked to participate in the interview and farmers who did not use antibiotics in their farms in the studied area were purposively selected through a snowball sampling technique. The interviews took the form of an interactive discussion between the researcher and farmer participant with an average duration of 120 minutes. The researcher then conducted direct observation on the farm after the interview, in order to add more depth to the analysis and findings (114). This also helped validate the information given by interview respondents such as comparing data collected during the interview with farmworkers' actual practices observed on the farm. For the observations, I looked at activities of farmworkers, labels of the feed, medicines used by farmers, general sanitation and farm management.

Animal drug detailers, food animal feed industry veterinarians and government officers were interviewed to assess the context in which pig farms operate and to explore other additional and related information. Each interviewee was selected using purposive sampling. Animal drug detailers who were working in the study area were identified by farmers and contacted for the interview. Relevant organisations such as government authorities in the field of antibiotic control, animal feed mill associations, veterinary associations, and health professional councils were asked to propose lists of their staffs or members who could provide information about the use of antibiotics in pig production. The researcher contacted each potential informant identified to see if they were able and willing to participate in the study. Animal drug retailers and food animal industry veterinarians were interviewed outside their shops and offices, and officers were interviewed in their offices. Each interview took one to three hours.

To gather in-depth data, I conducted the interviews and observations to ensure a good relationship between myself and the key informants. Details of the qualitative methodology is explained in full in chapter 6.

3.2.4 Ethical considerations

The study is approved by the ethical committees of the Institute for the Development of Human Research Protection at Ministry of Public Health, Thailand (reference number: IHRP2018007); and the London School of Hygiene and Tropical Medicine research ethics committee (reference number: 14860). Informed consent was obtained for all interviews. In keeping with confidentiality agreements, no name and affiliation of the respondents were reported in the presentation of results.

Chapter 4 Literature review

Summary

To inform the empirical research, I conducted two systematic literature reviews of antibiotic use in pig production. The aim of the first review was to gain a comprehensive overview of antibiotic use in global pig production. The results are presented in the first paper entitled "Patterns of antibiotic use in global pig production: A systematic review". The paper was published in Veterinary and Animal Science in April 2019. A further systematic review sought to understand the methods for quantification of antibiotic use and was undertaken in order to guide data collection in my empirical research to estimate the total amount of antibiotics used in pig production in Thailand. The paper was published in Preventive Veterinary Medicine in September 2018. Both systematic reviews are presented in subsection 2. Based on a further review of the literature, subsection 3 highlights potential factors influencing the use of antibiotics among different stakeholders at three different levels: individual level, systems level, and policy and regulation level. Finally, subsection 4 presents a summary of the knowledge gaps in existing research about antibiotic use in pigs.

4.1 Systematic literature review of antibiotic use in pig production

The literature review covered two main areas: a description of the patterns of antibiotic use and methods for quantification of antibiotic use in global pig production. In accordance with objective 1 of this study, the first review aims to describe what is known about how antibiotics are used and which factors are associated with the use of antibiotics in global pig production. The second review was conducted to identify the methods and measurements which are applied to quantify the use of antibiotics and identify the current quantity of antibiotics used in pigs.

4.1.1 Patterns of antibiotic use in global pig production: A systematic review

Understanding the current patterns of antibiotic use in livestock is important due to concerns about AMR. This systematic review aims to analyse and synthesise the available published information on patterns of antibiotic use in pigs. It describes the patterns of antibiotic use including classes and active ingredients of the antibiotic; the route of administration; the purpose of use including treatment, metaphylaxis, prophylaxis and growth promotion; and the frequency of use by different farms and different stages of pig production.

The studies included in the systematic review were conducted between 2000 and 2017; this time period was selected in order to get up-to-date information on antibiotic use in pig production. The analysis also considers the geographical gap of the studies conducted in HICs and LMICs.

(Cover sheet on next page)

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Student	Angkana Lekagul
Principal Supervisor	Professor Shunmay Yeung
Thesis Title	Understanding the use of antibiotics in pig production in Thailand

If the Research Paper has previously been published please complete Section B, if not please move to Section C

SECTION B – Paper already published

Where was the work published?	Veterinary and Animal Science		
When was the work published?	April 2019		
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Patterns of antibiotic use in global pig production: A systematic review

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ABSTRACT

This review assesses the evidence for patterns of antibiotic use in pig on the basis of papers published in peer-reviewed journals in English between 2000 and 2017. Thirty-six articles were identified and reviewed, of which more than 85% of studies were conducted in Europe and North America. Penicillins and Tetracyclines groups were the most commonly used antibiotics in many countries. Oral medication in suckling and post-weaning periods were the most common applications of antibiotic administration in pig production. Antibiotic use is driven by age-specific diseases and the common pathogens causing these conditions where epidemiological profiles varied greatly across countries. In addition, the type and size of farm were associated with antibiotic use with finisher and larger farms using more antibiotics than farrow-to-finish and smaller farms. There is variation in the use of the highest priority critically important antimicrobials in humans across studies. However, this review indicates that they are still commonly used in pig production, for treatment and prevention of infection. This evidence calls for global efforts on the prudent use of antibiotics in response to the emergence of antimicrobial resistance (AMR) in the agricultural sector.

1. Introduction

Antibiotics have been used routinely in farm animal production since the 1950s, in particular during intensive farming, in order to keep animals healthy and to increase productivity. The use of antibiotics in animals has raised concerns that the selective pressure on the bacteria population promotes antibiotic resistance. Despite the difficulties in demonstrating the transmission of resistant bacteria from animals to humans, many studies have shown evidence of human infection from resistant bacteria in animals (Liu et al., 2018; McCrackin et al., 2016; Nhung, Cuong, Thwaites, & Carrique-Mas, 2016). The discovery of a plasmid-mediated colistin resistant gene (MCR-1) in commensal *Escherichia coli* from pigs, pork products and humans in China, triggered global concern (Liu et al., 2016). Colistin is considered a last resort antibiotic as it is one of the only antibiotics active in severe infections caused by hospital acquired multidrug-resistant (MDR) pathogens such as *Pseudomonas aeruginosa, Acinetobacter baumannii* and *Enterobacteriaceae* (Catry et al., 2015).

Antibiotics in the same class usually have a similar mode of therapeutic action, with a range of effectiveness. Many classes of antibiotic used for humans are also used in food animals. The World Health Organisation (WHO) produces a list of all antimicrobials grouped into 3 categories based on their importance in treating human infections. (World Health Organization, 2017). The classes of drugs included in the list of critically important antimicrobials (CIA) for human medicine contain the last-resort antibiotics to treat severe infections caused by multidrug-resistant (MDR). The CIA list of Highest Priority Critically Important Antimicrobial includes Quinolones, 3rd and higher generation Cephalosporins, Macrolides and Ketolides, Glycopeptides and Polymixins class which includes colistin (World Health Organization, 2017). This WHO CIA list is referred to in the rest of this report.

In animals, the use of antibiotics is common for not only treatment, but also for controlling the spread of infection (metaphylaxis), preventing infection (prophylaxis) particularly in periods of stress and vulnerability to infections, and improvement of feed efficiency and promotion of animal growth (Aarestrup, 2005). According to American Veterinary Medical Association, the term "therapeutic" includes treatment, control, and prevention of disease (Association American Veterinary Medical, 2019). The use of antibiotics as a growth promoter is considered non-therapeutic. Many countries including USA, Canada and Australia have implemented policies and regulations that medically important antimicrobials are prescription only medicines by licensed veterinarians (Australian Veterinary Association, Guideline for prescribing, authorising and dispensing veterinary medicines, 2005; Government of Canada, 2018; US Food and Drug Administration, 2011). The use of antibiotics for growth promotion has been banned in the European Union since 2006 (Regulation (EC) No 1831/2003 of the European Parliament and of the councel on additives for use in animal

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nutrition, 2003). In contrast, other countries – including China and Brazil which are the large livestock producing and exporting countries – do not prohibit the use of antibiotics for growth promotion (Maron, Smith, & Nachman, 2013).

Despite the concerns about the relationship between the use of antibiotics and AMR in food animals and AMR in humans, there are limited studies exploring the use of antibiotic in livestock and the factors that influence how farmers use them. To promote the prudent use of antibiotics in livestock, it is vital to have a better understanding of the current situation. This systematic review aims to analyse and synthesise the available published information on the pattern of antibiotic use in pigs.

2. Method

2.1. Scope of study and research question

This study focuses on antibiotics. Before conducting the systematic review, the terms and explanations to be included were considered as follows. According to World Organisation for Animal Health (OIE) definition, an antimicrobial is considered as a naturally occurring, semi-synthetic or synthetic substance that exhibits antimicrobial activity (to kill or inhibit the growth of micro-organisms) at concentrations attainable in vivo. Anti-helminthic and substances classed as disinfectants or antiseptics are excluded from this definition (World Organisation for Animal Health, 2011). In this study the word 'pigs' refers to all stages of swine production including breeding and gestation, farrowing, nursery and feeding and finishing. The word 'pattern' explains the use of antibiotics in terms of active ingredient; the route of administration such as injection or medicated feed; the purpose of the use including treatment, metaphylaxis, prophylaxis and growth promotion; and the frequency of the use by different farms and different stages of life cycle of pig production. The research questions in the review is: "What are the patterns of antibiotic use in terms of classes, routes of administration and purpose of the use and its associations with pig production?".

2.2. Identifying relevant literature

The study applied the "SPIDER" tool, designed specifically to identify relevant quantitative studies (Cooke, Smith, & Booth, 2012). It covers the following: Sample: pig; Phenomenon of Interest: antibiotic use in pigs; Design: Observational studies; Evaluation: pattern of antibiotic use including active ingredient of antibiotic, route of administration, purpose of use including treatment, control, prevention and growth promotion; and Research: Quantitative research.

Literature on the use of antibiotics in pigs was systematically reviewed between July to October 2017. Relevant scientific papers published in English peer-reviewed journals were identified using the keyword combinations (antibiotic OR antimicrobial OR antibacterial) AND (livestock OR swine OR pig* OR farrow OR weaner OR finisher OR sow) AND (use OR utilisation OR consum* OR practice OR administration).

The online electronic database through LSHTM databases: MEDLINE (http://ovidsp.tx.ovid.com; 1946 until present), Scopus (http://www.scopus.com; 1823 until present) and Web of Science (http://apps.webofknowledge.com; 1970 until present) were searched with restriction of the date of publication between 2000 and 2017 to capture up-to-date data. To ensure a wide range of articles from different sources, additional searches were sourced through the reference lists of key articles.

2.3. Eligibility assessment of studies and inclusion criteria

Prior to a study being included within the review, the following criteria were considered: publication in English, and focus on antibiotic usage in pigs with high and moderate ranking of a quality assessment.

Citations of all identified studies were downloaded into a reference management software (EndNote X8.0.2). In the first screening step, the duplicated studies were removed, through consideration of the title and the abstract by comparison with the keywords. Full texts were further considered. Reviews, clinical research, pharmacokinetic, biopharmaceutical and experimental studies were excluded. In addition, studies focusing on antibiotic activity, specific diseases related to drug recommendations, associations of antibiotic use with antimicrobial resistance, relationship between interventions and antibiotic use, and effects of antibiotic treatment to AMR, animal productivity and animal management were excluded.

Studies included in the qualitative synthesis were those that presented the pattern of antimicrobial use, and medium (50–75%) and high-ranking quality assessment (>75%). If a study explored data over many periods of time, then the updated data was selected for the review.

2.4. Quality assessment

The Critical Appraisal Skills Programme (CASP) was applied for quality assessment) (Critical Appraisal Skills Programme, 2014). They were aggregated into a quality score based on four criteria: aim, method, result and application of the literature; Yes, No and Cannot tell are the assessment outcomes. With eleven questions, the score was categorised into three groups: weak means <50% having "yes" answers, moderate means 50–75% having "yes" answers, and high means >75% having "yes" answers (see Table B.1 of annex). If the assessment by the reviewer was 'no' or 'cannot tell', the score for that question was zero; the score for yes was one. In this review, the studies were ranked by quality criteria. The quality ranking was classified into three groups: High meant >75% of all eleven sub-criteria were met, moderate meant 50–75% were met and weak meant <50% of criteria were met.

2.5. Data extraction and synthesis

Fig. 1 shows the review process. All relevant articles in full texts were reviewed and summarised using a standardised data extraction table in an Excel spreadsheet.

3. Results

3.1. Eligible studies

Our search strategies identified a total of 2588 articles (Appendix A). After duplicates were removed and an initial review of titles and abstracts for relevance was conducted and 118 articles were found to be eligible for full-text screening on the basis of the inclusion criteria. Sixty-eight studies were found to be relevant and retained. Further screening excluded 31 papers; of which 16 papers were not related to pattern and factors influencing antibiotic use; two papers had inappropriate study design; four papers focused on specific diseases using recommended antibiotics and relationship between interventions and antibiotic use; and ten papers were not related to pigs. Finally, 36 studies were included in this systematic review. Fig. 1 showed the flow diagram of the process in screening papers.

3.2. Study characteristics

As shown in Table 1, twenty-seven of studies (75%) were conducted between 2010 and 2017; the remaining 9 studies were conducted between 2000 and 2010 (25%). Most studies (72%) were conducted in Europe, with four studies in North America (11%), three in Asia (8%), and one each in Africa (3%) and Australia (3%). Diverse sources of data were used for the study such as farm surveys (39%), national databases (19%), farm-based survey and prescription data (14%), prescription data (8%), antibiotic application records (8%), veterinary survey (6%), pharmaceutical producer survey (3%) and farm-based survey and national data (3%). Among total studies reviewed, 9 studies (25%) were nationally representative. The result of the quality assessment of 36 studies showed that 21 (58%) and 15 (42%) of studies are of high and medium quality respectively (see Table B.1 in Annex).

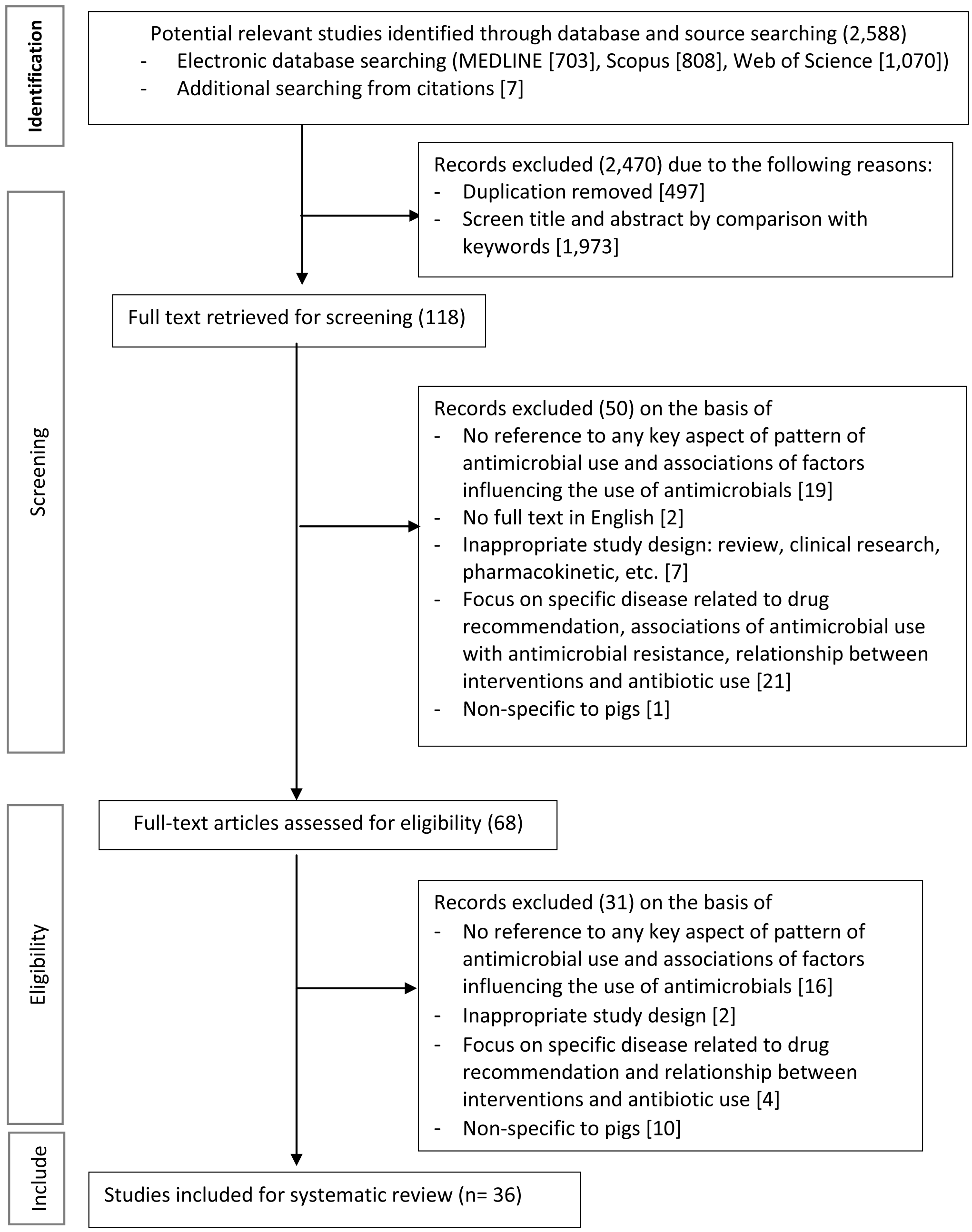

Fig. 1. Flow diagram of the screening process of the literature.

3.3. Patterns of antibiotic use in pigs

3.3.1. Patterns of antibiotic use

3.3.1.1. Classes and active ingredients of antibiotic. Some studies reported antibiotic use by active ingredient and others only by the class. In many studies the most common used antibiotic classes were the Penicillins and Tetracyclines. Benzylpenicillins consisted 61% of total use in a farm study in Sweden (Sjölund et al., 2016). Aminopenicillins were commonly reported accounting for 30–40% of total antibiotic use in studies from Sweden, Germany and Canada (Glass-kaastra et al., 2013; Sjölund et al., 2016; Van Rennings et al., 2015). Twelve studies reported that Tetracyclines class was the most commonly used including studies from Denmark, Japan, Netherlands, Australia, Spain and France (Bondt, Jensen, Puister-Jansen, & van Geijlswijk, 2013; Bos et al., 2013; Casal, Mateu, Mejía, & Martín, 2007; Chauvin, Beloeil, Orand, Sanders, & Madec, 2002; Dupont, Diness, Fertner, Kristensen, & Stege, 2017; Hosoi, Asai, Koike, Tsuyuki, & Sugiura, 2014; Jordan et al., 2009; Vieira, Pires, Houe, & Emborg, 2011), and was as high as 54.4% in a study from Germany (Merle et al., 2013). Within the Tetracyclines class, doxycycline was used 62.3% of total use in the study in Austria (Moreno, 2012). The share of chlortetracycline use was 23.9% in a farm study in Vietnam (Van Cuong et al., 2016), and formed the majority of antibiotics use in all pig stages in the United States (Apley, Bush, Morrison, Singer, & Snelson, 2012). In the farm study in Switzerland, the most common antibiotic class was the reductase inhibitors and combinations class" of drugs, specifically sulfadimidine, sulfathiazole and trimethoprim, accounting for 62.1% (Arnold, Gassner, Giger, & Zwahlen, 2004) while Bacitracin was the most reported of antibiotic use (24.8%) in the farm study in Vietnam (Van Cuong et al., 2016). Fattening farms in the study from Austria applied Lincosamides in 71.9% of antibiotic use (Trauffler, Griesbacher, Fuchs, & Köfer, 2014).

The use of highest priority Critically Important Antimicrobials in humans was also reported differently across countries. The studies from France and Austria reported the use of Macrolides at 20% and at 7.4% of total use

Table 1
Characteristics of the reviewed studies.

Characteristics	N = 36
2010–2017	27 (75%)
2000–2010	9 (25%)
Geographic area	
Europe[a]	27 (75%)
North America[b]	4 (11%)
Asia[c]	3 (8%)
Africa[d]	1 (3%)
Australia[e]	1 (3%)
Data source of antibiotics	
Farm based survey	14 (39%)
National database (consumption/sale/prescription)	7 (19%)
Farm based survey and prescription data	5 (14%)
Prescription data	3 (8%)
Antibiotic application records	3 (8%)
Veterinarian survey	2(6%)
Pharmaceutical producer survey	1 (3%)
Farm based survey and national data	1 (3%)
Quality assessment by authors	
High (>75%)	21 (58%)
Moderate (50–74%)	15 (42%)

[a] Europe: Denmark (n = 7), Germany (n = 6), Belgium (n = 5), France (n = 3), Netherlands (n = 3), Sweden (n = 3), Switzerland (n = 3), Austria (n = 2), Spain (n = 2), UK (n = 1).
[b] North America: Canada (n = 3), USA (n = 1).
[c] Asia: Vietnam (n = 2), Japan (n = 1).
[d] Africa: Sudan (n = 1).
[e] Australia: Australia (n = 1).

(Chauvin et al., 2002; Trauffler, Obritzhauser, Raith, Fuchs, & Köfer, 2014). Based on the electronic drug application records from 75 pig farms in Austria, Fluoroquinolones were reported at 2.4% of total use, third and fourth generation Cephalosporins were 2.2% of total use (Trauffler et al., 2014), while the use of Fluoroquinolones at 5% and third generation Cephalosporins at 11% were reported from 47 pig farms in the study in Belgium (Sjölund et al., 2016). The study in 60 French pig herds received colistin in 30% of total antibiotic use (Sjölund et al., 2016), 12.2% in the study in Vietnam using the internet-based survey of commercial feed producer (Van Cuong et al., 2016), 33% and 61% in the survey in 45 farrow-to-finish farms and 67 fattening farms in Spain (Moreno, 2012) and 34.4% in fattening farms in 75 pig farms in Austria (Trauffler et al., 2014).

3.3.1.2. Routes of administration. Generally, oral medication was the most common route of antibiotic administration in pig production. Several studies reported more than 90% of antibiotic substances were administered orally via both feed and water (Chauvin et al., 2002; Merle et al., 2012; Rajić, Reid-Smith, Deckert, Dewey, & McEwen, 2006; Van Rennings et al., 2015). About 70–90% of the oral use was reported in many countries, for example 87% in the study from France (Sjölund et al., 2016), 86% in the study from Austria (Trauffler et al., 2014), 73% in the study from Denmark (Dupont et al., 2017), 71% in the study from Germany (Sjölund et al., 2016) and 70% in the study from Belgium (Sjölund et al., 2016). In the UK farm study, 60–75% of the farmers had used medicated feeds for their weaners (Stevens et al., 2007). Another study indicated that oral use of antibiotics was higher than parenteral indication (97.43% VS 2.46%) (Merle et al., 2013).This is in contrast to another study that farmers applied very low levels of oral antibiotics, 13% of all routes (Sjölund et al., 2016).

A wide range of active ingredients was commonly used for oral medication, including: colistin (Filippitzi, Callens, Pardon, Persoons, & Dewulf, 2014; Moreno, 2012; Timmerman et al., 2006), amoxicillin(Filippitzi et al., 2014; Timmerman et al., 2006), sulfonamides (Bondt et al., 2013; Timmerman et al., 2006), oxycycline (Bondt et al., 2013), doxycycline (Moreno, 2012; Timmerman et al., 2006), chlortetracycline, lincomycin,tiamulin, tylosin, and penicillin G (in water) (Rosengren et al., 2008). However, ceftiofur (Filippitzi et al., 2014; Timmerman et al., 2006), enrofloxacin (Moreno, 2012), amoxycillin (Moreno, 2012; Timmerman et al., 2006), penicillin (Moreno, 2012; Rosengren et al., 2008) and tulztromycin (Filippitzi et al., 2014) were commonly used for parenteral medication.

The oral administration of antibiotics (either through feed or water) was commonly used for group treatment, while injection was the commonly applied for treatment of individual sick animals (Sjölund, Backhans, Greko, Emanuelson, & Lindberg, 2015; Trauffler et al., 2014). A study showed that 90% of group treatment was administered between birth and ten weeks of age; while only 20% of group treatment was administered during the fattening period (Callens et al., 2012). Group treatments were primarily administered via oral medication in weaners and via parenteral route for individual sucking piglets (Filippitzi et al., 2014), particularly after castration or when diarrhoea occurred (Timmerman et al., 2006). In one study reported ninety-four percent of group treatment at farm for a respiratory infection (prior to a definitive diagnosis) was carried out with tetracycline, beta-lactams and sulphonamides while 90% of group treatment at farm for enteric disease used colistin (Casal et al., 2007).

3.3.1.3. Indications: treatment, metaphylaxis, prophylaxis and growth promotion. Few studies in this review reported the indication for antibiotics use. A vast majority, 93% of total antibiotics administered were for prophylaxis, whereas metaphylaxis or treatments were much smaller at 7% of total antibiotics in Belgium (Callens et al., 2012; Filippitzi et al., 2014). Main therapy indications in farrow-to-finish and fattening farms were metaphylactic/prophylactic measures (Trauffler et al., 2014). Chlrotetracycline and carbadox were the most commonly used antibiotics for growth promotion, prevention and treatment of infectious diseases and tiamulin was commonly used for prevention and treatment of infectious diseases (Apley et al., 2012).

Only few studies reported the use of antibiotic by distinguishing between metaphylaxis and prophylaxis (Callens et al., 2012; Filippitzi et al., 2014), which 'prophylactic use' means treatment of healthy pigs to prevent disease from occurring and 'metaphylactic use' means treatment of clinically healthy pigs in the same group where some animals had showed clinical symptoms of disease. Based on American Veterinary Medical Association, both 'prophylaxis' and 'metaphylaxis' means therapeutic (Association American Veterinary Medical, 2019) and commonly described as "preventative use" as a general term. However, both terms are not applied in certain situations such as the use of antibiotics within a group of animals without definite diagnosis.

3.3.2. Association between the use of antibiotics and pig production

3.3.2.4. Phase of pig production. Six studies examined the association of antibiotic use and the phase of pig production. Antibiotics were commonly used during suckling and post-weaning periods. One study reported more than 80% of antibiotics were applied to pigs at less than ten weeks of age (Callens et al., 2012). Four studies reported that weaners received the most antibiotics (Chauvin et al., 2002; Fertner et al., 2015; Jensen, Emborg, & Aarestrup, 2012; Sjölund et al., 2016). However, another study showed that treatment of suckling piglets was more common than weaners (Sjölund et al., 2016), and similar findings were reported in two studies (Merle et al., 2013; Van Rennings et al., 2015).

Based on the cross-sectional study conducted among 227 farrow-to-finish pig herds in four European countries, there was a significant association between antibiotic use across different age categories. The lowest use of antibiotics among fatteners reported in France and Sweden, while the least use in breeders reported in Belgium and Germany (Sjölund et al., 2016). Similarly, the studies from Denmark and France reported the least application of antibiotics in sows, with about 26% and 17% of total use in all phases respectively (Chauvin et al., 2002; Jensen et al., 2012). Another study using veterinary prescription data reported almost zero use of antibiotic among the finishers in Denmark (Fertner et al., 2015). However, one study from Belgium reported that the use of antibiotics was higher in the farrowing period than fattening period (Callens et al., 2012). Another study showed that eight veterinarians in Saskatchewan and Alberta applied more than 90% of the antibiotics for treatment of disease in sows, compared to less than 20% in other phases (Rosengren et al., 2008). However, the farm study in Vietnam reported there was no significant difference in antibiotics use for prevention across three age groups (piglets, fatteners and sows) (Kim et al., 2013).

The class and active ingredient of antibiotic also varies by different phases of pig production (Table 2). Aminopenicillin, tetracyclines, trimethoprim-sulfonamides, tylosin and colistin were commonly used in all studies (5 studies each). Chlortetracycline (4 and 3 studies), oxytetracycline (3 and 4 studies), tylosin (5 studies) and lincosamide (4 studies) were commonly used in weaners and finishers. Colistin in Polymyxin class was used in weaners in five studies, while aminoglycosides were mostly used in finishers (4 studies).

One study reported the route of administration in relation to the phase of production. Weaners and finishers were more likely to receive oral antibiotics while sows and piglets received parenteral administration (Jensen et al., 2012).

There are variations in the indication for antibiotic use by phases of pig production (Table 3). For example, more than half of pig farms (58%) used oral antibiotics as a routine prophylaxis for fatteners (Casal et al., 2007); medicated feeds are used mostly as growth promoters for weaners (Stevens et al., 2007); and there was less use of antibiotic as a growth promoter and therapeutic use in sows than in piglets; but it was equally used for piglets and fattening pigs (Kim et al., 2013).

3.3.2.5. Diseases in pigs. Five studies reported the use of antibiotics by type of diseases in different geographical areas. A farm study in Denmark, showed herds received more frequent use of antibiotics for gastrointestinal infections (74–83% of total indication in weaners and 56–65% in finishers), 9–24% for respiratory indication, and 15–30% for treatment of locomotor and central nervous systems conditions, skin and urinary tract infections (Jensen et al., 2012). The farm study in Canada showed that 27% of antibiotic treatment reported by ten veterinarians was for multiple systems infection (Glass-kaastra et al., 2013). Base on 303 French pig veterinarians survey, 10% of antibiotics are used for treatment of diseases and conditions such as cough, porcine proliferative enteropathy and post-weaning *Escherichia coli* (Chauvin et al., 2002).

In all age-groups, the most commonly-used antibiotic classes for the treatment of gastrointestinal infections were tetracyclines, lincosamides, Pleuromutilins (Jensen et al., 2012) and Macrolides (Jensen et al., 2012; Trauffler et al., 2014), while the most common use for the treatment of respiratory infections were chlortetracycline, tetracycline and amoxicillin (Van Rennings et al., 2015). Considering the phase of pig, the most commonly used was colistin in piglets and weaners, and tylosin in fatteners for gastrointestinal conditions (Van Rennings et al., 2015). Pleuromutilins were commonly used for respiratory tract infections in sow and piglets (Jensen et al., 2012). Use of antibiotics for gastrointestinal infection in breeding farms was also common (Trauffler et al., 2014).

3.3.2.6. Farm characteristic and management. Six studies reported a relationship between antibiotic use and type of farm. Overall, finisher farms were more likely to use antibiotics than farrow-to-finish farms (84–94% versus 43%–92% respectively) (Merle et al., 2012), (90% versus 54.3% respectively) (Moreno, 2012). (van der Fels-Klerx, Puister-Jansen, van Asselt, & Burgers, 2011). Sow farms used fewer antibiotics than farrow-to-finish farms (van der Fels-Klerx et al., 2011). Moreover, finisher farms had the highest use (14.91%) of the highest priority and critically important antimicrobials, while it was 7.83% in breeding farms and 12.54% in farrow-to-finish farms (Trauffler et al., 2014). In finishing farms, fattening units were more likely to use a routine antimicrobial prophylaxis than farrow-to-finish farms (OR = 11.7, 95CI: 4.1 – 33.3) and use antibiotics for growth promotion (OR = 2.8, 11.7, 95CI:1.2 – 6.9) (Casal et al., 2007); about a half (46%) and one third (30%) of antibiotics were applied for metaphylatic and prophylactic purposes in farrow-to-finish and fattening farms (Trauffler et al., 2014).

Table 2
Number of studies reporting data sources of active by geographical areas.

	Europe (27)	North America (4)	Asia (3)	Africa (1)	Australia (1)
Farm based survey (14)	11 (Callens et al., 2012; Casal et al., 2007; Dupont et al., 2017; Jensen, Jorsal, & Toft, 2017; Moreno, 2012; Sjölund et al., 2016, 2015; Stevens et al., 2007; Timmerman et al., 2006; Visschers et al., 2014, 2015)	1 (Rajić et al., 2006)	1 (Kim et al., 2013)	1 (Eltayb et al., 2012)	–
National database (consumption/sale/ prescription) (7)	5 (Aarestrup, Vibeke, Jacobsen, & Wegener, 2010; Bondt et al., 2013; Bos et al., 2013; Jensen et al., 2012; Vieira et al., 2011) (Bondt et al., 2013; Bos et al., 2013; de Jong et al., 2014; Jensen et al., 2012)	1 (Apley et al., 2012)	1 (Hosoi et al., 2014)	–	–
Farm based survey and prescription data (5)	4 (Merle et al., 2012, 2013, 2014; Van Rennings et al., 2015)	–	–	–	1 (Jordan et al., 2009)
Prescription data (3)	2 (Arnold et al., 2004; Fertner et al., 2015)	1 (Glass-kaastra et al., 2013)	–	–	–
Antibiotic application records (3)	3 (Trauffler et al., 2014; Trauffler et al., 2014; van der Fels-Klerx et al., 2011)	–	–	–	–
Veterinarian survey (2)	1 (Chauvin et al., 2002)	1 (Rosengren et al., 2008)	–	–	–
Pharmaceutical producer survey (1)	–	–	1 (Van Cuong et al., 2016)	–	–
Farm based survey and national data (1)	1 (Filippitzi et al., 2014)	–	–	–	–

Table 3
Number of studies reporting use of antibiotic class and active ingredient, by phase of pig production.

Antibiotic class and active ingredient	Total studies (N)	Phase of pig production Breeders	Sucking piglet	Weaner	Fattener/finisher
Penicillins	2 (Jensen et al., 2012; Rajić et al., 2006)	2 (Jensen et al., 2012; Rajić et al., 2006)	–	2 (Jensen et al., 2012; Rajić et al., 2006)	2 (Jensen et al., 2012; Rajić et al., 2006)
– Benzylpenicillins	2 (Sjölund et al., 2015, 2016)	1 (Sjölund et al., 2016)	2 (Sjölund et al., 2015, 2016)	1 (Sjölund et al., 2016)	1 (Sjölund et al., 2016)
– Aminopenicillin	5 (Dupont et al., 2017; Jensen et al., 2012; Sjölund et al., 2015, 2016; Van Rennings et al., 2015)	5 (Dupont et al., 2017; Jensen et al., 2012; Sjölund et al., 2015, 2016; Van Rennings et al., 2015)	4 (Dupont et al., 2017; Sjölund et al., 2015, 2016; Van Rennings et al., 2015)	5 (Jensen et al., 2012, 2017, Sjölund et al., 2015, 2016; Van Rennings et al., 2015)	4 (Jensen et al., 2012; Sjölund et al., 2015, 2016; Van Rennings et al., 2015)
–Procaine penicillin (&dihydrostreptomycin)	2 (Dupont et al., 2017; Sjölund et al., 2015)	2 (Dupont et al., 2017; Sjölund et al., 2015)	2 (Dupont et al., 2017; Sjölund et al., 2015)	1 (Sjölund et al., 2015)	2 (Dupont et al., 2017; Sjölund et al., 2015)
–Amoxicillin-clavalunic acid	1 (Jensen et al., 2017)	–	–	1 (Jensen et al., 2017)	–
Tetracyclines	5 (Jensen et al., 2017, 2012; Sjölund et al., 2016; Van Rennings et al., 2015; Merle et al., 2012)	4 (Jensen et al., 2012; Merle et al., 2012; Sjölund et al., 2016; Van Rennings et al., 2015)	3 (Merle et al., 2014; Sjölund et al., 2016; Van Rennings et al., 2015)	4 (Jensen et al., 2012, 2017; Sjölund et al., 2016; Van Rennings et al., 2015)	4 (Jensen et al., 2012; Merle et al., 2014; Sjölund et al., 2016; Van Rennings et al., 2015)
–Doxycycline	2 (Dupont et al., 2017; Sjölund et al., 2015)	–	–	1 (Dupont et al., 2017)	2 (Dupont et al., 2017; Sjölund et al., 2015)
–Chlortetracycline	4 (Apley et al., 2012; Dupont et al., 2017; Rajić et al., 2006; Van Rennings et al., 2015)	2 (Rajić et al., 2006; Van Rennings et al., 2015)	1 (Van Rennings et al., 2015)	4 (Apley et al., 2012; Dupont et al., 2017; Rajić et al., 2006; Van Rennings et al., 2015)	3 (Apley et al., 2012; Rajić et al., 2006; Van Rennings et al., 2015)
–Oxytetracycline	3 (Apley et al., 2012; Rajić et al., 2006; Sjölund et al., 2015)	2 (Rajić et al., 2006; Sjölund et al., 2015)	1 (Sjölund et al., 2015)	3 (Apley et al., 2012; Rajić et al., 2006; Sjölund et al., 2015)	3 (Apley et al., 2012; Rajić et al., 2006; Sjölund et al., 2015)
Sulphonamides	1 (Merle et al., 2014)	1 (Merle et al., 2014)	1 (Merle et al., 2014)		1 (Merle et al., 2014)
–Trimethoprim–sulphonamides	5 (Dupont et al., 2017; Jensen et al., 2017, 2012; Sjölund et al., 2015, 2016)	4 (Dupont et al., 2017; Jensen et al., 2012; Sjölund et al., 2015, 2016)	3 (Dupont et al., 2017; Sjölund et al., 2015, 2016)	4 (Jensen et al., 2012, 2017, Sjölund et al., 2015, 2016)	3 (Jensen et al., 2012; Sjölund et al., 2015, 2016)
–Sulfadiazine	1 (Van Rennings et al., 2015)	1 (Van Rennings et al., 2015)	1 (Van Rennings et al., 2015)	1 (Van Rennings et al., 2015)	1 (Van Rennings et al., 2015)
Macrolides	4 (Jensen et al., 2012; Merle et al., 2014; Sjölund et al., 2015, 2016)	4 (Jensen et al., 2012; Merle et al., 2014; Sjölund et al., 2015, 2016)	3 (Merle et al., 2014; Sjölund et al., 2015, 2016)	3 (Jensen et al., 2012; Sjölund et al., 2015, 2016)	4 (Jensen et al., 2012; Merle et al., 2014; Sjölund et al., 2015, 2016)
–Tylosin	5 (Apley et al., 2012; Dupont et al., 2017; Rajić et al., 2006; Sjölund et al., 2015; Van Rennings et al., 2015)	2 (Rajić et al., 2006; Van Rennings et al., 2015)	1 (Van Rennings et al., 2015)	5 (Apley et al., 2012; Dupont et al., 2017; Rajić et al., 2006; Sjölund et al., 2015; Van Rennings et al., 2015)	5 (Apley et al., 2012; Dupont et al., 2017; Rajić et al., 2006; Sjölund et al., 2015; Van Rennings et al., 2015)
–Tilmicosin	2 (Apley et al., 2012; Rajić et al., 2006)	–	–	1 (Apley et al., 2012)	2 (Apley et al., 2012; Rajić et al., 2006)
Pleuromutilins	2 (Merle et al., 2014; Sjölund et al., 2016)	2 (Merle et al., 2014; Sjölund et al., 2016)	2 (Merle et al., 2014; Sjölund et al., 2016)	1 (Sjölund et al., 2016)	2 (Merle et al., 2014; Sjölund et al., 2016)
–Tiamulin	4(Apley et al., 2012; Dupont et al., 2017; Rajić et al., 2006; Sjölund et al., 2015)	1 (Dupont et al., 2017)	1 (Dupont et al., 2017)	3 (Apley et al., 2012; Dupont et al., 2017; Sjölund et al., 2015)	4 (Apley et al., 2012; Dupont et al., 2017; Rajić et al., 2006; Sjölund et al., 2015)
Lincosamides					
–Lincosamides	4 (Apley et al., 2012; Merle et al., 2014; Rajić et al., 2006; Sjölund et al., 2016)	1 (Merle et al., 2014; Rajić et al., 2006; Sjölund et al., 2016)	2 (Merle et al., 2014; Sjölund et al., 2016)	4 (Apley et al., 2012; Jensen et al., 2017; Rajić et al., 2006; Sjölund et al., 2016)	4 (Apley et al., 2012; Merle et al., 2014; Rajić et al., 2006; Sjölund et al., 2016)
–Lincosamides and spectinomycin	3 (Jensen et al., 2012; Rajić et al., 2006; Sjölund et al., 2016)	3 (Jensen et al., 2012; Rajić et al., 2006; Sjölund et al., 2016)	1 (Sjölund et al., 2016)	3 (Jensen et al., 2012; Rajić et al., 2006; Sjölund et al., 2016)	3 (Jensen et al., 2012; Rajić et al., 2006; Sjölund et al., 2016)
Polymyxin					
Colistin	5 (Jensen et al., 2012, 2017, Sjölund et al., 2015, 2016; Van Rennings et al., 2015)	3 (Jensen et al., 2012; Sjölund et al., 2016; Van Rennings et al., 2015)	3 (Sjölund et al., 2015, 2016; Van Rennings et al., 2015)	5 (Jensen et al., 2012, 2017, Sjölund et al., 2015, 2016; Van Rennings et al., 2015)	3 (Jensen et al., 2012; Sjölund et al., 2016; Van Rennings et al., 2015)
Aminoglycosides	4 (Jensen et al., 2012; Merle et al., 2014; Sjölund et al., 2016)	3 (Jensen et al., 2012; Merle et al., 2014; Sjölund et al., 2016)	2 (Merle et al., 2014; Sjölund et al., 2016)	3 (Jensen et al., 2012, 2017; Sjölund et al., 2016)	4 (Jensen et al., 2012; Merle et al., 2014; Sjölund et al., 2016)
Amphenicols	2 (Jensen et al., 2012; Sjölund et al., 2016)	2 (Jensen et al., 2012; Sjölund et al., 2016)	1 (Sjölund et al., 2016)	2 (Jensen et al., 2012; Sjölund et al., 2016)	2 (Jensen et al., 2012; Sjölund et al., 2016)

(*continued on next page*)

Table 3 (*continued*)

Antibiotic class and active ingredient	Total studies (N)	Phase of pig production Breeders	Sucking piglet	Weaner	Fattener/finisher
Cephalosporins	2 (Jensen et al., 2012; Merle et al., 2014)	2 (Jensen et al., 2012; Merle et al., 2014)	1 (Merle et al., 2014)	1 (Jensen et al., 2012)	2 (Jensen et al., 2012; Merle et al., 2014)
–3rd & 4th generation cephalosporins	1 (Sjölund et al., 2016)	1 (Sjölund et al., 2016)	1 (Sjölund et al., 2016)	1 (Sjölund et al., 2016)	1 (Sjölund et al., 2016)
Fluoroquinolones	3 (Jensen et al., 2012; Merle et al., 2014; Sjölund et al., 2016)	3 (Jensen et al., 2012; Merle et al., 2014; Sjölund et al., 2016)	2 (Merle et al., 2014; Sjölund et al., 2016)	2 (Jensen et al., 2012; Sjölund et al., 2016)	3 (Jensen et al., 2012; Merle et al., 2014; Sjölund et al., 2016)
–Enrofloxacin	1 (Sjölund et al., 2015)	1 (Sjölund et al., 2015)	1 (Sjölund et al., 2015)	1 (Sjölund et al., 2015)	1 (Sjölund et al., 2015)

Pig density had a positive association with the use of antibiotics (Bos et al., 2013; Stevens et al., 2007). The number of sows presented on the farm has a positive correlation with the amount of antibiotic use (van der Fels-Klerx et al., 2011). Different findings in few studies showed that small herd size had significantly higher antibiotic use than moderate and large herd size (Vieira et al., 2011); and the number of pigs in farms had no association with the use of antibiotics (Casal et al., 2007) and the use of growth promoters (Stevens et al., 2007). One study reported that industrial production system had higher antibiotic use than a semi-industrial production system and small farm holders (Kim et al., 2013).

There was only one study that documented the association between vaccination and antibiotic use. The vaccination of suckling piglets and weaners was significantly associated with the greater use of in-feed antibiotics (Stevens et al., 2007). In terms of farm management, one study found that weaner production in indoor pig farming systems had higher use of antibiotics in medicated feed (64–74%) than the outdoor farming (60%); it is noted that UK is the only country that raise commercial sow outdoor(Stevens et al., 2007). One study showed that improved farm sanitation and management contributes to a reduction in antibiotic consumption without productivity losses (Fertner et al., 2015); however, another study reported that the use of antibiotics had no association with farm management (Casal et al., 2007).

3.3.2.7. Other factors. Other factors also contribute to the use of antibiotics. The volume of tetracycline used in the spring was five-fold higher than other seasons (Van Rennings et al., 2015). In the study from the UK, there was a large variations of in-feed antibiotics in weaners and growers, and in individual weaners in different pork quality assurance schemes (Stevens et al., 2007). In term of farm location, farms located in high pig-density areas have a positive correlation with the amount of antibiotic use (van der Fels-Klerx et al., 2011).

Only one study examined the educational status of farmers, and there was a significant association between low education and poor knowledge on antibiotic use (Eltayb, Barakat, Marrone, Shaddad, & Sta, 2012). Farmers perceived that use of antibiotic contributes to their profitability from raising pigs (Stevens et al., 2007).

4. Discussion

Understanding the current pattern of antibiotic use in livestock is important in order to support optimal antibiotic use, which may potentially slow down the emergence of AMR in animal production. Studies on antibiotic use have increased considerably over the last decade, and in this review, the majority of studies were conducted between 2010 and 2017. Most of the studies were conducted in Europe, particularly in high-income countries (HICs) where there are higher research capacities and data availability. Due to the population size, demand for animal-source food is higher among low- and middle-income countries (LMICs) than in HICs (Robinson & Pozzi, 2011). More evidence on consumption of antibiotics in LMICs is required for proper and timely responses to AMR such as optimizing consumptions and uses of antibiotics.

4.1. Pattern of antibiotic use

Common classes of antibiotics used varied across countries. Overall, Penicillins and Tetracyclines class were the most commonly used antibiotic in pigs. These findings were similar to another review which reported Penicillins, Tetracyclines and Macrolides were the most common use in pig production (Cuong, Padungtod, Thwaites, & Carrique-Mas, 2018). This was probably because they are relatively cheap and cost-effective compared to other antibiotics ("OIE LIST OF ANTIMICROBIALS OF VETERINARY IMPORTANCE Criteria used for categorisation List of antimicrobials," 2007). Penicillins have bactericidal actions against Gram-negative and Gram-positive pathogens (Lobanovska & Pilla, 2017). They were commonly used for prophylaxis and treatment of septicaemia, respiratory and urinary tract infections in a broad range of animal species. Tetracyclines were widely used for the treatment of respiratory diseases caused by *Actinobacillus pleuropneumonia* and *Pasteurella multocida*; however, resistance to tetracyclines is common. For example, 22% of *Pasteurella multocida*, 15% of *Actinobacillus pleuropneumoniae* and 82% of *Streptococcus suis* were reported to be resistant to tetracyclines (de Jong et al., 2014).

This review confirms that antibiotics of veterinary importance defined in the highest priority critically important antimicrobials in human in WHO's list (World Health Organization, 2017), were still commonly used in swine production.

The use of antibiotics without definitive diagnosis and proper indications has raised global concern, especially with the emergence of AMR in the agricultural sector. The first attempt to withdraw non-therapeutic antibiotics was in the UK in 1969 when the Swann Joint Committee suggested restricting the use of medicated feed at a sub-therapeutic level in livestock (Swann, Baxter, & Field, 1969). Many countries have banned antibiotic use for growth promotion. However, this review shows that the use of antibiotics for infection prevention is still globally common in pig production, in order to prevent production loss in particular in intensive industrial farming. The standard prophylactic protocol for the whole herd can be more convenient to administer and less labour-intensive to manage than treatment of individual sick animals.

4.2. Antibiotics choice and route of administration associated with specific diseases and age groups

Choices of antibiotics were driven by age-specific diseases and the common pathogens for these conditions. Gastrointestinal and respiratory tract infections are common in pigs at all stages and are easily transmitted within and between herds. However, some specific diseases are more common in weaners such as septicaemia caused by *Actinobacillus suis* and Mycoplasma infection than others. In finishers, diarrhoea, porcine haemorrhagic enteropathy (*Lawsonia intracellulalis*) and swine dysentery (*Bachyspira hyodysentary*) are common pathogens causing gastrointestinal infection, whereas enzootic pneumonia (*Mycoplama hyopnuemoniae*), mycoplasma induced respiratory disease (*Pasturella multocida*), pleuropnuemonia (*Actinobacillus pleuropnueumoniae*) are common pathogens causing respiratory infection (Burch, 2013). Type of bacteria in animal are drivers for type of antibiotic use (Jordan et al., 2009).

Colistin was most commonly used for gastrointestinal conditions in piglets and weaners, tylosin in fatteners and sows (Van Rennings et al., 2015). Farmers used Pleuromutilins for respiratory tract infections in sow and piglets (Jensen et al., 2012) and beta-lactam antibiotics in piglets, weaners and fattening pigs (Van Rennings et al., 2015). However, the choice of antibiotics depends on market availability and cost in different countries. For example, while the most common respiratory pathogens in Danish swine production, *Actinobacillus pleuropneumoniae, Pasturella multocida*, and *Streptococcus suis* infections are fully susceptible to penicillin (Aarestrup, Oliver Duran, & Burch, 2008), penicillin only constitutes a minor share of the prescriptions for respiratory disease, whereas Tetracyclines and Pleuromutilins are widely used. Possibly they have relatively lower costs; aminopenicillins are more expensive and parenteral use of benzylpenicillins is less convenient in administration (Jensen et al., 2012).

Choices of antibiotic are also guided by route of administration. Oral application is a major route in weaners and fatteners, whereas parenteral is applied more in sows than piglets and fatteners, such as through the use of benzylpenicillin (Merle et al., 2014). In finishers, however, parenteral benzylpenicillins are applied to individual treatment of sick pigs, although other drugs such as tylosin and lincomycin are mainly administered through feed (Rajić et al., 2006; Rosengren et al., 2008).

4.3. The use of antibiotic associated with farm management

Farm management can be associated with antibiotic use, such as the type of farm, size of farm and vaccination status. This review shows that finisher farms used higher volumes of antibiotics than farrow-to-finish farms (24,30), in particular for metaphylactic and prophylactic measures, and growth promotion (Casal et al., 2007; Trauffler et al., 2014).

Large farms were more likely to use medicated feeds compared to smaller-sized farms (Bos et al., 2013; Kim et al., 2013; Stevens et al., 2007; van der Fels-Klerx et al., 2011). One possible explanation of the high use of antibiotics is that larger-sized farms have a greater risk of transmission of pathogens within herds than smaller farms, although this review is inconclusive as contradictory findings were reported (Vieira et al., 2011). However, there are multiple factors which influence the use of antibiotics, such as farm biosecurity practices, density, level of stress in the herd, vaccination status, quality of feed, farmer knowledge and disease prevalence rates. Good farm biosecurity such as all-in all-out production and a single supplier of weaners has been identified as common practice in herds which lead to a reduction in disease transmissions and lower antibiotic use (Fertner et al., 2015) . Vaccination has been recommended as an alternative strategy to prevent disease contributing to optimizing antibiotic usage (Postma et al., 2015). It has shown beneficial return of investment despite the costs for vaccines (Alarcon, Rushton, Nathues, & Wieland, 2013). However, the higher use of in-feed antibiotics was significantly associated with the vaccination of pigs in some age groups including suckling piglets, weaners and sows (Stevens et al., 2007). This finding can be confounded by other factors such as poor bio-security and farm management, low health status of the herd and high disease prevalence.

4.4. The use of antibiotic associated with other factors

The use of antibiotics was highly dependent on the farm management and person in charge of the daily routines. The initiation of treatment depended on the ability of early detection of diseased animals and the level of farmers' perceptions and responses to the clinical signs in animals (Fertner et al., 2015). Farmers were likely to have a limited understanding of antibiotics, particularly those in low- and middle-income countries. One study in Cambodia indicated that none of the farmers demonstrated an understanding about the action and indication for antibiotics (Om & Mclaws, 2016). A study in Sudan found a significant association between farmers' low education level and poor knowledge on antibiotic use and AMR awareness (Eltayb et al., 2012). All these challenges can lead to inappropriate use of antibiotics.

Veterinarians play important roles in animal health and antibiotic stewardship; and often farmers rely on veterinarian's advice on pig health, choices and use of antibiotics (Visschers et al., 2015). Despite their critical role, veterinarians' prescription decisions are based on "expert opinion" or views from "opinion leaders" or from internet sources, rather than scientific and peer-reviewed data (Vandeweerd et al., 2012) or laboratory resistant profiles. Representatives from pharmaceutical companies, when serving as advisors to farmers on disease management, may have conflict of interests to offer their products. In Belgium, on average, 43% of the income among pig veterinarians came from selling pharmaceutical products (Maes et al., 2010) for which prudent use of antibiotics can be at risk due to potential conflict of interests.

The prevalence of pathogens in pigs and levels of resistance and susceptibility to different antibiotics is an important evidence to guide antibiotic selection and support prudent use. Despite critical contributions, nearly half of all veterinarians in a study in 25 European countries (44.3%) seldom collect a sample for bacterial identification and drug sensitivity tests in laboratory (De Briyne, Atkinson, Pokludová, Borriello, & Price, 2013). In addition, law and enforcement and availability of antibiotics influences the use of antibiotics. Sweden and Denmark's law restricts the use of fluoroquinolones and third and fourth generation Cephalosporins in pigs (*Guidelines for the prudent use of antimicrobials in veterinary medicine. Practical examples.*, 2015).

4.5. Limitations of the review

There are a number of limitations which need to be considered in interpreting the findings from this review. This review covers 36 studies published in English; where studies in non-English speaking countries may offer different or similar findings. More than 85% of the studies reviewed were conducted of in Europe and North America, limiting the relevance of the findings to LMIC. Diversity in study design is a major challenge for an in-depth comparative analysis and synthesis; a few studies could be considered nationally representative, while others were small scale studies. These challenges require careful interpretation. Different data collection methods including face-to-face interviews with farmers, internet-based surveys, and mail surveys to pig farmers or veterinarians may affect the validity of the findings. Use of antibiotics based on survey questionnaires cannot detect the misuse and off-label use, where other approaches are needed such as prescription reviews. As noted in our recent review there is also huge variability in how studies have measured the quantity of antibiotic use making it very difficult to make any comparisons. Some studies measure the use of antibiotics as a percentage of total use, while other studies calculated in specific units such as animal daily dose. Some studies reported the use by class of antibiotic, while other studies reported active ingredient of antibiotic (Lekagul, Tangcharoensathien, & Yeung, 2018). The EU is developing a standard unit for antibiotic measurement, called defined daily dose for animal (DDDvets) of active ingredient which take into account differences in dosing, pharmaceutical forms and routes of administration used (European Medicines Agency, 2015).

5. Conflict of interest statement

The authors declare that they have no financial and personal relationships with other people or organisations that could inappropriately have influenced the present study and manuscript.

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Supplementary materials

Supplementary material associated with this article can be found, in the online version, at doi:10.1016/j.vas.2019.100058.

Appendix A

I. Search Strategy

Structured Database Search (Search terms and results)

○ MEDLINE: *N* = 703 articles

- (Antibiotic.mp. or exp Anti-Bacterial Agents) (704,921)
- (Antimicrobial agents.mp. or Anti-Infective Agents) (61,091)
- (livestock or swine or pig* or farrow or weaner or sow).mp. [mp = title, abstract, original title, name of substance word, subject heading word, keyword heading word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier, synonyms] (519,570)
- (Use* or usage or consume or consumption or practiceor or administration or oral or feed or injection).mp. [mp = title, abstract, original title, name of substance word, subject heading word, keyword heading word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier, synonyms] (6635,975)

○ Scopus: *N* = 808 articles

(TITLE-ABS-KEY (antibiotic OR antimicrobial OR antibacterial) AND TITLE-ABS-KEY (livestock OR swine OR pig* OR farrow OR weaner OR finisher OR sow) AND TITLE-ABS-KEY (use OR utilisation OR consum* OR practice OR administration)) AND (LIMIT-TO (PUBYEAR, 2017) OR LIMIT-TO (PUBYEAR, 2016) OR LIMIT-TO (PUBYEAR, 2015) OR LIMIT-TO (PUBYEAR, 2014) OR LIMIT-TO (PUBYEAR, 2013) OR LIMIT-TO (PUBYEAR, 2012) OR LIMIT-TO (PUBYEAR, 2011) OR LIMIT-TO (PUBYEAR, 2010) OR LIMIT-TO (PUBYEAR, 2009) OR LIMIT-TO (PUBYEAR, 2008) OR LIMIT-TO (PUBYEAR, 2007) OR LIMIT-TO (PUBYEAR, 2006) OR LIMIT-TO (PUBYEAR, 2005) OR LIMIT-TO (PUBYEAR, 2004) OR LIMIT-TO (PUBYEAR, 2003) OR LIMIT-TO (PUBYEAR, 2002) OR LIMIT-TO (PUBYEAR, 2001) OR LIMIT-TO (PUBYEAR, 2000)) AND (LIMIT-TO (DOCTYPE, "ar") OR LIMIT-TO (DOCTYPE, "sh")) AND (LIMIT-TO (SUBJAREA, "AGRI") OR LIMIT-TO (SUBJAREA, "VETE")) AND (LIMIT-TO (LANGUAGE, "English")) AND (LIMIT-TO (SRCTYPE, "j"))

○ Web of Science: *N = 1070 articles*

TOPIC: (antibiotic or antimicrobial or antibacterial) AND TOPIC: (livestock or swine or pig or farrow or weaner or finisher or sow) AND TOPIC: (use or utilisation or consum* or practice or administration)

Refined by: PUBLICATION YEARS: (2016 OR 2006 OR 2015 OR 2005 OR 2014 OR 2004 OR 2012 OR 2002 OR 2013 OR 2003 OR 2017 OR 2000 OR 2011 OR 2001 OR 2009 OR 2010 OR 2007 OR 2008) AND WEB OF SCIENCE CATEGORIES: (VETERINARY SCIENCES) AND DOCUMENT TYPES: (ARTICLE)

Indexes = SCI-EXPANDED, SSCI, A&HCI, CPCI-S, CPCI-SSH, ESCI Timespan = 1970–2018

Table A.1
Search terminology to be used in literature review.

	Search term
I	Antimicrobial (Free text) OR antimicrobial (MeSH term) OR antibacterial (Free text) OR antibacterial (MeSH term) OR antibiotic (Free text) OR antibiotic (MeSH term)
II	Livestock (Free text) OR swine (Free text) OR pig* (Free text) OR farrow (Free text) OR weaner (Free text) OR finisher (Free text) OR sow (Free text)
III	Use (Free text) OR utilisation (Free text) OR consum* (Free text) OR practice (Free text) OR administration (Free text)

Appendix B

.

Table B.1
Quality assessment of included studies.

Author, year	Q1	Method					Result			Application		Rank*
		Q2	Q3	Q4	Q5	Q6	Q7	Q8	Q9	Q10	Q11	
2017												
Dupont et al. (2017)	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	H
Jensen, Jorsal, and Toft (2017)	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	H
2016												
Van Cuong et al. (2016)	Y	Y	N	N	Y	Y	Y	Y	Y	Y	Y	H
Sjölund et al. (2016)	Y	Y	N	N	Y	Y	Y	Y	Y	Y	Y	H
2015												
Fertner et al. (2015)	Y	CT	N	N	Y	N	Y	Y	Y	Y	Y	M
Van Rennings et al. (2015)	Y	Y	Y	N	Y	Y	Y	Y	Y	Y	Y	H
Visschers et al. (2015)	Y	Y	N	N	Y	Y	Y	Y	Y	Y	Y	H
(Sjölund et al.(2015)	Y	Y	Y	N	Y	Y	Y	Y	Y	Y	Y	H
2014												
Filippitzi et al. (2014)	Y	Y	CT	N	CT	CT	Y	Y	Y	Y	Y	M
Hosoi et al. (2014)	Y	Y	CT	N	N	N	Y	N	Y	Y	Y	M
Merle et al. (2014)	Y	Y	N	N	Y	N	Y	Y	Y	Y	Y	M
Trauffler et al. (2014)	Y	Y	N	N	Y	N	Y	Y	Y	Y	Y	M
Trauffler et al. (2014)	Y	Y	N	N	Y	N	Y	Y	Y	Y	Y	M
Visschers et al. (2014)	Y	Y	CT	Y	Y	Y	Y	Y	Y	Y	Y	H
2013												
Bondt et al. (2013)	Y	Y	Y	CT	CT	Y	Y	Y	Y	Y	Y	H
Bos et al. (2013)	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	H
Glass-kaastra et al. (2013)	Y	Y	N	N	Y	CT	Y	Y	Y	Y	Y	M
Kim et al. (2013)	Y	Y	N	N	Y	CT	Y	Y	Y	Y	Y	M
Merle, et al. (Merle et al., 2013)	Y	Y	N	N	Y	N	Y	Y	Y	Y	Y	M
2012												
Apley et al. (2012)	Y	Y	Y	N	Y	Y	Y	N	Y	Y	Y	H
Callens et al. (2012)	Y	Y	Y	N	Y	Y	Y	Y	Y	Y	Y	H
Eltayb et al. (2012)	Y	Y	CT	N	Y	CT	Y	N	Y	Y	Y	M
Merle et al. (2012)	Y	Y	N	N	Y	N	Y	Y	Y	Y	Y	M
Moreno (2012)	Y	Y	Y	N	Y	Y	Y	Y	Y	Y	Y	H
2011												
JJensen et al. (2012)	Y	Y	N	N	Y	Y	Y	Y	Y	Y	Y	H
van der Fels-Klerx et al. (2011)	Y	Y	Y	N	Y	Y	N	Y	N	Y	Y	M
Vieira et al. (2011)	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	H
Aarestrup, Vibeke, Jacobsen, and Wegener (2010)	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	H
2009												
Jordan et al. (2009)	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	H
2008												
Rosengren et al. (2008)	Y	CT	N	N	Y	N	Y	Y	Y	Y	Y	M
2007												
Casal et al. (2007)	Y	Y	N	N	Y	Y	Y	Y	Y	Y	Y	M
Stevens et al. (2007)	Y	Y	N	N	Y	N	Y	Y	Y	Y	Y	M
2006												
Rajić et al. (2006)	Y	Y	N	N	Y	Y	Y	Y	Y	Y	Y	M
Timmerman et al. (2006)	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	H
2004												
Arnold et al. (2004)	Y	Y	Y	N	Y	Y	Y	Y	Y	Y	Y	H
2002												
Chauvin et al. (2002)	Y	Y	Y	N	Y	Y	Y	Y	Y	Y	Y	H

Note:
Q1 = Did the study address a clearly focused issue?
Q2 = Did the authors use an appropriate method to answer their question?
Q3 = Were the subjects recruited in an acceptable way?
Q4 = Were the measures accurately measured to reduce bias?
Q5 = Were the data collected in a way that addressed the research issue?
Q6 = Did the study have enough participants to minimize the play of chance?
Q7 = How are the results presented and what is the main result?
Q8 = Was the data analysis sufficiently rigorous?
Q9 = Is there a clear statement of findings?
Q10 = Can the results be applied to the local population?
Q11 = How valuable is the research?
Y = Yes (clearly described)
N = No (Not described)
CT = Cannot tell (described but with limited detail

* Score >75 = high (H), 50–74 = medium (M) and <50 = low (L) *score >75 = high (H), 50–74 = medium (M) and <50 = low (L).

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4.1.2 The use of antimicrobials in global pig production: A systematic review of methods for quantification

The measurement of antibiotic consumption varies widely in terms of types of data, methods, and units of measurement. The systematic review aims to describe and compare the methods and measurements that have been used to quantify antibiotic use in pigs. Having standardised measurements of antibiotic consumption will help to monitor the impact of interventions aimed at reducing the amount of antibiotic use in livestock. The findings of the review were also used to inform the approach I used to collecting data on antibiotic use in pig production in Thailand.

(Cover sheet on next page)

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Student	Angkana Lekagul
Principal Supervisor	Professor Shunmay Yeung
Thesis Title	Understanding the use of antibiotics in pig production in Thailand

If the Research Paper has previously been published please complete Section B, if not please move to Section C

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The use of antimicrobials in global pig production: A systematic review of methods for quantification

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A B S T R A C T

Background: Overuse of antimicrobials in both humans and animals is recognized as one of the main drivers of Antimicrobial Resistance (AMR); and the optimisation of their use has been advocated as a key strategy for dealing with AMR. The measurement of antimicrobial use is vital for the design, monitoring and evaluation of such strategies. This systematic review describes and compares methods and measurements used to quantify antimicrobial use in pigs in order to inform efforts to standardize measurement.

Methods: The peer-reviewed literature was systematically searched using four online databases: MEDLINE, ScienceDirect, Scopus and Web of Science. Eligibility criteria for inclusion in the review included: articles published in English, involving pigs of any age and types of production, providing quantitative data on antimicrobial use, containing a clear description of the methodology, and having moderate to high rank in the quality assessment.

Results: Of 2,362 abstracts reviewed, a total of 25 studies were included based on the eligibility criteria. All studies were published between 2001 and 2017. Twenty of the studies were conducted in eight European countries. Twelve studies estimated antimicrobial use and eight studies were primarily methodological papers comparing different methods or variables, or developing new methods. The two main sources of antimicrobial use data were farm surveys and national sales data.

A large variety of units of measurement was found. In this review, the ten measurements identified were categorized into four groups: 1) antimicrobials use measured by milligrams of active substance per animal weight; 2) antimicrobials use measured by daily dose per weight at treatment; 3) antimicrobial use measured by daily dose per treatment period; and 4) antimicrobials use measured by daily dose per period at risk of treatment.

Conclusion: There is no global standardized measurement of antimicrobial use in pigs. Given the importance of monitoring the use antimicrobials, we recommend that at a minimum, all countries should develop macro-level monitoring using national sales data and report use by milligram of active ingredients per Population Correcting Unit. Monitoring in specific animal species requires the development of systems to capture prescription at national or farm level. Findings from monitoring antimicrobial use may help to guide effective interventions for optimising use of antimicrobials, as recommended by the WHO Global Action Plan on AMR.

1. Background

Antimicrobial Resistance (AMR) is an increasingly serious threat to global public health. Overuse of antimicrobials can accelerate the emergence of antimicrobial resistance (World Health Organization, 2015b). In livestock industries, large amounts of antimicrobials are used for both therapeutic and non-therapeutic purposes including growth promotion (Aarestrup, 2005). In response to global concerns

Abbreviations: ADD, animal daily dose; ADDD, animal defined daily dose; AMR, antimicrobial resistance; CASP, critical appraisal skills programme; DADD, defined animal daily dosage; DDD, defined daily dose; DDDA, daily doses animal; DDDvet, defined daily dose; DCDvet, defined course dose; DPD, daily product dose; EMA, european medicines agency; ESVAC, european surveillance of veterinary antimicrobial consumption; FAO, food and agriculture organization; nDDay, daily dose per animal year; OIE, organization for animal health; PCU, population correction unit; PDD, prescribed daily dose; PrDD, product-related daily doses; TI, treatment incidence; UDD, used daily dose; WHO, world health organisation

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about AMR, in 2008, the World Organization for Animal Health (OIE) launched guidelines on the prudent use of antimicrobials in veterinary medicines, which describes the respective responsibilities of relevant stakeholders such as veterinarians, regulators, pharmaceutical industries, animal producers and consumers (World Organisation for Animal Health (OIE), 2008).

Measuring antimicrobial use is critical to understanding the magnitude and profile of antimicrobial resistance in countries. Measurement is the first step to detecting whether there is excessive and inappropriate use and monitoring whether policies aimed at optimizing use are successful. Recognising this, international organizations such as FAO, OIE and WHO, have recommended that countries develop systems for monitoring antimicrobial consumption (World Health Organization, 2015a, OIE, 2016; FAO, 2016). The World Health Organization (WHO) guidelines defines antimicrobial "consumption" data captured from aggregate sales data such as form importer, local manufacturer or wholesales, whilst data on antimicrobial "use" are collected from patient-level data such as medical records and prescriptions (World Health Organization, 2017). Whilst there has been significant progress in the monitoring of antimicrobial use and consumption in the human health sector, action in the animal health sector has lagged behind (Schar et al., 2018). Some European countries established national programs for the surveillance of antimicrobial consumption in animals for more than 20 years ago, specifically DANMAP in Denmark in 1995 (Statens Serum Institut, 2012), MARAN in Netherlands in 1998 (Anonymous, 2012) and SWEDRES-SVARM (SWEDRES and SVARM, 2014). The European Medicines Agency established the European Surveillance of Veterinary Antimicrobial Consumption (ESVAC) project in 2009 (Agency, 2017). ESVAC compiles, verifies and reports on antimicrobial consumption of veterinary antimicrobial agents in 29 European countries. Data are collected through a network of national focal points. Furthermore, ESVAC has been striving to set up a standardised methodology to allow for cross country comparisons. The monitoring of antimicrobial consumption serves various objectives. It monitors time trends of antimicrobial use, compares use by different antimicrobial classes, identifies high users and promotes more prudent use, and studies the association between level of usage and bacterial resistance (Collineau et al., 2017).

Currently, there is a wide variation in the availability and type of data, methods and use measurement across countries. The lack of uniformity hampers cross-country comparisons (Collineau et al., 2017). In order to guide the strengthening of existing monitoring systems and the development of new ones to facilitate cross-country comparisons, it is essential to understand the different existing methods, their strengths, limitations and operational feasibility.

This systematic review will describe and compare methods and measurement to quantify antimicrobial use in pigs, in order to contribute to the process of future guideline development of monitoring the antimicrobial use.

2. Method

2.1. Scope of study and research question

The operational definitions of the terms used in this review are as follows.

Term	Definition
Antimicrobials	According to OIE definition, an antimicrobial is considered as a naturally occurring, semi-synthetic or synthetic substance that exhibits antimicrobial activity (it kills or inhibits the growth of micro-organisms) at concentrations attainable *in vivo*. Anti-helminthic and substances classed as disinfectants or antiseptics are excluded from this definition (World Organisation for Animal Health (OIE), 2015).
Pig	The term refers to all stages of swine production including breeding and gestation, farrowing (from birth to weaning), nursery and feeding and finishing.
Use and consumption	As explained above WHO defines "use" data as estimates derived from patient-level data. It may focus on how and why antimicrobials are being used by health care providers and patients. "Consumption" data are usually reported when information on antimicrobial use in patients is not available. It can be collected from several sources such as import data, wholesale data or aggregated health insurance data. Consumption data provides a proxy estimate of the use of antimicrobials (World Health Organization, 2017). However, in this study, for simplicity the term "use" is applied to refer to both use at farm level and consumption at aggregate national or sub-national level.
Biomass	The weight or total quantity of living organisms of one animal species or of all the species in the community. Using biomass for antimicrobial consumption aims to compare the weight of animals between different species and between human and animals.

This review covers use of antimicrobials in pigs, with the following research question: "What methods and measurements are used to quantify the use of antimicrobials?"

2.2. Search strategy

2.2.1. SPIDER tool

A "SPIDER" tool was applied in order to specifically identify relevant quantitative and mixed-method studies. It covers the Sample, Phenomenon of interest, Design, Evaluation and Research type) (Cooke et al., 2012).

S: 1) Surveys based on end-point antimicrobial usage: veterinary prescription, usage by pig farmer

2) Antimicrobial sales data (from pharmaceutical operators, such as importer,

manufacturer, wholesaler)

P and I: Antimicrobial use in pigs D: Observational studies, intervention studies

E: Methods used for the measurement of antimicrobial use R: Quantitative study

2.2.2. Eligibility assessment of studies and inclusion criteria

The following inclusion criteria were considered:

(i) the paper was published in, or translated into, the English language,
(ii) the study involved pigs of any age and type of production,
(iii) the study provided quantitative data on antimicrobial use with a focus or clear explanation of the methodology in pigs or other food producing animals including pigs,
(iv) The study had moderate to high ranking of a quality assessment.

2.2.3. Search protocol

Literature on the use of antimicrobials in pigs was systematically

Table 1
Search terminology to be used in literature review.

	Search term
I	antimicrobial (Free text) OR antimicrobial (MeSH term) OR antibacterial (Free text) OR antibacterial (MeSH term) OR antibiotic (Free text) OR antibiotic (MeSH term)
II	livestock (Free text) OR swine (Free text) OR pig* (Free text) OR farrow (Free text) OR weaner (Free text) OR finisher (Free text) OR sow (Free text)
III	use (Free text) OR utilisation (Free text) OR consum* (Free text) OR practice (Free text) OR administration (Free text)
IV	measure* (Free text) OR indicator (Free text) OR surveillance (Free text) OR survey (Free text) OR monitor (Free text)

reviewed between May to August 2017. Relevant scientific papers published in English peer-reviewed journal were identified using the keywords combinations in the title, abstract and content. All search terms were combined, see Table 1.

2.2.3.1. Structured Database Search. Online electronic databases were searched in English language literature with restriction of the date of publication being after 2000: MEDLINE (http://ovidsp.tx.ovid.com; 1946 until present), ScienceDirect (http://www.sciencedirect.com; 1996 until present), Scopus (http://www.scopus.com; 1823 until present) and Web of Science (http://apps.webofknowledge.com; 1970 until present). The initial scope of the search focused on low- and middle-income countries. Due to the limited number of publications, it was expanded to cover studies in high-income countries.

2.2.3.2. Grey literature. In addition to the structured database searches, articles were sourced through searches from the reference lists of key articles identified as in line with the research questions and inclusion criteria. This combination ensured that a wide range of articles from different sources was retrieved.

2.2.4. Screening relevant records

After the searches, the duplicate studies and inconsistencies between titles, abstracts and keywords were removed. Then, full texts were reviewed; those which were reviews, clinical research, pharmacokinetic, biopharmaceutical studies and laboratory studies were excluded.

Studies were excluded for the following reasons:

- No report on pattern or volume of antimicrobial use in pigs
- Inappropriate study design: such as review, clinical research, pharmacokinetic and biopharmaceutical studies
- Focus on laboratory study, on human health or antimicrobial activity, relationship with AMR, specific disease related to drug recommendation
- Measurements of antimicrobial levels in farm waste, faeces and environment, residue in animal products
- Low level of quality from assessment (< 50%)

2.3. Quality assessment

The methodological quality of the studies was assessed using an instrument adapted from the Critical Appraisal Skills Programme (CASP) (Critical Appraisal Skills Programme (CASP), 2014). The four criteria of quality assessment were a) aim, b) method, c) result and d) application. The answer to the four criteria are either ‘yes’, or ‘no’ or ‘cannot tell’. Each criterion has certain a number of sub-criteria, there were in total eleven sub-criteria for quality assessment; see Table A2 (annex). If the assessment by the two independent reviewers (AS and VT) was ‘no’ or ‘cannot tell’, the score for that question was zero; the score for yes was one. When there were conflicting views, the reviewers discussed and sought consensus. In this review, the studies were ranked by quality criteria. The quality ranking was classified into three groups: High meant > 75% of all eleven sub-criteria were met, moderate meats 50–75% were met, weak meant < 50% were met.

2.4. Data extraction and synthesis

The full text of all relevant articles was reviewed and summarised using a standardised data extraction table in Excel which supported the sifting, sorting and annotation of primary source materials and data. Data extraction was categorised by three sets of variables: a) context variables: author, year of publication, year of study, title, journal, geographical area, objective and b) methodology variables: type of study, data source, sampling technique, sample size, methods for antimicrobial use measurement. See Table A1 in annex for variables assessed in the study.

3. Results

3.1. Search processes

The search from the four database and hand search identified 2362 articles. After screening and removal of duplications, 90 manuscripts remained for further screening. Of these 90 manuscripts, 37 manuscripts were selected on the basis of the inclusion criteria. Of these 37 manuscripts, seven articles described antimicrobials without essential information on the pattern or volume of antimicrobials use; these were excluded. Two articles were not included, because they were review articles. Another three articles were excluded as they only focused on the association between specific groups of antimicrobial and AMR. No studies were excluded due to low rank of quality assessment (< 50%). In summary, a total of 12 studies were excluded from the set of 37 studies, leaving 25 manuscripts that met the inclusion criteria and were included in this systematic review. Fig. 1 describes flow of screening processes.

3.2. Description of the studies

Of the 25 studies, 22 studies were published between 2010 and 2016, with the remaining three being published between 2000 and 2010. One study analysed global level use data and the others reported data from 12 countries. Twenty studies were from eight European countries of which six were conducted in Denmark; two were multi-country studies; one study in Belgium, France, Germany and Sweden, and the other included Denmark and Netherlands. Two studies were conducted in African countries (South Africa and Kenya). Another two studies reported data from China and Japan. See Table 2 for characteristic of these studies.

The quality assessment is reported in Table A2 of the Annex. In general, the hypotheses and the objectives of the study were clearly described. Fifteen (60%) studies were ranked as high quality (meeting more than 75% of all eleven sub-criteria). Ten remaining studies were of moderate quality. None had low quality assessment.

3.3. Methods for measuring antimicrobial use

A large variation in terms of the methodological approaches and units of measurement of antimicrobial use was found.

3.3.1. Types of studies and data sources

As shown in Table 2, eight studies were primarily methodological, for example comparing antimicrobial use by using different methods or variables (Carmo et al., 2017; Dupont et al., 2016; Taverne et al., 2015; Trauffler et al., 2014a; Bondt et al., 2013; Timmerman et al., 2006) or developing new methodologies (Ferner et al., 2014; van Rennings et al., 2015). Twelve studies aimed to estimate antimicrobial use (Jensen et al., 2004; Mitema et al., 2001b; Sjolund et al., 2016; Krishnasamy

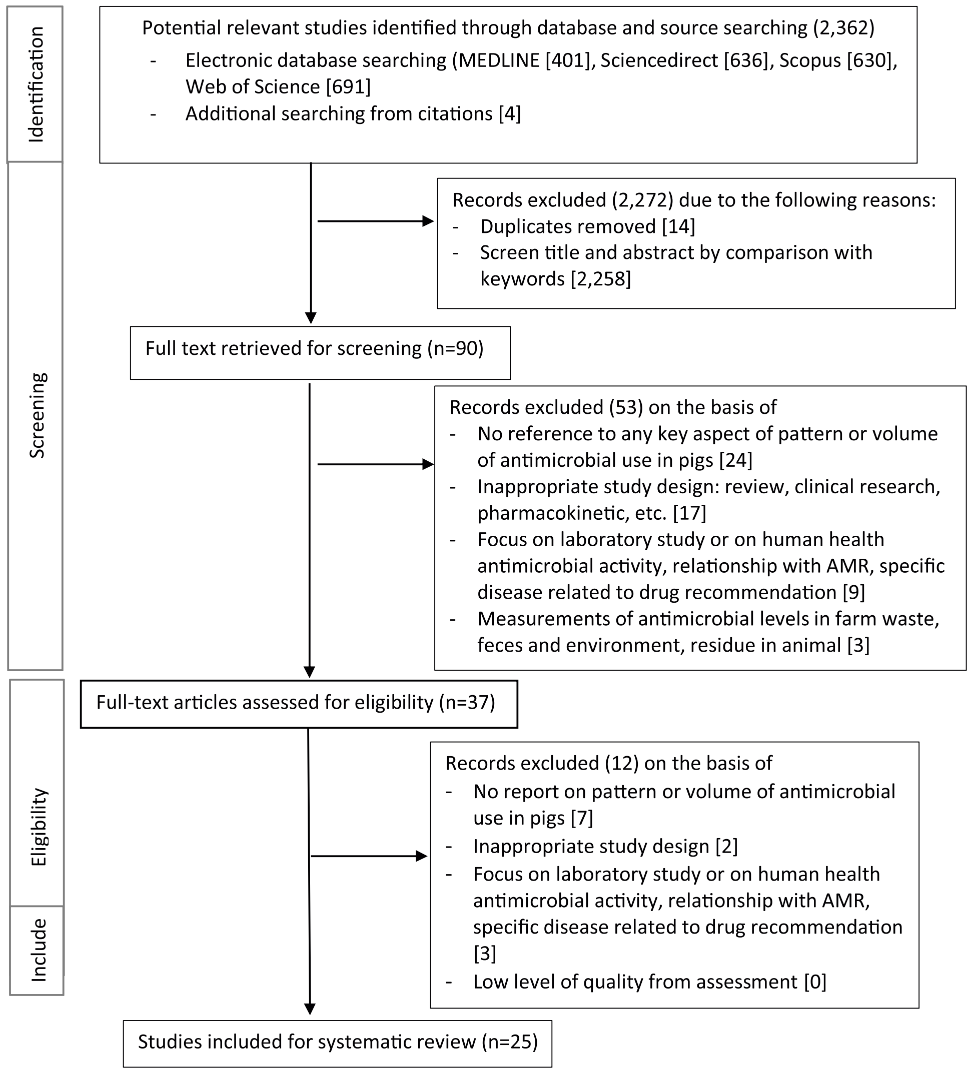

Fig. 1. Flow diagram of the review process.

et al., 2015; Sjolund et al., 2015; Van Boeckel et al., 2015; Hauck et al., 2014; Hosoi et al., 2014; Bos et al., 2013; Callens et al., 2012; Eagar et al., 2012; Merle et al., 2012). One study examined both improving the national surveillance and measuring the antimicrobial use (Filippitzi et al., 2014). The remainder of studies assessed the association between the use of antimicrobials and farm management practice (Fertner et al., 2015; Vieira et al., 2011; Arnold et al., 2004).

Eleven studies (44%) presented data at national level (Carmo et al., 2017; Dupont et al., 2016; Krishnasamy et al., 2015; Van Boeckel et al., 2015; Filippitzi et al., 2014; Hauck et al., 2014; Hosoi et al., 2014; Bondt et al., 2013; Jensen et al., 2012; Eagar et al., 2012; Mitema et al., 2001b). Fourteen studies (56%) presented data at sample farm level (Sjolund et al., 2016; Fertner et al., 2015; van Rennings et al., 2015; Sjolund et al., 2015; Taverne et al., 2015; Ferner et al., 2014; Trauffler et al., 2014a, b; Bos et al., 2013; Callens et al., 2012; Merle et al., 2012; Vieira et al., 2011; Timmerman et al., 2006; Arnold et al., 2004) with four of these studies complete farm data at a national level (Sjolund et al., 2016; Taverne et al., 2015; Bos et al., 2013; Vieira et al., 2011).

Data on antimicrobial use were collected from various sources. Of 25 studies, seven collected data through farm surveys (Sjolund et al., 2016, 2015; Ferner et al., 2014; Trauffler et al., 2014a, b; Callens et al., 2012; Timmerman et al., 2006), six compiled national data from the surveillance of antimicrobial consumption(Carmo et al., 2017; Dupont et al., 2016; Taverne et al., 2015; Van Boeckel et al., 2015; Filippitzi et al., 2014; Bondt et al., 2013; Vieira et al., 2011), four collected data through veterinary prescriptions (Fertner et al., 2015; Bos et al., 2013; Jensen et al., 2012; Arnold et al., 2004), and four from a review of sales of pharmaceutical products (Carmo et al., 2017; Hauck et al., 2014; Hosoi et al., 2014; Eagar et al., 2012; Mitema et al., 2001b). Three studies drew information from more than one data source (van Rennings et al., 2015; Filippitzi et al., 2014; Merle et al., 2012) and one study used data on food animal antimicrobial utilisation from the US, estimating the quantity of antimicrobials used in China (Krishnasamy et al., 2015).

Twenty-two studies (88%) reported antimicrobial use by major classes, while three studies (12%) reported in aggregation all classes of antimicrobial (Ferner et al., 2014; Fertner et al., 2015; Van Boeckel et al., 2015). Twenty studies (80%) reported the use of antimicrobials specific to pigs or other animal species but five studies (20%) only reported total use in all animal species (Van Boeckel et al., 2015; Ferner et al., 2014; Hauck et al., 2014; Eagar et al., 2012; Mitema et al., 2001a).

3.3.2. Numerators: the amount of antimicrobial use

Measuring numerators varied greatly, for example, by milligrams or kilograms of active ingredient and other more sophisticated adjustments such as defined daily dose, daily product dose, animal daily dose, used daily dose, prescribed daily dose, (see detail in Fig. 2).

Table 2
Characteristics of included studies.

Characteristics	N = 25
Quality assessment (mean)	
Published year	
2000-2010	3 (12%)
2010-2016	22 (88%)
Geographic area	
Europe	20[a] (80%)
Africa	2 (8%)
Asia	2 (8%)
Global	1 (4%)
Quality assessment	
High (> 75%)	15 (60%)
Moderate (50–74%)	10 (40%)
Unit of analysis	
National level	11 (44%)
Farm level	14 (56%)
Data collection on antimicrobial use	
Farm based survey	7 (28%)
National data	6 (24%)
Prescription data	4 (16%)
Pharmaceutical product sold review	4 (16%)
Mixed method (> 1 data source)	3 (12%)
Data from another country[b]	1 (4%)
Report by type of antimicrobials	
Sum of all antimicrobials	3 (12%)
Disaggregated by classes	22 (88%)
Report by animal species	
Sum of antimicrobials in all animal species	5 (20%)
Specific in pig/ disaggregated by animal species	20 (80%)
Unit of measurement used	(N = 40)
- Volume	9 (23%)
- Volume per biomass	6 (15%)
- Daily Product Dose (DPD)	3 (8%)
- Animal Daily Dose (ADD)	8 (20%)
- Defined Daily Doses per Animal year (DDDA)	3 (8%)
- Used Daily Dose (UDD)	3 (8%)
- Prescribed Daily Dose (PDD)	1 (3%)
- Treatment incidence rate	1 (3%)
- Treatment frequency	1 (3%)
- Treatment incidence	5 (13%)

[a] Including two multi-country studies.
[b] The study estimated the quantity of antimicrobials used in animal feeds in China by using antimicrobial utilisation data from the US livestock production.

3.3.3. Denominators: the number or mass of animals

For denominator data, eight studies used national level animal population which was retrieved from government agencies such as National Statistics, Central registry for livestock (Carmo et al., 2017; Dupont et al., 2016; Taverne et al., 2015; Filippitzi et al., 2014; Hosoi et al., 2014; Bondt et al., 2013; Jensen et al., 2012; Vieira et al., 2011). Two studies applied data from the Food and Agriculture Organization (FAOSTAT) (Krishnasamy et al., 2015; Van Boeckel et al., 2015). For the twelve studies at farm level, the number of animals reported by a certain production type and the time period during the study period (Sjolund et al., 2016; Fertner et al., 2015; van Rennings et al., 2015; Sjolund et al., 2015; Ferner et al., 2014; Trauffler et al., 2014a, Trauffler et al., 2014b, Bos et al., 2013; Callens et al., 2012; Merle et al., 2012; Timmerman et al., 2006; Arnold et al., 2004).

Several studies applied different standard weights for animal (Carmo et al., 2017). For example, the weights of an animal at treatment in Denmark (32) were: weaner 15 kg, slaughtered pig 50 kg and sows 200 kg. In Austria (26) weights were: piglets 1.5–10 kg, weaners 10-30 kg, fattened pigs < 60 kg, and sow and boar > 60 kg. In Sweden (18) weights were: sucking piglets 7 kg, weaners 7 kg, fatteners 35 kg and adult pigs 220 kg (Sjolund et al., 2015).

3.3.4. Unit of measurement: indicators used

Of the total 25 studies, there were ten different units of measurement. Nine studies calculated the total volume of antimicrobials used in the country per year (Carmo et al., 2017; Krishnasamy et al., 2015; van Rennings et al., 2015; Ferner et al., 2014; Filippitzi et al., 2014; Hauck et al., 2014; Eagar et al., 2012; Merle et al., 2012; Mitema et al., 2001b). Five of these studies (Hauck et al., 2014; Merle et al., 2012; Mitema et al., 2001b; Carmo et al., 2017; Filippitzi et al., 2014) calculated the volume of antimicrobial substances by multiplying the number of packages (package size) with the potency (strength of active substance) for each antimicrobial. One study (Eagar et al., 2012) calculated the volume of antimicrobials in kilograms of active pharmaceutical ingredient from the reports provided by pharmaceutical companies, while two other studies (van Rennings et al., 2015), Ferner et al., (2014) used treatment data at the farms. Only one study attempted to estimate non-therapeutic antimicrobial use in livestock. This was done by multiplying the number of animals in different phases of production by the estimated feed consumed per day and the duration in days in each phase that the swine received antimicrobials through feed and doses of antimicrobials in the feed (Krishnasamy et al., 2015).

3.3.4.1. Antimicrobials use measured by milligrams of active substance per animal weight. Six studies used some measure of the biomass of animals in order to indicate the intensity of antimicrobial use (Carmo et al., 2017; Van Boeckel et al., 2015; Filippitzi et al., 2014; Hosoi et al., 2014; Trauffler et al., 2014a, b). Biomass is the total weight of live animals. Two studies (Trauffler et al., 2014a, b) calculated biomass at farms by multiplying the number of animals and the average weight. One study estimated biomass by using the carcass weight, which is the whole-body weight of a slaughtered animal after blood is drained, evisceration and skinning (Hosoi et al., 2014).

Biomass can be calculated by using a population correction units (PCU). The PCU provides a better measurement of animal weight exposed to antimicrobial treatment: one PCU is equivalent to one kilogram of biomass of live animal or slaughtered animals where the animal had been exposed to antimicrobials throughout their lifecycle. For example, gross weight at slaughter was 150 kg, but the PCU was 65 kg and 25 kg for slaughtered and fattening pigs (Agency, 2013). Two studies (Carmo et al., 2017; Filippitzi et al., 2014) calculated the total national PCU, with reference to the guidelines produced by ESVAC, by multiplying the numbers of livestock animals and slaughtered animals by the theoretical weight at the time they were exposed to antimicrobial treatment. Another study estimated the PCU by multiplying the numbers of live animals in a production period and a ratio of carcass weight to live weight of animals (Van Boeckel et al., 2015).

3.3.4.2. Antimicrobials use measured by daily dose per weight at treatment. The daily dosage is a measure of the amount of a specific active pharmaceutical ingredient (*e.g.* in milligrams) required to treat one kilogram of animal in one day with that antimicrobial preparation, and is based on the average dosage of a medicine per kilogram per day for a specific type of animal.

Defined Daily Dose (DDD) is a technical unit of measurement of antimicrobial consumption in humans, calculated by standard DDD-value. In animals, measuring antimicrobial by defined daily dosage is calculated by using a specified dose of medicine (Animal Daily Dose value (ADD-value)), so called Animal Daily Dose (ADD) (Dupont et al., 2016; Fertner et al., 2015; Taverne et al., 2015; Ferner et al., 2014; Trauffler et al., 2014a, b; Bondt et al., 2013; Jensen et al., 2012) or by using the mean authorised dosage (Taverne et al., 2015; Bos et al., 2013; Merle et al., 2012) so called Daily Doses Animal (DDDA).

The ADD-value is specifically defined as the average maintenance dose per day for a drug used for its main indication for each animal species. The ADD-value was used in Denmark and Austria. They were

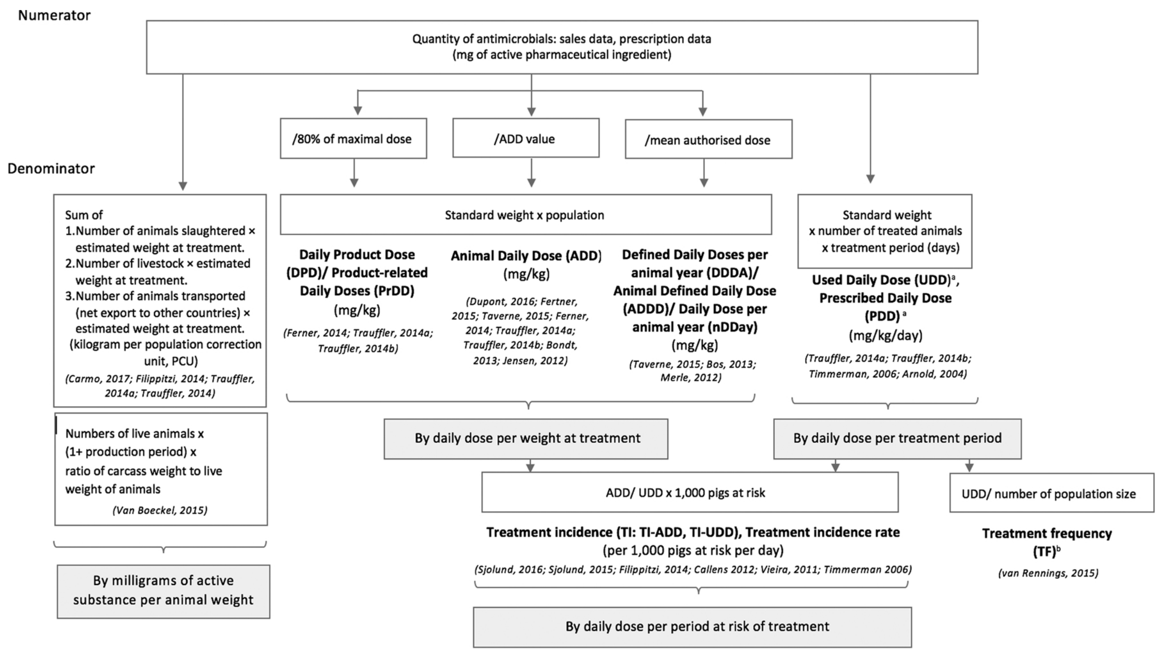

Fig. 2. describe the ten different measurements, categorised in four groups.
[a]Actual consumption data which calculated antimicrobial per a number of treated animal; [b]Additional measurement: calculated from ADD, UDD

based on the dose recommendations of each medicinal product registered in a country for each antimicrobial agent, administration route and animal species and when appropriate, also age group (Dupont et al., 2016; Fertner et al., 2015; Taverne et al., 2015; Ferner et al., 2014; Trauffler et al., 2014a, b; Bondt et al., 2013; Jensen et al., 2012).

For the DDDA, antimicrobial use is equal to the amount of active substances divided by the total weight of the number of livestock in the farm and mean authorised dosage. Other studies applied the same formula but called the unit of measurement differently as Animal Defined Daily Dose (ADDD) (Bos et al., 2013) and Daily Dose per animal year (nDDay) (Merle et al., 2012). One study used Defined Animal Daily Dosage (DADD), which is a measure established at the level of the active ingredient, route of administration and pharmaceutical form and not at the level of a specific antimicrobial class (Taverne et al., 2015).

Product-related Daily Doses (PrDD) or Daily Product Dose (DPD) calculated the daily dose to an assumed factor of 0.8, correcting for the fact that the maximum doses are not used in every treatment (Ferner et al., 2014); this means only 80% of the maximal dosage of the active substances were administered per day per kilogram biomass (Trauffler et al., 2014a, b).

3.3.4.3. Antimicrobial use measured by daily dose per treatment period. The Used Daily Dose (UDD) is the actual administered daily dose per kilogram biomass of a drug based on administered data reported by the farmer at farm level by a specific study. The formula for the UDD calculation is the weight of active substance divided by the number of treated animals, multiplied by the average weight of animals and treatment duration. Three studies applied UDD (Carmo et al., 2017; Trauffler et al., 2014a,b, Timmerman et al., 2006).

One study quantified antimicrobial use as a Prescribed Daily Dose (PDD). This was calculated for each active pharmaceutical ingredient and for each prescription according to the amount of active pharmaceutical ingredient per prescription (mg) divided by the average weight of the animals multiplied by the number of animals and treatment period (Arnold et al., 2004).

3.3.4.4. Antimicrobials use measured by daily dose per period at risk of treatment. To compare each administered antimicrobial in specific individual species, the treatment incidence was used in five studies (Sjolund et al., 2016, 2015; Filippitzi et al., 2014; Callens et al., 2012; Timmerman et al., 2006). It was defined as the number of pigs per 1000 pigs that are treated daily with one ADD or UDD, which is equivalent to how many pigs per 1000 pigs receive a dose of antimicrobials each day. In order to calculate the treatment incidence, the total UDD or ADD is divided by the treatment period, standard weight and population, then multiplied by 1000. One study applied 'treatment incidence' rate for slaughtered pigs by dividing the number of ADD by 100 slaughtered pigs at risk (Vieira et al., 2011).

One study calculated 'treatment frequency' by using the sum of all UDD divided by population size. It identified how many days, on average, an animal in a herd is treated with one active pharmaceutical ingredient (van Rennings et al., 2015).

3.3.5. Volume of antimicrobial use

As described above, this review uncovered a large variation in how antimicrobial use was measured, and the actual magnitudes of use. The annual antimicrobial use in pigs ranged from 20,000 kg to72,300 kg at different farm and country levels. One study estimated 34 million kilograms of antimicrobials was found in medicated feed in pigs in China due to the massive number of livestock (Krishnasamy et al., 2015). However, more than one million kilograms were quantified in the studies in food animals in Germany (Hauck et al., 2014) and South Africa (Eagar et al., 2012) and about 63 million kilograms globally (Van Boeckel et al., 2015). On the other hand, lower use was documented in Kenya where only 15,000 kg of antimicrobials were used in one year in all animal species (Mitema et al., 2001b). A wide range of volume per biomass was reported, ranged from 33.9 mg per biomass in Austria (Trauffler et al., 2014a) with about 400 mg per biomass in Japan (Hosoi et al., 2014).

The ADD varied from lower than one (Fertner et al., 2015) to 16 ADD (Taverne et al., 2015) in different phases of pig production and countries. Treatment incidence per 1000 pigs at risk per day ranged from lower than 10 (Carmo et al., 2017; Sjolund et al., 2016, 2015) to more than 200 treatment incidences (Sjolund et al., 2016; Callens et al., 2012).

However, careful interpretation across countries is needed as these

Table 3
Summary antimicrobial usage data from studies included in this review.

Unit of measurement	Antimicrobial usage data
Antimicrobials use measured by milligrams of active substance per animal weight	- 67,423–72,300 kg; - 34 (min) to 178.6 (max) mg/biomass (Switzerland) (Carmo et al., 2017) - 34 million kg (in medicated feed) (China) (Krishnasamy et al., 2015) - 20,373.6 kg (Germany) (van Rennings et al., 2015) - 63,151, 000 kg (Global level) (Van Boeckel et al., 2015)[a] - > 5,400 kg (Austria) (Ferner et al., 2014)[a] - 222,500 kg; - 137 mg/biomass (Belgium) (Filippitzi et al., 2014)[a] - 1,706 tons (2011) and 1,619 tons (2012) (Germany) (Hauck et al., 2014)[a] - 392 to 423 mg/ biomass (Japan) (Hosoi et al., 2014) - 33.89 mg/ biomass (Austria) (Trauffler et al., 2014a,b) - 1,538,443 kg (South Africa)*(Eagar et al., 2012) - 31,622 kg (Germany) (Merle et al., 2012) - 14,594 kg (Kenya) (Mitema et al., 2001)[a]
Antimicrobials use measured by daily dose per weight at treatment (ADD, DDDA, DPD)	- 9.4, 10.4, 11.6 ADD (Denmark) (Dupont et al., 2016) - 0.6-7.37 ADD (Denmark) (Fertner et al., 2015) - 11.78-19.20 DDDA; 10.43 (min) to 16.0 (max) ADD (Netherlands and Denmark) (Taverne et al., 2015) - DPD-LU 631,939; ADD-LU 576,242(Austria) (Ferner et al., 2014)[a] - 2.51 DPD; 1.95 ADD (Austria) (Trauffler et al., 2014a,b) - 19 ADD (Netherlands); 14 ADD (Denmark) (27) - 16.9 DDA, 9.6 DDDA (Netherlands) (Bos et al., 2013) - 60.86 DDDA (piglet), 28.60 DDDA (fattener), 2.89 DDDA (sow) Germany) (Merle et al., 2012) - 1.40–2.14 ADD (sow), 5.02–5.90 ADD (weaner), 1.12–1.37 ADD (finisher) (Denmark) (Jensen et al., 2012)
Antimicrobial use measured by daily dose per treatment period (UDD, PDD, Treatment incidence rate, Treatment frequency)	- Treatment frequency: 0.86 days (sows), 14.74 days (piglets), 6.62 days (weaners) and 3.67 (fattener) (Germany) (van Rennings et al., 2015) - 4.88 UDD (Austria) (Trauffler et al., 2014a,b) - Treatment incidence rate: Tetracycline 0.28–0.70, Macrolide 0.40–0.44 (Denmark) (Vieira et al., 2011) - 3.3–6.1 PDD (Switzerland) (Arnold et al., 2004)
Antimicrobials use measured by daily dose per period at risk of treatment (TI-ADD, TI-UDD)	- TI-ADD (per 1,000 pigs at risk per day): 176 (suckling piglet), 406 (weaner), 33 (fattener), 143 (grower), 16 (breeder) (Belgium); 59 (suckling piglet), 374 (weaner), 7 (fattener), 108 (grower), 22 (breeder) Germany: 245 (suckling piglet), 633 (weaner), 53 (fattener), 243 (grower), 42 (breeder) (France); 76 (suckling piglet), 21 (weaner), 6 (fattener), 23 (grower), 11 (breeder) (Sweden) (Sjolund et al., 2016) - TI-ADD (per 1,000 pigs at risk per day): 54.7 (suckling piglet), 6.2 (weaner), 2.8 (fattener), 14.3(grower), 8.4 (breeder) (Sweden) (Sjolund et al., 2015) - TI-ADD (per 1,000 pigs at risk per day): 235.8, TI-UDD 200.7 (Belgium) (Filippitzi et al., 2014; Callens et al., 2012) - TI-ADD (per 1,000 pigs at risk per day): 178.1, TI-UDD 170.3 (Belgium) (Timmerman et al., 2006)

[a] Data combined other species.

measurements are not standardized. Also, the magnitudes of use are determined by the type of pig farms, animal demographic and the socio-economic context of a country. See details in Table 3.

4. Discussion

4.1. Data sources

Two main sources of data emerge from this review: national sales data and primary data collected through pig farm surveys. In many European countries, the national monitoring of antimicrobial consumption relies on national sales data of pharmaceutical products, the disadvantage of sales data is the lack of information on which species they are being used for, the indication, dose and duration of treatment. Farm or pharmaceutical company surveys apply prospective longitudinal or cross-sectional studies which provide additional detailed use by species and production types (European Medicines Agency, 2013). One study applies bottom up approach for national consumption data estimate, it collects data from some herds and extrapolates to the national level (Filippitzi et al., 2014). However, this approach could be inaccurate as the sampled farms are not designed as national representative samples.

Data sources for animal populations can be retrieved from total national data collection by government agencies such as slaughter house and production information, or it can be obtained from other sources such as the Association of Pig Farmers. Data from international organizations such as the FAOSTAT database hosted by the Food and Agriculture Organization is another source of the size of animal populations (Krishnasamy et al., 2015; Van Boeckel et al., 2015). Even though, FAOSTAT information is limited such as estimates for non-responses and incomplete report, and the lack of granularity on number of animal of species; it can be applied when data at the country is not available. Using different weights of animals at treatment across studies resulted in substantial differences in use and hinders comparability (Carmo et al., 2017; Dupont et al., 2016).

4.2. Methods and units of measurement

This systematic review describes methods for measuring antimicrobial use. All the studies in the review were conducted after 2000.

Most of the literatures on the pattern of use of antimicrobials are derived from high-income countries in the European region; while very few studies were conducted in Asia and Africa, which applied the traditional measurement by weight of active substance per animal weight.

This review indicates that there is no global harmonised system for measuring antimicrobial use in animals. The proliferation of indicators using different measurements of both numerators and denominators hampers cross-country comparisons.

Several studies reported the quantity of use in kilograms of active ingredient without denominator data. Though simple, its main limitation is that it does not give any indication of intensity of use. To address this deficiency, measurements of use per weight have been widely used. However, using kilogram of active ingredients does not take into account the differences in drug strengths, doses administered and pharmacokinetics. The use of higher strengths, dosage and more treatment days led to higher antimicrobial use than those which were applied at lower strengths and dosage (van Rennings et al., 2015).

There is also a large variation in strengths and dosages of antimicrobials use in human health. In order to standardise the measurement, the DDD was developed and is now used globally to measure antimicrobial consumption in humans with standardised reporting by DDD per 1000 inhabitant-days. This facilitates international comparison on antimicrobial use (Natsch et al., 1998). However, a similar universal standardised unit of DDD measurement has not yet been developed for veterinary antimicrobial agents; hence different countries have established their own national ADD-value, based upon medicine specifications registered by their National Regulatory Authorities. The different ADD-values for veterinary medicines hampers cross country comparisons, as using different sets of ADD-values affected the estimate of use (Dupont et al., 2016; Taverne et al., 2015). Moreover, there are not only different units of measurement, but countries also name their measurement differently, such as ADD in Denmark (Jensen et al., 2004) and ADDD in Netherlands (NETHMAP and MARAN, 2013).

There has been an attempt to establish a consensus on DDDA for each active substance and administration route for veterinary antimicrobial products authorised in four European countries (Postma et al., 2015); this effort has yet to scale up to all European countries. Another approach to calculate the daily dose is by using an actual dose administered to animal. Instead of using ADD-value, a DPD is proposed to by adjusting the recommended maximum daily dose by a factor of 0.8 of maximal dose for specific medicinal products; assuming that the maximum doses are not used in every treatment (Ferner et al., 2014; Trauffler et al., 2014a, b).

To differentiate antimicrobial use between herds, antimicrobial per treatment periods were calculated based on real use data at farm level. In 2006, a measurement called UDD was introduced firstly in a study in pig farms (Timmerman et al., 2006). The UDD was calculated based on the definite number of treated animals in a treatment period and the dosages of antimicrobials to animals in farms; the UDD avoids differences between ADD-values and supports comparison of use across countries and across studies. Moreover, the ratio between UDD/ADD reflects the appropriateness of dosing where the higher the ratio, the more excessive the use. Another measurement of antimicrobial use that takes into account the treatment period was PDD; it reports antimicrobial use by antimicrobial prescription. PDD also shows the veterinarian's prescribing pattern. However, antimicrobial prescription is not always equal to the actual antimicrobial administration (Chauvin et al., 2001).

There are several methods that relate to the association between the actual volume of specific antimicrobials used in a specific time period such as 'treatment frequency' (van Rennings et al., 2015) and 'treatment incidence rate' (Vieira et al., 2011). Furthermore, the 'treatment incidence' has been introduced for a comparison of data between farms, considering the period at risk of treatment (Sjolund et al., 2016, 2015; Filippitzi et al., 2014; Callens et al., 2012; Timmerman et al., 2006). The treatment incidence rate can compare the antimicrobial use per animal species and details of antimicrobial use in terms of dosage and route of administration which can be compared between herd and production types. It can be calculated based on both ADD-values or UDD. However, comparison of 'treatment incidence' to other studies should be done with caution when ADD-value is used (Sjolund et al., 2015).

The wide variation in methods and indicators across the studies, and the relative lack of swine-specific data prevent this review from making valid comparisons of antimicrobial use in swine production or documenting trends.

4.3. European experiences and international recommendations

In European countries, the European Medicines Agency (EMA) (2014) established the ESVAC project in 2009. The antimicrobial consumption reported by ESVAC members is comparable across countries by using a standardised measurement of mg of active ingredient per population correction unit (mg/PCU). The total volume of antimicrobials used in 30 European countries was 8361.3 tonnes of active ingredients or 135.5 mg/PCU on an average of consumption in food producing animals in 2015 (European Medicines Agency, 2015).

The ESVAC project has contributed significantly to the standardised methods for antimicrobial consumption in 30 countries in Europe and has also spill over effects to developing countries, in particular Thailand (Tangcharoensathien et al., 2017). In addition to the current reporting of mg per PCU, the ESVAC project has established standardised units of measurement in three major animal species (pigs, cattle and broilers) called Defined Daily Dose (DDDvet) and Defined Course Dose (DCDvet). It aims to harmonize and standardise reporting data on veterinary antimicrobial consumption across European countries. The values are based on an assumed average DDDvet or DCDvet of active substance, which take into account differences in dosing, pharmaceutical forms and routes of administration used by these three species (European Medicines Agency, 2015).

To rectify the weakness of national sales data, in 2013, the EMA recommended that countries conduct farm surveys of veterinary prescriptions or antimicrobial administration records in the logbooks kept by farmers, specific for different species (see ESVAC guidelines of data collection at farm level) (European Medicines Agency, 2013). Though this additional data collection from farms demands substantial resources, infrastructure development and enforcement of veterinary prescriptions at farm level, the benefit is high as it provides accurate information on antimicrobial use by classes and animal species and indications, and evidence can be used to facilitate the development of specific interventions and improve the specific training and education in veterinarians and farmers.

To date, the OIE has also relied on antimicrobial sales data as indicators of actual use, and also recommends that OIE member countries to collect and report data on quantity of antimicrobial consumption in kilogram of antimicrobial agents for different types of indication (therapeutic use or growth promotion), different animal species group and different routes of administration. In the second OIE annual report in 2017 on the use of antimicrobial agents intended for use in animals, OIE recommended to use animal biomass as a denominator so that the quantitative data on antimicrobial agent can be compared among countries. Animal biomass is calculated as the total weight of the live domestic animals, used as a proxy to represent those likely to have exposed to the quantities of antimicrobial agents reported (World Organisation for Animal Health (OIE), 2017).

From the review, data of the volume of antibiotic use in low- and middle-income countries are limited while these countries have a large livestock production. Only three studies are included in this review, which includes Kenya (lower-middle-income economies), and China and South Africa (upper-middle-income economies). Data from South Africa and Kenya was reported in kilogram of antimicrobials used in all livestock. Total antibiotics were calculated by the review of sales of pharmaceutical product. Whereas, the study in China reported antimicrobials in medicated feed by estimation. The quantity of antimicrobials was calculated by using antimicrobial utilisation data from the US livestock production. This review indicates an urgent need to build up national capacity to develop system which monitors antimicrobial consumption in LMIC. The monitoring systems of antimicrobial consumption can be developed in a phased manner (Schar et al., 2018).

4.4. Policy utilities

Data on antimicrobial usage is needed for a number of reasons such as monitoring time trends of use and assessing the effectiveness of interventions. Ideally it should be disaggregated by different antimicrobial classes in particular the critically important for human health. It can also be used to investigate the association between the magnitude of use and bacterial resistance (Collineau et al., 2017; Schar et al., 2018).

5. Conclusion

We systematically reviewed the peer-reviewed literatures on the methods and measurements for antimicrobial use in pigs globally. Ten different units of measurement were identified from 25 studies of high- and medium-quality studies; which vary greatly in term of objectives, data sources and units of measurement both numerators and denominators. The non-homogeneity of the unit of measurement limits the cross-study comparative analysis. Additionally, different levels of data such as from farm surveys and national sales data used by these studies also produce different magnitude of use across studies.

6. Recommendations

Given the importance of measuring antimicrobial use in monitoring progress of policies in optimizing use, at a minimum, all developing countries should develop macro-level monitoring using national sales data and report consumption by milligram of active ingredients per biomass, while at the same time, when there are improved capacities, gradually develop sentinel sites which capture prescription of antimicrobial use by species with the application of DDDvet and DCDvet. The EMA initiative on standardised units of measurement in three main animal species using DDDvet and DCDvet, should be scaled up in Europe and can be applied by developing countries in responses to the GAP-AMR which calls for monitoring and optimizing antimicrobial use.

Conflict of interest

The authors declare that they have no financial and personal relationships with other people or organizations that could inappropriately have influenced the present study and manuscript.

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Appendix A

Table A3

Table A1
Variables assessed in the study.

Variables	Results
1. Context variables	Author, year of publication, year of study, title, journal, geographical area, objective
2. Methodology variables	2.1 Research (Observational study: cohort studies/case–control studies/ cross-sectional surveys/routine-data-based studies); national report 2.2 Data source: primary data (survey, interview) from pig producer, veterinarian; secondary data from company (sales data), veterinarian (prescription data), government, level of data (national or specific small-scale farm level) 2.3 Sampling technique, if it is a primary data collection: simple random sampling, stratified sampling, cluster sampling, systematic sampling, Probability Proportional to Size (PPS), quota sampling, convenience sampling, purposive sampling, self-selection sampling, snowball sampling 2.4 Sample size: number of respondent, response rate (%) 2.5 Methods for antimicrobial use measurement and indicators
Comments (including strengths, weaknesses)	

Table A2
Quality assessment of included studies.

Author, year	Clearly focused issue	Method					Result			Application		Rank[a]
		Appropr-iateness	Recruitment	Bias reduction	Data collection	Number of participants	Presentation	Sufficiently rigorous	Clear statement finding	To local population	Research value	
2016												
Carmo et al. (Carmo et al., 2017)	Y	Y	CT	CT	Y	Y	Y	Y	Y	Y	Y	H
Dupont et al. (Dupont et al., 2016)	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	H
Sjolund et al. (Sjolund et al., 2016)	Y	Y	N	N	Y	Y	Y	Y	Y	Y	Y	H
2015												
Krishnasamy et al. (Krishnasamy et al., 2015)	Y	N	N	CT	CT	CT	Y	N	Y	Y	Y	M
Rennings et al. (van Rennings et al., 2015)	Y	Y	Y	N	Y	Y	Y	Y	Y	Y	Y	H
Sjolund et al. (Sjolund et al., 2015)	Y	Y	Y	N	Y	Y	Y	Y	Y	Y	Y	H
Taverne et al. (Taverne et al., 2015)	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	H
Van Boeckel et al. (Van Boeckel et al., 2015)	Y	Y	N	Y	CT	CT	Y	CT	Y	Y	Y	M
2014												
Ferner et al. (Ferner et al., 2014)	Y	Y	N	N	Y	N	N	N	Y	Y	Y	M
Fertner et al (Fertner et al., 2015)	Y	CT	N	N	Y	N	Y	Y	Y	Y	Y	M
Filippitzi et al. (Filippitzi et al., 2014)	Y	Y	CT	N	CT	CT	Y	Y	Y	Y	Y	M
Hauck et al. (Hauck et al., 2014)	Y	Y	Y	CT	CT	Y	Y	Y	Y	Y	Y	H
Hosoi (Hosoi et al., 2014)	Y	Y	CT	N	N	N	Y	Y	Y	Y	Y	M
Trauffler et al. (a) (Trauffler et al., 2014a)	Y	Y	N	N	Y	N	Y	Y	Y	Y	Y	M
Trauffler et al. (b) (Trauffler et al., 2014b)	Y	Y	N	N	Y	N	Y	Y	Y	Y	Y	M
2013												
Bondt et al. (Bondt et al., 2013)	Y	Y	Y	CT	CT	Y	Y	Y	Y	Y	Y	H
Bos et al (Bos et al., 2013)	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	H
2012												
Callen et al. (Callens et al., 2012)	Y	Y	Y	N	Y	Y	Y	Y	Y	Y	Y	H
Eagar et al. (Eagar et al., 2012)	Y	Y	N	N	Y	N	Y	Y	Y	Y	Y	M
Merle et al. (Merle et al., 2012)	Y	Y	N	Y	Y	Y	Y	Y	Y	Y	Y	H
Jensen et al. (Jensen et al., 2012)	Y	Y	N	N	Y	Y	Y	Y	Y	Y	Y	H
2011 Vieira et al. (Vieira et al., 2011)	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	H
2006 Timmerman et al. (Timmerman et al., 2006)	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	H
2004 Arnold et al. (Arnold et al., 2004)	Y	Y	Y	N	Y	Y	Y	Y	Y	Y	Y	H
2001 Mitema et al. (Mitema et al., 2001a)	Y	Y	CT	N	Y	CT	Y	N	Y	Y	Y	M

CT: Cannot tell.
[a] Score > 75 = high (H), 50–74 = medium (M) and < 50 = low (L).

Table A3
Summary of unit of measurement from included studies.

Definition and unit of measurement	Numerator	Denominator	Variable						Reference
			Amount of antimicrobials	Dose	Animal weight	Number of animals	Treatment period	Additional variable	
By population									
A. Volume of antimicrobial use (kilogram)	1. Number of animals 2. Estimated (medicated) feed) consumed per day 3. Duration that swine received antimicrobial 4. Dose of antimicrobial	NA	Y (medicated feed)	Dose in the feed	N	Y	Y	N	Krishnasamy et al., 2015
B. Volume of antimicrobial use per biomass (mg/PCU; 1 PCU = 1 kilogram of biomass of livestock and slaughtered animals)	Active pharmaceutical ingredient (sold, prescription)	1. Number of slaughtered animals 2. Number of livestock 3. Number of imported/ exported animals 4. AW	Y	N	N	Y	N	Average weight at treatment	Carmo et al., 2017
(mg/PCU)	Active substance	Numbers of live animals x (1 + production period) x ratio of carcass weight to live weight of animals	Y	N	N	Y	N	Production period, ratio of carcass/ live weight	Van Boeckel, 2015
(mg/biomass)	Active substance (sold)	Carcass weight	Y	N	Carcass	N	N	N	Hosoi et al., 2014
Daily dose and weight at treatment									
C. Product-related Daily Doses (PrDDkg) or **Daily Product Dose (DPD)**	Active substance (prescription)/ 80% of maximal dose	Standard weight x population	Y	80% of maximal dose	Std. weight	Y	N	N	Trauffler, 2014a,b; Ferner et al., 2014
D. Animal Daily Dose (ADD) (mg/kg bodymass/day)	Active substance (administered/ prescription)/ ADD-value (average maintenance dose per day per kg animal of a drug use for main indication in the target species)	Standard weight x number of animal	Y	Maintenance dose	Std. weight	Y	N	N	Dupont et al., 2016; Taverne et al., 2015; Fertner et al., 2015; Ferner et al., 2014; Trauffler et al., 2014a;b; Bondt et al., 2013; Jensen et al., 2012
Definition and unit of measurement	Numerator	Denominator	Variable Amount of antimicrobials	Dose	Animal weight	Population	Treatme-nt period	Additional variable	Reference
• ADD-LU (livestock unit; LU) (mg/500 kg LU biomass/day)	ADD x 500	NA	N	N	N	N	N	ADD	Ferner et al., 2014
• Number of animal daily doses per livestock unit (nADDsLU)	ADD-LU	Number of treated LUs (total number of LU produced in one year by all farm, in which at least treatment was recorded)	N	N	N	N	N	N	Ferner et al., 2014

(continued on next page)

Table A3 (*continued*)

Definition and unit of measurement	Numerator	Denominator	Variable						Reference
			Amount of antimicrobials	Dose	Animal weight	Number of animals	Treatment period	Additional variable	
E. Defined Daily Doses per animal year (DDDA) or **Animal Defined Daily Dose (ADDD)** or **Daily Dose per animal year (nDDay)**	Active substance (prescription)	Recommended dose x total animal mass that can be treated for one day with the supplied antimicrobials x mean total weight (kilogram) of animals on the farm	Y	Recommended dose	Mean weight	Y	N	N	Taverne et al., 2015; Bos et al., 2013; Merle et al., 2012
Daily dose and treatment period									
F. Used Daily Doses per kg biomass (UDDkg) (mg/ kilogram biomass/ day)	Active substance (administered)	Number of treated animals x Standard weight (kilogram) x Treatment duration (days)	Y	N	Std. weight	Y	Y	N	Timmerman et al., 2006; Trauffler et al., 2014a, b
G. Prescribed Daily Dose (PDD) (mg/kg* day)	Active substance (prescription)	Average weight of the animals x number of animals (n) x treatment period (days))	Y	N	Avg. weight	Y	Y	N	Arnold et al., 2004
H. Treatment frequency	UDD	Population size	N	N	N	Y	N	UDD	Van Rennings et al., 2015
I. Treatment incidence rate	ADD	Sum of delivered animals in the period * 112 (112 = days of fattening period) OR 100 slaughter pig-days at risk	N	N	N	Y	N	N	Vieira et al., 2011
Daily dose and period at risk of being treated									
J. Treatment incidence- DDA (TI-DDA), UDDA (TI-UDDA)	DDA/ UDD(mg/kg) x 1,000 population		Y	N	Avg. weight	Y	Y	UDD, ADD	Sjolund et al., 2016;2015; Filippitzi et al., 2014; Callens et al., 2012; Timmerman, 2006

Appendix B

Search Strategy
Structured Database Search (Search terms and results)

- MEDLINE: N = 401 articles
- (antibiotic or antimicrobial).mp. [mp = title, abstract, original title, name of substance word, subject heading word, keyword heading word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier, synonyms] (251,939)
- ("use" or "utilisation" or "consume*" or "practice" or "administration" or "oral" or "feed" or "injection" or "amount" or "quantit*" or "qualit*").mp. [mp = title, abstract, original title, name of substance word, subject heading word, keyword heading word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier, synonyms] (5,584,129)
- ("livestock" or "swine" or "pig" or "farrow" or "weaner" or"sow").mp. [mp = title, abstract, original title, name of substance word, subject heading word, keyword heading word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier, synonyms] (285,470)
- ("measurement" or "indicator" or "surveillance" or "survey" or "report" or "method").mp. [mp = title, abstract, original title, name of substance word, subject heading word, keyword heading word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier, synonyms] (3,766,673)
- Sciencedirect: N = 636 articles:
  "Antibiotic" AND ("swine" OR "pig") AND ("use" OR "survey" OR "surveillance" OR "consumption")
  Filter: Topics, "pig", "animal"; Content type, "Journal".
- Scopus: N = 630 articles:
  (TITLE-ABS-KEY (antibiotic OR antimicrobial OR antibacterial) AND TITLE-ABS-KEY (livestock OR swine OR pig OR farrow OR weaner OR finisher OR sow) AND TITLE-ABS-KEY (use OR utilisation OR consume* OR consumption OR practice OR administration OR provision) AND TITLE-ABS-KEY (measure* OR indicator OR surveillance OR survey OR monitor)):
- Web of Science: *N = 691 articles*:
  TOPIC:(antibiotic OR antimicrobial OR antibacterial) AND TOPIC: (livestock OR swine OR pig OR farrow OR weaner OR finisher OR sow) ANDTOPIC: (use OR utilisation OR consume* OR consumption OR practice OR administration OR provision) AND TOPIC: (measure* OR indicator OR surveillance OR survey OR monitor)

Filter: DOCUMENT TYPES: (ARTICLE) AND WEB OF SCIENCE CATEGORIES: (VETERINARY SCIENCES OR MICROBIOLOGY OR AGRICULTURE DAIRY ANIMAL SCIENCE)

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4.2 Potential factors influencing the use of antibiotics in livestock

As described in Chapter 1, my previous study demonstrated that the use of antibiotics in the agricultural sector could be influenced by complex determinants at different levels including: (1) farmer lack of knowledge of antibiotics and awareness about AMR; (2) health professionals lack of AMR information and diagnostic tools to guide prescription; and (3) loose regulatory systems such as no requirement for prescriptions to acquire antibiotics.

In addition, I reviewed the literature on antibiotic use in livestock and factors influencing antibiotic use, searching online electronic databases including MEDLINE, ScienceDirect, Scopus and Web of Science between January-November 2017. The review showed that a wide range of factors have been described, and different stakeholders across different levels.

Farmers are likely to have a limited understanding of antibiotics, particularly in LMICs. Poor knowledge and lack of understanding among farmers about the impact of antibiotic use might lead to inappropriate use of antibiotics. One study in Cambodia showed that none of the farmers demonstrated an understanding of the action and indication for antibiotics (115). Another study in Sudan found a significant association between farmers' poor knowledge of antibiotic use and the low education of farmers; only a quarter of farmers in the study had heard about antibiotic resistance (116). One study in smallholder dairy farms in India showed that among farmers, a low level of knowledge relating to antibiotics was associated with the presence of active informal service providers (117).
Antibiotic use was found to be related to pig production system. In my systematic review of the pattern of antibiotic use in pigs (section 3.1.1), the frequency of antibiotic use on different farms is associated with the type of pig production. Farm characteristics are associated with antibiotic use, such as the type of farm, size of farm and vaccination status. Studies in European and Asian countries demonstrated that large farms (111,118,119) and industrial production systems (111) are more likely to use medicated feeds compared with smaller-sized farms. Another relevant study showed that antibiotic use on Dutch farms located in densely pig-populated areas and a high number of sows present on the farm are positively correlated with the volume of antibiotic consumption (119). In addition, farm management is associated

with the use of antibiotics, such as farm biosecurity practices[5], animal density, stress levels in the herd, vaccination status, quality of feed, and disease prevalence rates. Good farm biosecurity is identified as common practice in herds which leads to a reduction in disease transmissions and lower antibiotic use (120). Vaccination is recommended to optimise antibiotic usage (121).

Veterinarians play important roles in the antibiotic utilisation system including dispensing, prescribing, providing information and taking responsibility for control over farmer practices. However, one prior study demonstrated that the decisions made by veterinarians to prescribe antibiotics are based on "expert opinion" or on other colleagues' views who are "opinion leaders" or from internet sources, rather than scientific and peer-reviewed data (122). Antimicrobial sensitivity testing is an important tool to identify bacteria and select antibiotics. Nevertheless, nearly half of all veterinarians in European countries (44.3%) seldom collect a sample for bacterial diagnosis in a laboratory. Pharmaceutical companies have common marketing strategies to increase their sales (123,124), which may influence the higher use of antibiotics by farmers.

Antibiotic use by farmers also relies on policies and regulations. Previous studies have shown that access to antibiotics also influence farmers' use of antibiotics. A study in Ghana showed that easy access to antibiotics by poultry farmers facilitated the use of antibiotics (125). In India, dairy farmers reported the direct marketing of drugs and easily available antibiotics which contributed to self-administered use of antibiotics (117). Cambodian farmers reported that antibiotics can be purchased without a veterinary prescription from any animal feed retailer, where not all of them are employed trained veterinarians (115).

Based on the review of the literature, factors can be categorised into three levels: individual level, systems level, and policy and regulation level. Individual-level factors include the knowledge, attitudes and practices of farmers and communities in relation to antibiotic use. Systems-level factors are defined based on a relationship between farmers and systems including pig production systems and antibiotic supply systems (production, distribution, prescription, sale and use of antibiotics). Factors also include association among farmers and key stakeholders such as veterinarians, pharmaceutical actors and pork consumers who

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[5] OIE defines bio-security as a set of management and physical measures designed to reduce the risk of introduction, establishment and spread of animal diseases, infections or infestations to, from and within an animal population (108)

contribute to antibiotic use on farms. Policy-level factors include drivers that are associated with the government, regulations and policies concerning the use of antibiotics in pig farms.

4.3 Conclusions and knowledge gaps

Drawing on the literature presented above, it is evident that antibiotics have been used routinely in livestock production to treat, control and prevent disease, and to increase productivity for many decades. Due to the possible association between antibiotic use in livestock and AMR in humans, there are concerns that their level of use is unnecessarily high including for sub-therapeutic use for growth promotion and disease prevention, and particularly for the use of antibiotics that are important in humans. Many classes of antibiotics used in animals are also used in humans, particularly Critically Important Antimicrobials for human medicine. These uses are considered as important drivers to the selection of resistant bacteria.

The literature review shows that the use of antibiotics in pigs is complex and associated with interrelating domains including knowledge and attitudes of farmers and communities. Antibiotic use is also related to pig production and antibiotic utilisation systems under the government, regulations and policies controlling the use of antibiotics in pig farms.

However, data about antibiotic use are scarce. There is a lack of explicit information concerning how much, and how different types of antibiotics are being used, and which determinants contribute to antibiotic use in pig production, particularly in LMICs. This gap in knowledge limits understandings of both the barriers and facilitators which can be addressed to optimise the use of antibiotics in livestock.

The empirical research in this thesis aims to contribute to closing the gaps identified in the literature by exploring the use of antibiotics, and factors influencing the use of antibiotics in pig production. This will enhance understanding of the use of antibiotics in pig production, and lead to recommendations for optimising the use of antibiotics in pig production. The following chapter will develop the aims and methods of the empirical research.

SECTION B: RESULTS

Chapter 5 Mixed-methods study: Pattern of antibiotic use in pig farms and the total amount of antibiotics used in pig production in Thailand

(Cover sheet on next page)

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Thesis Title	Understanding the use of antibiotics in pig production in Thailand

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How antibiotics are used in pig farming: a mixed-methods study of pig farmers, feed mills and veterinarians in Thailand

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ABSTRACT

Background Rising global concern about antimicrobial resistance has drawn attention to the use of antibiotics in livestock. Understanding the current usage of antibiotics in these animals is essential for effective interventions on the optimisation of antibiotic use. However, to date few studies have been conducted in low- and middle-income countries. This study aimed to explore the use of antibiotics and estimate the total amount of antibiotics used in pig production in Thailand.

Methods This was a mixed-methods study including a cross-sectional questionnaire-based survey of 84 pig farmers, secondary analysis of data from a survey of 31 feed mills to estimate the amount of antibiotics mixed in pig feed and interviews with five veterinarians involved in the feed mill industry to gain an understanding of medicated feed production.

Findings Half of the farmers reported using antibiotics for disease prevention. Use was significantly associated with farmers' experience in raising pigs, farm income, having received advice on animal health and belonging to a farm cooperative. The estimated total amount of active ingredients mixed into medicated feed for pigs for the whole country was 843 tonnes in 2017. Amoxicillin was the most commonly used antibiotic reported by both pig farms and feed mills. The use of Critically Important Antimicrobials including colistin was common, with one-third of farmers reporting their use as oral or as injectable medication, and accounting for nearly two-thirds of antibiotics contained in medicated feed.

Conclusion A majority of antibiotics used in Thai pig farms belonged to the category of Critically Important Antimicrobials. Progressive restriction in the use of antibiotics in pigs is recommended through using prescriptions to control the distribution of certain antibiotics. The government should strengthen veterinary services to improve access of farmers to animal health advice and explore alternative interventions.

Key questions

What is already known?

- Rising global concern about antimicrobial resistance has drawn attention to the use of antibiotics in animals, in particular the use of last-resort antibiotics normally reserved for severe infections in humans.
- Low- and middle-income countries are large livestock producers and consumers. There are many studies about the use of antibiotics in livestock in high-income countries yet very few have been conducted in low- and middle-income countries.

What are the new findings?

- Over half of the farmers used antibiotics for disease prevention in pig production.
- The total amount of active ingredients mixed into medicated feed for pigs was estimated to be 843 tonnes in 2017.
- Amoxicillin was the most common antibiotic used for disease prevention and mixed into medicated feed.
- Half the oral and injectable antibiotics used in farms and two-thirds of antibiotics added in medicated feed belonged to the category of Critical Important Antimicrobials (CIA).

What do the new findings imply?

- Alternative approaches need to be sought to maintain herd health and productivity in order to protect the effectiveness of antibiotics. These solutions need to be tested and demonstrated to farmers to show their relative cost-effectiveness.
- We recommend progressive restriction in the use of antibiotics in pigs with an emphasis on CIA. This can be achieved by controlling the distribution of certain antibiotics for animal use with medicines available only on prescription.

BACKGROUND

Rising global concern about antimicrobial resistance (AMR)[i] has drawn attention to the

[i]In general, this study focuses on antibiotics. The term antimicrobials are used when we refer to standard terminology such as antimicrobial resistance, WHO Critically Important Antimicrobials or when we refer to published literature which use antimicrobials.

use of antibiotics in livestock[ii] with an estimated 70% of the antibiotic consumption in Europe being in the animal sector.[1] Many of the antibiotics commonly used in animals are categorised as Critically Important Antimicrobials (CIA) for treating humans according the WHO list of Critically Important Antimicrobials for Human Medicine (WHO CIA list). The WHO CIA list categorises Medically Important Antimicrobials into three categories: Important, Highly Important and Critically Important, and further divides the last category (CIA) into 'high priority' CIA including aminoglycosides, aminopenicillins and carbapenems; and 'highest priority' CIA including cephalosporins (third, fourth and fifth generation), glycopeptides, macrolides, polymyxin (colistin) and quinolones.[2 3] Of particular concern has been the use of CIA, the last-resort antibiotics normally reserved for the most severe infections in humans.[4–6] Indeed there is emerging evidence of the threat including a recent report describing the discovery of a plasmid-mediated colistin-resistant gene in commensal *Escherichia coli* from tests on pigs, pork products and humans in China.[7]

The use of antibiotics in pigs is complex and associated with the interrelating domains of animal health, animal welfare and economics. Antibiotics have been used routinely in farm animal production since the 1950s to treat, control and prevent disease and to increase productivity. Based on the predicted continued rise in global demand for livestock products, global antimicrobial consumption of livestock is predicted to increase by two-thirds over the next 10 years.[8] Within this sector, antimicrobial consumption is estimated to be highest in pigs, compared with chicken and cattle.[8] It has been a common practice for decades to use subtherapeutic doses of antibiotics in food-animals for a number of reasons: to control the spread of symptomatic infections between animals in close contact some of which may be subclinically infected; to prevent disease at points of high risk prior to the onset of symptoms, particularly when animals are under stress (eg, extreme weather, post vaccination or moving pen) and to improve production performance.[9 10] In pigs, antibiotics can be applied to whole groups including by mixing antibiotics into feed (medicated feed) or adding antibiotic powder or solution into drinking water (medicated water).[11–15]

In order to design and implement effective interventions that will reduce the unnecessary use of antibiotics in livestock, an understanding of current usage is essential. However, while data are available from high-income countries on the use of antibiotics in pigs, there are few studies from low- and middle-income countries. In 2018, Thailand was the first middle-income country in Asia to publish data on the total consumption of antimicrobials and reported that 3690 tonnes of antimicrobials were used in livestock production in 2017.[16] However, these data do not help understand use by animal species, production system or indications. To address this knowledge gap, this study aimed to explore the use of antibiotics and to estimate the total amount of antibiotics used in pig production in Thailand. A better understanding of antibiotic use in pigs, particularly in low- and middle-income countries, can help design appropriate intervention strategies to optimise the use of antibiotics in livestock production.

[ii]Domesticated animals kept mainly for meat, milk, egg and wool production.

METHODS

Thailand has very diverse livestock production systems, including large agro-industrial conglomerates, contract farming (where the buyer of fatteners also provides piglets, feed, vaccines and technical support to the contract farmers) and smallholder farms. A few large agro-industrial companies dominate the livestock production business with integrated operations including animal breeding, feed production and processing meat products. In 2017, about 19.5 million pigs were raised by 180 000 pig farmers, of whom 40% were smallholder farmers (less than 50 pigs per farm) raising indigenous pig breeds.[16 17]

In order to determine the patterns and total amount of antibiotic use in pig production in Thailand, mixed methods were used: a survey of farmers, secondary data analysis of a survey of feed mill operators and interviews with veterinarians. Data collection was carried out between March 2018 and December 2018.

Survey of pig farmers

Questionnaire development

To guide the development of the questionnaire, a literature review and exploratory interviews with five veterinarians were conducted. Following piloting, some questions were modified to suit the local context of pig production. The questionnaire consisted of both closed and open-ended questions covering general information about the farms (type of farm, number of workers, current number of pigs at different stages, health management), pig production, antibiotic use for prevention of infectious diseases, the source of antibiotics and medicated feed and farmers' knowledge and awareness about antibiotics and antibiotic resistance (online supplementary file 1).

Study site and sample population

The cross-sectional study was conducted in a province in the central region of Thailand, which has one of the highest pig populations, accounting for about 20% of total annual Thai pig production. The province has an area of about 5000 square kilometres subdivided into 10 districts, some with many pig and cattle farms, and some with very few. Based on the best available data and discussions with each district health office, the three districts with the highest number of pig farms were purposively selected and within each district, the two subdistricts with the highest number of pig farms were selected. Due to practical and budgetary constraints, a census and random sampling were not possible.

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Selection and recruitment process

Within the six selected subdistricts, all pig farmers were invited to participate in the study via an official letter. Village health volunteers and public health staff in the subdistrict health centres also encouraged pig farmers to participate.

Data collection

Between March 2018 and December 2018, interviews with pig farmers took place in the local health centres and were conducted face-to-face in Thai by 10 interviewers with a healthcare background, who were provided with basic information about pig farming as well as specific data collection training. Most interviews took between 45 and 60 min. Data were collected on tablets offline and synchronised onto a cloud-based server when the internet was available.

Data management and analysis

The data were exported into Microsoft Excel and Stata/SE 15 for cleaning and analysis. Based on the number of pigs on the farm at the time of the study, farms were categorised by size as per the Department of Livestock Development (DLD) definition: smallholder farm (less than 50 pigs), small commercial farm (from 51 to 500 pigs), medium commercial farm (from 501 to 5000 pigs) and large commercial farm (more than 5001 pigs). The farms were grouped by type into farrow-to-finish (breeder, suckling piglet, nursery pig, fattener), fattening (fattener-only) and breeding (breeder-only). Pig farms were also classified according to whether they held a Good Agriculture Practice (GAP) certificate from the DLD, indicating they had satisfied a certain practice standard. Farms were also classified into a contract or non-contract farm. Contract farmers provide animal housing and labour while the contracting company provides pigs, feed, medicines and technical support to farmers. Non-contract farmers are independent of contracting companies. Pig farms were also grouped based on whether they were members of a district or provincial cooperative.

Descriptive analyses including examination of means and frequencies were conducted to describe the characteristics of participants, reported pig health problems and the use and source of antibiotics on the farm. Univariate analysis was used to assess the association between the dependent variable (the use of antibiotics in pigs) and each independent variable (size of farm, type of farm, etc).

Survey of feed mills

To estimate the total amount of antibiotics mixed in pig feed in Thailand, we used data from a 2017 national survey of feed mills conducted by the International Health Policy Program (IHPP), Ministry of Public Health, which estimated the total national consumption of medicated feed by food-producing animal species.[16] The target population was the 238 feed mills registered with the DLD in 2018. IHPP met representatives of the 53 feed mills who were members of the Thai Feed Mill Association (TFMA) to explain the study in March 2018 prior to sending the survey form via email and fax. The official letter and survey form were also sent to the non-TFMA members (185 feed mills). In May 2018, all non-responders were followed up by phone.

The respondents were asked to extract the volume of antibiotics added to feeds from the feed production records which were usually kept in an electronic format. They were asked to fill in separate forms for each animal species for the calendar year 2017. For the secondary data analysis for this study, we extracted the data from the forms related to pigs and used the following variables:

- Name of the antibiotic (added to the medicated premix) according to the veterinary anatomical therapeutic chemical (ATCvet) classification system.
- Thailand Food and Drug Administration (Thai-FDA) market authorisation identification number.
- Trade name of the medicated premix and the market authorisation holder.
- Type and amount of the antibiotic added to the feed.
- Stage of pig production for which the medicated feed was intended.

Data management and analysis

Data from survey forms were entered into in Microsoft Excel and checked for completeness. Descriptive statistical analyses were performed using Stata/SE 15 software. Antimicrobial consumption was measured by kilograms of active ingredient per year (2017) and calculated as the volume of active ingredients multiplied by the strength of each antibiotic according to Thai-FDA market authorisation identification number. The market authorisation identification number and ATCvet codes were used to categorise different active ingredients of antibiotics used in the medicated feed and verified with Thai-FDA database. Consumption of each active ingredient was classified into different stages of pig production: breeding pig, pig less than 25 kg and fattener.

Interviews with veterinarians in the feed industry

To gain a deeper understanding of medicated feed we conducted in-depth interviews with veterinarians working in the feed mill industry. As there was no list or systematic way to approach all potential participants directly, we solicited the help of the TFMA to identify veterinarians fulfilling the following criteria: (1) they could provide information about the use of antibiotics in animal feed, (2) they had worked in the animal feed area for more than 10 years and (3) they were willing to be interviewed. Five veterinarians have met these criteria identified by the TFMA.

All interviews were conducted face-to-face in Thai by the researchers (AL and VT) between October 2018 and December 2018 using a semi-structured interview guide with three sections: common antibiotics mixed in feed including type, dosage and duration of use; common diseases and pathogens and common conditions in pigs that require the use of antibiotics. The interviews were audio-recorded and lasted between 1.5 to 2 hours. The key informants were also asked to complete a one-page closed-ended questionnaire and return it online within 14 days.

Data management and analysis

The interview audio recording was transcribed verbatim and anonymised by AL. The questionnaire data were transferred to Microsoft Excel and Prism 8 for data management and visualisation. The information in relation to the use of antibiotics was plotted over a period of pigs' age in weeks according to different stages including suckling piglet, nursery pig and fatteners. The maximum or minimum dose range was reported if there were different reports from more than one veterinarian. The information was returned to the informants for review.

Consent and ethical considerations

Prior to the interviews, pig farmers and feed mills' representatives were provided with a participant information form and asked to sign an informed consent form if they agreed to participate. Veterinarians working at feed mills gave their verbal consent to take part in an interview. Permission was requested to record the interview and written notes were also taken.

The data were manually checked for completeness and for entry errors by the researcher (AL). Information including the name of respondents and feed mills were deleted from the data set. Data were protected by access authentication with only the researcher (AL) able to access the survey and interview data.

Patient and public involvement

No patients were involved in this study.

RESULTS

Pig farmer survey

Characteristics of farmers and farms

In total, 84 of 102 farmers agreed to participate (response rate 82.4%). Over half (59.5%) were female and over two-thirds (72.6%) owned the farm that they worked on. About two-thirds (69.0%) of respondents were running commercial farms and the remainder were running smallholder farms. Over 60% of the farms were farrow-to-finish farms and over 30% were fattening farms. Thirty-six per cent of the farms had a GAP certificate. Twenty per cent were members of cooperative farms and only 9.5% were contract farms.

One-third reported a monthly income of less than THB 10 000 (US$ 317; US$ 1=31.5 THB) and over half reported a significant reduction in income over the last 3 years due to oversupply and lower market prices for live pigs. Of the 84 farmers, 21.4% reported spending an average of more than THB 50 000 (US$ 1590) per month on purchasing feed and a third (36.9%) reported spending an average of less than THB 1000 (US$ 32) on medicines. Marketing of the animals was variable with a third of farmers using brokers (32.1%), a fifth using pork retailers (21.4%) and 14.3% using both brokers and retailers. The remainder used a mixture of routes that mainly related to local consumption (online supplementary table A1).

Table 1 Use of antibiotics and medicated feed, and their sources, from the farmer survey

	Antibiotic (n=84, %)	Medicated feed (n=84, %)
Use of antibiotics or medicated feed		
▶ Use	62 (73.8)	11 (13.1)*
▶ Do not use	22 (26.2)	18 (21.4)
▶ Do not know	–	19 (22.6)
▶ Not willing to respond	–	36 (42.9)
Source of antibiotics and medicated feed		
▶ Pharmaceutical company/ feed mill	16 (25.8)	2 (18.2)
▶ Pharmacy	11 (17.7)	–
▶ Both pharmaceutical company and pharmacy	29 (46.8)	–
▶ In-house mixing	–	8 (72.7)
▶ Internet, online	–	–
▶ Others	6 (9.7)	1 (99.1)

*At least one feed formula at farm.

Across all pig age groups, gastrointestinal infections, respiratory infections and lameness were reported at least occasionally in the previous 12 months by more than half of respondents. In suckling piglets and nursery pigs, gastrointestinal infections were reported to have occurred regularly, 34.0% and 12.2%, respectively. In sows, reproductive infections were also reported as occurring by half of farmers (online supplementary figure A2).

Use of antibiotics at farm

Three-quarters of farmers reported using antibiotics, but most farmers were not willing to say that they used medicated feed or did not know whether or not the feed they used contained antibiotics. Pharmaceutical companies and pharmacies were common sources of antibiotics. The majority of farmers reported adding antibiotics to feed in-house. No farmer reported buying antibiotics or medicated feed online (table 1).

Oral and injectable antibiotics for disease prevention

About half of farmers reported using oral antibiotics (oral solution or adding solution or powder to drinking water, excluding medicated feed) and injectable antibiotics for disease prevention for the whole group. Overall, one-third of farmers reported using oral and injectable antibiotics in the CIA group. Half of the farmers used only one active ingredient in each stage of pig production (table 2A,B).

In total, farmers reported using 11 different antibiotic active ingredients for disease prevention. Although amoxicillin was the most commonly reported, about half

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Table 2 Number of farms, by type of pig, reporting (A) use of oral and injectable antibiotics for prevention, (B) number of different types of active ingredient used and (C) active ingredient categorised by WHO CIA list from the farmer survey

		By type of pig in farm (no. of farms)			
(A) Number (%) of farms	**All farms (n=84)**	**Sow (n=54)***	**Suckling pig (n=54)***	**Nursery pig (n=54)***	**Fattener (n=84)**
Reporting any use of antibiotics for prevention	48 (57.1)	31 (36.9)	26 (31.0)	17 (20.2)	26 (31.0)
Reporting any use of Critically Important Antimicrobials for human medicine for prevention	26 (31.0)	17 (31.5)	11 (20.4)	9 (16.7)	14 (16.7)
	All farms (n=48)†	Sow (n=31)	Suckling pig (n=26)	Nursery pig (n=17)	Fattener (n=26)
(B) Number (%) different types of active ingredient used					
One active ingredient	24 (50.0)	21 (67.7)	19 (73.1)	9 (52.9)	15 (57.7)
Two active ingredients	12 (25.0)	3 (9.7)	5 (19.2)	6 (35.2)	5 (19.2)
Three active ingredients	6 (12.5)	4 (12.9)	2 (7.1)	2 (11.8)	2 (7.7)
Four active ingredients	6 (12.5)	3 (9.7)	–	–	4 (15.4)
(C) Number of farms (%) reporting use of named active ingredients (WHO ATCvet code)					
(I) Critically important antimicrobials - highest priority					
Ceftiofur (QJ01DD90)	2 (4.2)	–	–	–	2 (7.7)
Enrofloxacin (QJ01MA90)	11 (22.9)	4 (12.9)	6 (23.1)	5 (29.4)	9 (34.6)
(II) Critically important antimicrobials - high priority					
Amoxicillin (QJ01CA04)	19 (39.6)	15 (48.4)	5 (19.2)	7 (41.2)	7 (26.9)
Gentamicin (QJ01GB03)	1 (2.1)	–	–	–	1 (3.8)
Kanamycin (QJ01GB04)	3 (6.3)	3 (9.7)	2 (7.7)	0	3 (11.5)
Streptomycin (QJ01GA01)	1 (2.1)	1 (3.2)	–	–	
(III) Highly important antimicrobials					
Chloramphenicol (QJ01BA01)	1 (2.1)	1 (3.2)	1 (3.8)	–	–
Lincomycin (QJ01FF02)	5 (10.4)	3 (9.7)	1 (3.8)	4 (23.5)	4 (15.4)
Penicillins, combinations with other antibacterials (QJ01RA01)	6 (12.5)	5 (16.1)	4 (15.4)	1 (5.9)	4 (15.4)
Tetracycline (QJ01AA07)	6 (12.5)	5 (16.1)	1 (3.8)	2 (11.8)	2 (7.7)
(IV) Important antimicrobials					
Tiamulin (QJ01XQ01)	3 (6.3)	2 (6.5)	–	–	1 (3.8)
Unknown	22 (45.8)	11 (35.5)	10 (38.5)	8 (47.1)	11 (42.3)

*Number of farms reporting raising pigs in this stage.
†Number of farms reporting antibiotic use for prevention.
ATCvet, veterinary anatomical therapeutic chemical; WHO CIA list, WHO list of Critically Important Antimicrobials for Human Medicine.

of farmers could not specify the name of the antibiotic used, either by trade name or active ingredient (table 2C)

Source of advice

Of all farmers, 81% reported having received advice on animal health, 77.4% on antibiotic administration and 42.9% on the use of feed. It is worth noting that most farmers sought advice on animal health management (45.6%), antibiotics (45.8%) and feed (44.4%) from 'others'. These were unqualified sources such as relatives, peers, other farmers or someone they called 'doctor' who may or may not have been a veterinarian. Pharmaceutical companies and feed mills were also a source of advice for farmers (online supplementary file 2 table A2).

Factors associated with the use of antibiotics for prevention

The farmers' characteristics that appear to be risk factors for using antibiotics for prevention in the past 12 months are shown in table 3. The use of antibiotics for prevention of disease was significantly associated with farmers' experience in raising pigs, farm income, farm type, having received advice on animal health and belonging to a farm cooperative.

Feed mill survey

Characteristics of feed Mills

Of the 238 questionnaires distributed, 31 were returned (response rate 13%). However, it is estimated that the 31 feed mills that did participate in the survey, account for

Table 3 Factors associated with the use of antibiotics for prevention of disease in the past 12 months from the farmer survey

Characteristics	Categories	Number of farms with data available	Use of antibiotic for prevention (%)	OR (95% CI)	P-value
Farmer's highest level of education	Primary school	37	17 (46.0)	rv	
	Secondary school and higher	47	30 (63.8)	2.28 (0.92–5.65)	0.10
Farmer's experience	≤10 years	37	16 (43.3)	rv	
	>10 years	47	31 (66.0)	2.82 (1.01–8.08)	0.04*
Farmer's knowledge [a]	Score<60%	29	14 (48.3)	rv	
	Score≥60%	52	32 (61.5)	1.86 (0.72–4.75)	0.19
Size of farm	Smallholder farm	26	11 (42.3)	rv	
	Commercial farm	58	36 (62.1)	2.54 (0.96–6.71)	0.05
Type of farm	Farrowing to finisher farm	54	37 (68.5)	rv	
	Fattening	30	10 (33.3)	0.33 (0.12–0.87)	0.02*
GAP certified farm	No	53	26 (49.1)	rv	
	Yes	31	21 (67.7)	2.54 (0.96–6.71)	0.05
Member of cooperative farm	No	67	33 (49.3)	rv	
	Yes	17	14 (82.4)	7.73 (1.49–40.01)	0.01*
Contracted farm	No	76	42 (55.3)	rv	
	Yes	8	5 (62.5)	1.28 (0.28–5.80)	0.75
Household income per month	Less than BHT 50,000	47	21 (44.7)	rv	
	More than BHT 50,000	23	18 (78.3)	4.46 (1.32–15.05)	0.01*
Advice on animal health	Not receiving advice	16	5 (31.3)	rv	
	Receiving advice	68	42 (61.8)	3.78 (1.12–12.73)	0.02*

*Statistically significant at p<0.05.
†Knowledge: five true/false statements in relation to the use of antibiotics and AMR, taken from the AMR module in the 2017 National Health Welfare survey form.
AMR, antimicrobial resistance; GAP, Good Agriculture Practice; rv, reference value.

approximately 80% of the total national production of pig feed (data from a market survey via personal communication). Twenty-five out of the 31 participating feed mills reported that they had added antibiotics to some feeds in 2017, while the remaining 6 feed mills denied having done so.

Use of medicated feed

Based on the analysis of the feed mill survey data, the total amount of active ingredients mixed into medicated feed for pigs was 843 tonnes in 2017 (table 4). Among these, the top three active ingredients were amoxicillin, contained in almost half of feeds, then halquinol and tiamulin. Of the total production, 64.3% of medicated feed contained antibiotics on the CIA group, including an estimated total of over 40 tonnes of colistin.

Of the total amount of antibiotics added in medicated feed, 39.7% was targeted at suckling and nursery pigs, followed by fatteners (37.3%) and breeding pigs (23.0%). Regarding choices of antibiotics across the different stages of pig production, the majority of colistin (87.2%) and haquinol (60.4%) were intended for suckling and nursery pigs, while the majority of tylosin (81%), lincomycin (61.7%) and tiamulin (44.3%) was added to feed for fatteners. Most bacitracin (87.6%) and oxytetracycline (83.5%) were added to feed for sows (figure 1).

Feed industry veterinarian interviews

All five of the animal feed industry veterinarians who were interviewed had practised in the animal feed field for more than 20 years (maximum=37 years). They were asked to explain the use of common antibiotics in relation to common diseases and common management at different stages of pig production (by week) (figure 2). Amoxicillin and tiamulin were commonly recommended for use at all stages; the dose range was between 300 and

Table 4 Amounts of active ingredients mixed in medicated feed from the feed mill survey, categorised by WHO CIA list

	Amount of antibiotic added to medicated feed in kg			
		By stage of pig production		
Active ingredient (WHO ATCvet code)	All feeds (kg, %)	Feeds for breeding pig (sow)	Feeds for pigs <25 kg (suckling and nursery pigs)	Feeds for fatteners
(I) Critically important antimicrobials highest priority	145 805.3 (17.3)	18 487.3	62 399.5	64 918.6
Colistin (QA07AA10)	40 378.5 (4.8)	2251.7	35 209.4	2917.4
Fosfomycin (QJ01XX01)	767.2 (0.1)	79.6	11.2	676.4
Kitasamycin (QJ01FA93)	9435.4 (1.1)	2153.7	588.9	6692.9
Tilmicosin (QJ01FA91)	54 738.9 (6.5)	10 271.0	21 045.6	23 422.3
Tylosin (QJ01FA90)	38 507.1 (4.6)	1764.2	5543.5	31 199.4
Tylvalosin (QJ01FA92)	1978.2 (0.2)	1967.1	0.9	10.2
(II) Critically important antimicrobials high priority	395 971.6 (47.0)	102 994.7	152 266.0	140 710.9
Amoxicillin (QJ01CA04)	395 950.1 (47.0)	102 994.7	152 244.5	140 710.9
Apramycin (QJ01GB90)	21.5 (<0.1)	–	21.5	–
(III) Highly important antimicrobials	48 328.3 (5.7)	17 851.5	11 247.7	19 229.0
Chlortetracycline (QJ01AA03)	32 889.4 (3.9)	11 853.7	7515.2	13 520.4
Doxycycline (QJ01AA02)	2686.6 (0.3)	1661.2	881.7	143.7
Lincomycin (QJ01FF02)	7881.0 (0.9)	270.9	2749.2	4860.9
Oxytetracycline (QJ01AA06)	4871.3 (0.6)	4065.7	101.6	704
Sulfadimidine (QJ01EQ03)	240.2 (0.1)	–	24.0	216.1
(IV) Important antimicrobials	128 519.1 (15.3)	41 809.6	33 433.7	53 275.9
Bacitracin (QA07AA93)	9285.3 (1.1)	8136.5	710.1	438.7
Tiamulin (QJ01XQ01)	119 233.8 (14.2)	33 673.1	32 723.6	52 837.2
(V) Antimicrobial classes currently not used in humans	123 707.1 (14.7)	12 763.9	74 844.6	36 098.7
Avilamycin (QA07AA95)	281.5 (<0.1)	–	143.0	138.6
Bambermycin (QA07AA96)	78.2 (<0.1)	–	78.2	–
Halquinol (QA07A×91)	123 347.4 (14.6)	12 763.9	74 623.4	35 960.1
Total	842 571.7	193 906.9	334 215.5	314 449.2

ATCvet, veterinary anatomical therapeutic chemical; WHO CIA list, WHO list of Critically Important Antimicrobials for Human Medicine.

400 ppm (1 ppm equivalent to 1 mg of active ingredient per 1 kg of feed) and 150 and 200 ppm, respectively. Halquinol and colistin were commonly recommended for addition to medicated feed for suckling piglets and nursery pigs for the prevention of gastrointestinal tract infection. Tylosin, tilmicosin and chlortetracycline were recommended for fatteners. According to the indication label on feed packages and veterinary supervision, the duration of antibiotic use was commonly about 4 to 6 weeks. No medicated feed was said to be provided to fatteners 1 month prior to slaughter (20^{th} to 24^{th} week).

The veterinarians reported that the choice of active ingredients in the feed was designed for both treatment and prevention of common diseases and animal health management at different stages of pig production, particularly when the animals are under stress or prone to infection. For example, during the first week, piglets undergo teeth and tail clippings and castration. During the second week, pigs start having feed and are weaned in the fourth week. The feed is changed at the fifth, ninth, thirteenth and nineteenth weeks. Between the second and seventh week, pigs are vaccinated against common infectious diseases. These procedures, including handling animals and movement between pens, cause pigs stress.

DISCUSSION

Use of antibiotics by different active ingredients

To our knowledge, this is one of the first studies to assess in detail antibiotic use in pig production in a low- or middle-income country. This study indicated that amoxicillin, a broad-spectrum antibiotic, was the most used oral and injectable antibiotic for prevention of disease (39.6% of total farms) and in the medicated feed (47% of the total amount of antibiotics). The national surveillance consumption data confirm that amoxicillin was

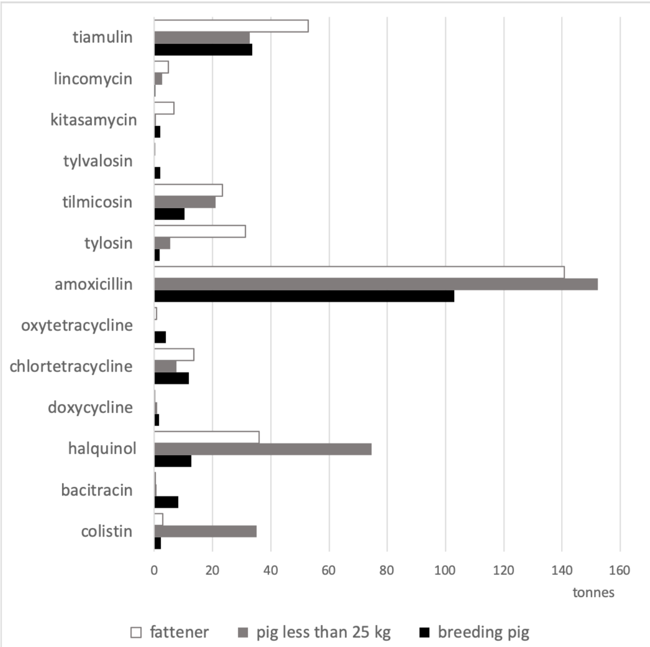

Figure 1 Amount (tonnes) of active ingredients mixed in medicated feed from the feed mill survey, by stage of pig production (antibiotics including 1 tonne at less of the active ingredient).

the most used antibiotic in both humans and animals, and that a quarter (24.6%) of total consumption was in animals.[16] In animals, amoxicillin is reportedly widely used for prophylaxis and treatment of generalised infections in many countries. [18 19] However, when given orally to pigs via medicated feed, absorption and bioavailability are low [20–23] . This may lead to chronic exposure of gut microbiota to amoxicillin and an associated high selective pressure in the intestine of animals, making them more likely to develop antibiotic resistance. [24]

Our previous reviews observed differences in antibiotic use among stages of pig production, mainly due to differences in diseases, epidemiology and administration route of the available drugs.[19] In this study, gastrointestinal infection reportedly mostly affects suckling piglets and nursery pigs. These are periods when pigs are most susceptible to getting diarrhoea from common pathogens such as post-weaning *E. coli* and salmonellosis. The use of colistin in pigs has been shown to lead to the development of a plasmid-mediated colistin-resistant gene in humans in China.[7 25] Consequently, in 2018, DLD restricted the use of colistin for disease prevention in livestock, and farmers replaced it with halquinol. Halquinol is not used in humans and not listed on the WHO CIA list. It is now widely used in pig and poultry production for prevention control and treatment of diarrhoea caused or complicated by *E. coli* and Salmonella spp in pigs. However, the maximal residue limit of halquinol has not been established by Codex Alimentarius due to a lack of information about the characterisation of residues in animal tissues.[26 27]

Feed industry veterinarians considered that the use of antibiotics in the fattening period for disease prevention was crucial for farms, particularly those which could not effectively control common diseases. Antibiotics were used in the medicated feed for fatteners, including lincomycin, tiamulin and tylosin. Tylosin belongs to the macrolides class of antibiotics and is classified as a highest priority CIA. Macrolides are used to treat infections in humans and are also reserved as second-line treatments

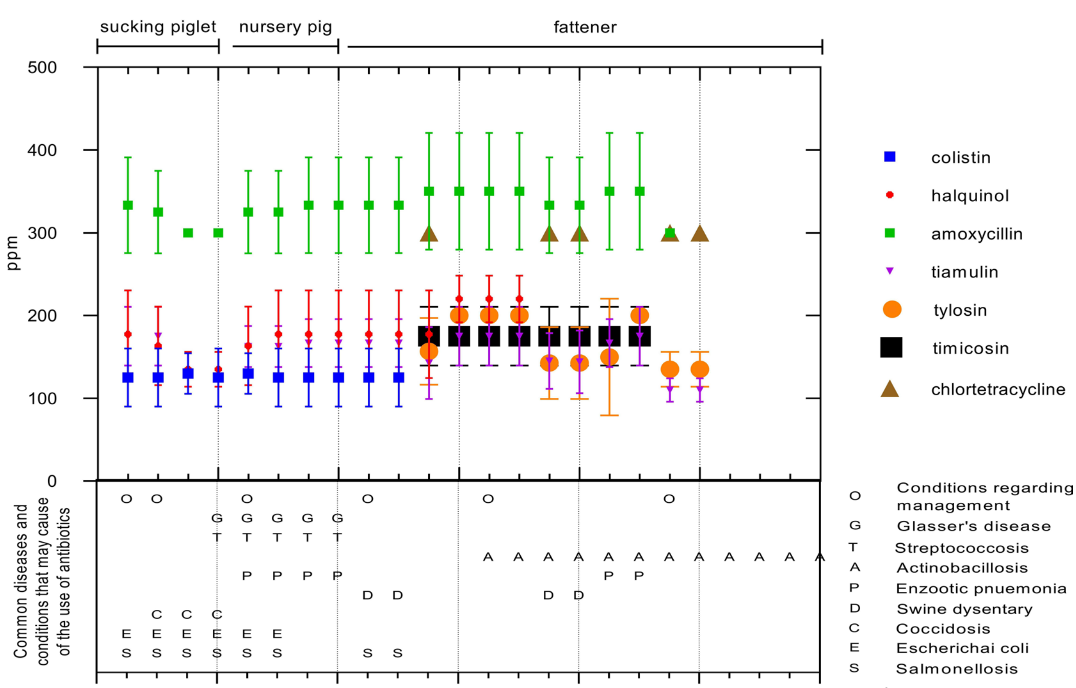

Figure 2 Common active ingredients in medicated feed, dose and duration of use, synthesised from the interview with veterinarians.

for patients who are allergic to penicillins.[28] Resistance to macrolides in human enterococci and enterococci from animal sources in Europe [29 30] has been well documented. High levels of resistance to tylosin in several bacteria including zoonotic pathogens are also reported in pigs in many European Union countries; for example, 43% to 59% of *Streptococcus suis* isolates are tylosin resistant in the UK,[31] and 69% of all pathogens collected from pigs in 2017 are resistant to tylosin in France.[32] In Thailand, a high level of *S.suis* isolates resistant to erythromycin (belonging to macrolides class) (80.9%) were found in human patients and pigs.[33] Other potential zoonotic bacteria such as *Salmonella* spp showed a high level of resistance to common antibiotics including tetracycline (82.6%) and ampicillin (81.4%) in Thailand. In food chain, 53.7% of Salmonella and 60.6% of *E. coli* are resistant to ampicillin. Resistance of *E. coli* to colistin is low, 3% and none are resistant to meropenem.[34]

Use of antibiotics at farm level

Our results show that 57.1% of farmers reported the use of oral and injectable antibiotics for prevention. Common sources of antibiotics for farmers were pharmacies and pharmaceutical companies. In Thailand, most antibiotics are classified as dangerous drugs, which do not require a prescription but do need to be dispensed by licensed pharmacists or veterinarians at licensed pharmacies; a few are classified as 'special control medicines' and require a prescription. In 2017, there were about 24 000 retailers and wholesalers licensed for pharmaceutical sales.[35] This large number of antibiotic sellers serving human health needs provides easy access to antibiotics for use in animals. In addition, pharmacists may have limited knowledge about pig disease and farm management due to the absence of veterinary medicine content in the pharmacist undergraduate syllabus.

Pharmaceutical companies can sell antibiotics to livestock producers through veterinarians (mostly in commercial farms). Therefore, veterinarians are likely to play a dual role as animal healthcare providers and drug distributors leading to a conflict of interest where they make a direct profit from the sales of medical products including antibiotics. In the Netherlands, the government decoupled the functions of prescription from the selling of drugs by veterinarians.[36] There is currently no similar intervention in Thailand to address the potential financial incentives for both veterinarians and pharmacists to sell medical products for animals.

Factors influencing the use of antibiotics in farms

Farmers' number of years' experience and belonging to a farm cooperative were associated with the use of antibiotics for prevention. Experienced farmers may have an established protocol or programme of using antibiotics without a detailed examination of animals' health conditions. Belonging to a farm cooperative probably increased the opportunity among farmers to exchange information about animal health and antibiotic use. Some studies have found that the opinions of peers affected farmers' decision-making on antibiotic use.[37–39] In addition, farms with higher incomes were more likely to use antibiotics for prevention, perhaps reflecting greater ability to purchase.

The majority of farmers reportedly received advice on animal health and antibiotic use from unqualified sources, possibly contributing to the positive correlation between advice on animal health and high level of antibiotic use for prevention in this study. Other studies have shown that farmers perceive veterinarians to be the most trusted information source on disease control[40] and influence their decisions.[38 41]

However, other risk factors with a lower impact may not have been detected. Possible factors associated with antibiotic use for prevention reported in other studies include the density of pig population in the area and the number of pigs on the farm,[42–44] production systems,[45] the type of farm[13 46 47] and pig age groups.[12 48 49]

Medicated feed

In this study, based on data from the feed mill survey, the largest proportion of medicated feed was applied to suckling and nursery pigs (39.7%) and fatteners (37.3%), similar to some other studies.[48–50] This study estimated that at a national level, the total volume of antibiotics mixed into pig feed was around 843 tonnes. The 2017 national antimicrobial consumption report[16] states that a total 3690 tonnes of veterinary antimicrobials were used by all food-producing animals, of which 2007 tonnes (54%) was premix for medicated feed however these data do not provide a breakdown by animal type. Our estimation from the feed mill survey is likely to be an underestimate of the true volume of antibiotics in medicated feed due to a number of reasons. One being that many farmers add antibiotics to the feed in-house at the farm level. For example, the farm survey indicated that 72.7% of farmers produced their own medicated feed using mixers. In addition, the mix of medicated feed in farms implies a lack of quality control in ensuring homogeneous distribution of antibiotics in the feed, a concern also in Europe.[51] This is an area which requires effective regulation.

Policy implications

The majority of antibiotics added to the medicated feed (64.3% of total amount of medicated feed) and used as oral and injectable medications at farm level (31% of total farms) belonged to the category of Critically Important Antimicrobials for human health. Recently in March 2018, in response to the AMR threat, the DLD stipulated that medicated feed can only be produced, sold and used with a veterinary prescription. It also prohibited the addition of five classes of antibiotics (polymyxin, penicillins, fluoroquinolones, fosfomycin and cephalosporins) to medicated feed for disease prevention. Additionally, cephalosporins are not allowed in medicated feeds for any indications.[52]

In order to promote antibiotic stewardship in animal health, the use of antibiotics should be based on guidelines with clear guidance on the indication for use, choice of antibiotic, dose and duration and these should be based on local microbiological surveillance data. Where possible non-WHO CIA list antibiotics should be recommended, and where this is not possible then antibiotics in the lower tiers on this list should be recommended first. Ideally, the use of antibiotics in the CIA category should be limited to treatment, with specific indications and only when there is no lower tier alternative. However, one challenge is that there are currently very few such guidelines available in veterinary field, especially in low- and middle-income countries.[53] The development and dissemination of such guidelines is an important priority.[54]

For disease prevention, ideally the use of antibiotics should be avoided according to the WHO and European Union guidelines for the use of antibiotics in animals.[10 55] For alternatives to antibiotics, farmers may consider improving husbandry and farm management such as good ventilation, good feed quality and water and farm bio-security. Vaccinations are likely to play an important role in reducing the risk of infection and the need for antibiotics for prevention. The use of probiotics or prebiotics and immunomodulators such as natural herbal remedies have also been proposed as alternatives.[56]

Limitations

This study had some limitations. First, as described in our recent review, there is no standard approach to collecting data on the volume of antibiotics used on farms, and a wide range of methods have been applied for example farm-based survey, inspection of discarded antibiotic packaging in bins and veterinary prescription data.[57] In high-income countries where recording systems are available at farms, antibiotic prescription or treatment records are the most common sources of farm-level data on antibiotic use. These provide accurate data on the type of antibiotic, indications, doses and duration, the number of animals receiving antibiotics and can inform the relationship between antibiotic use and antibiotic resistance. However, none of these data collection methods were applicable in this study: antibiotic treatment and medicated feed use were often not recorded; feed packages lacked labels and counting discarded packages of antibiotics was not feasible (online supplementary figure A1). The collection of on-farm data is thus a great challenge in a country such as Thailand, and demanded the mixed methods used here. Changing the regulations to require a prescription is critical to improved audit data.

Second, apart from the large proportion of farmers who did not know if they used antibiotics in feed as the feed package did not label antibiotic content, a large proportion of farmers were not willing to disclose this. In 2018, the DLD issued a new regulation which mandated all feed mills to print on all medicated feed the antibiotics' names and concentration (PPM), and all farmers were required to keep records of veterinary prescriptions and administration. This should help in the monitoring of antibiotic use on farms, if the regulation is effectively enforced and monitored.

The third challenge was the sample representativeness. For reasons of feasibility, the survey of pig farms was conducted in only one province. Additionally, the list of pig farms was out of date and many farms especially smallholder farms had closed down due to a significant reduction in the market price for pigs over the last few years. This meant that it was difficult to conduct a random selection of farms across the province and instead a complete sampling of farms in selected subdistricts was carried out. However, the full range of farm types was included: from smallholder farms with only a few pigs through to large commercial farms with thousands of pigs and the province with one of the highest number of farms was chosen. Moreover, an outbreak of African swine fever was reported in neighbouring countries[58] over the data collection period, probably affecting the willingness to be part of the study. Due to a small sample size, only univariate analysis could be conducted, and it revealed that the use of antibiotics in pig farms was significantly associated with certain farm characteristics such as belonging to a farm cooperative, type of farm and farmer's income.

Nonetheless, this study covered 84 pig farms with a high response rate of 82.4%. Of 18 farmers who did not participate in the study, 12 smallholder farmers (26%, 12/46 farmers in the studies areas) and 6 commercial farmers (11%, 6/56 farmers in the studies areas). In terms of geographical distribution, among six subdistricts, the response rate in two subdistricts was 100% and about 90% in other three subdistricts. The response rate was low in only one subdistrict (38%) (online supplementary file 3 tableA1). The results are therefore likely to represent a significant proportion of pig production in the province, and meaningful conclusions about farmers' antibiotic use in the studied province can be drawn.

Besides, the farm survey data was supplemented by data from the feed mill survey. Although only 31 feed mills participated, they included the large agro-industrial conglomerates responsible for an estimated 80% of the national production of medicated feed and are therefore an important target for future interventions.

CONCLUSION

This is one of the first studies outside high-income countries to obtain information on the critical question of antibiotic use in pig farming. It used multiple approaches to investigate the use of antibiotics in pig production in Thailand. From the data, we established patterns of antibiotic use and estimated consumption of antibiotics through farmer and feed mill surveys. Our results clearly show the majority of antibiotics used in Thai pig farms are considered the Highest and High Priority Critically Important Antimicrobials for human health according to the WHO-CIA list, with concerning implications in terms of the potential for AMR in pigs and humans.

We recommend progressive restriction in the use of antibiotics, in particular, those highest tier on the WHO CIA list. This includes through controlling distribution by reclassifying certain antibiotics as prescription-only medicines and restricting the use of CIA for specific indications and guided by local microbiological and sensitivity evidence. The DLD should strengthen the veterinary service system at all levels to improve access of farmers, smallholder farms in particular, to quality animal health information and potential alternative interventions to antibiotic use including farm management improvement, vaccines and immunomodulators.

Alternative solutions need to be carefully tested for their cost-effectiveness in comparison to the antibiotics they would replace. Those solutions with the greatest impact need to be demonstrated to the farmers in order to build confidence in new solutions. Future studies about factors contributing to the use of antibiotics are required to fill these important knowledge gaps and introduce effective policies.

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Competing interests None declared.

Patient consent for publication Not required.

Ethics approval The study protocol was approved by the Research Ethics Committee at the Thai Ministry of Public Health's Institute for Development of Human Research (reference number: IHRP2018007) and the London School of Hygiene and Tropical Medicine (reference number: 14860).

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Data availability statement Data are available upon request. The questionnaire survey form is available within the article supplementary material. Due to the ethically sensitive nature of the research, interview transcripts will be made available to researchers only, on condition they provide evidence of ethics approval and sign a consent form. Other data that support the findings of this study are available on request from the corresponding author.

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Chapter 6 Qualitative study: Factors contributing to the use of antibiotics in pigs in Thailand

(Cover sheet on next page)

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Understanding antibiotic use for pig farming in Thailand: a qualitative study

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Abstract

Background: Antimicrobial resistance (AMR), recognised as a serious and growing threat to global health, is promoted by multiple drivers, including antibiotic use in the livestock sector. Thus, understanding factors influencing antibiotic use in livestock production is essential to the design and implementation of effective interventions to reduce AMR. This qualitative study aimed to explore the experiences and views of the key actors associated with the use of antibiotics for pig farming in Thailand, from local farmers to officers in central government institutions.

Methods: A total of 31 in-depth interviews were conducted with different categories of actors: pig farmers (n = 13), drug retailers (n = 5), veterinarians (n = 7), government officers (n = 3) and representatives of animal and human health associations (n = 2). Themes emerging from the interviews were identified and explored using thematic analysis. In addition, direct observations were conducted in the pig farms.

Results: The findings highlight the multi-faceted nature of the views and practices that may contribute to misuse or overuse of antibiotics in the study locations, including misconceptions about the nature of antibiotics and AMR (particularly among smallholders), lack of facilities and financial means to establish an antibiotic-free farm, lack of sufficient training on AMR and antibiotic prescribing for veterinarians, the profit motive of pharmaceutical companies and their ties to farm consultants, and lack of sufficient regulatory oversight.

Conclusions: Our study indicates a clear need to improve antibiotic use for pig production in Thailand. Farmers need better access to veterinary services and reliable information about animal health needs and antibiotics. Innovative investments in biosecurity could improve farm management and decrease reliance on antibiotics, although the cost of these interventions should be low to ensure wide uptake in the livestock sector. Lastly, further development of professional training and clinical guidelines, and the establishment of a code of conduct, would help improve antibiotic dispensing practices.

Introduction

Antimicrobial resistance (AMR), recognised as a serious and growing threat to global health, is driven by many factors including antibiotic use not only in humans but also in animals. In many countries, antibiotics are widely applied to promote growth in livestock in addition to preventing and treating infections [1]. This practice has potential risks to human health that need to be addressed [2–4]. Of great concern is the emergence of resistance to those antibiotics categorised by the WHO as Critically Important Antimicrobials (CIA), such as colistin, which are reserved for treating the most severe human infections [5].

In the pig sector, intensive use of antibiotics has promoted resistance of both commensal and pathogenic bacteria [6, 7], particularly in low- and middle-income countries (LMICs) [8, 9]. In view of this, research efforts have been made to explore the factors influencing

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antibiotic use in pig farms [10–16]. A recent systematic review showed that antibiotics are commonly used during the suckling and post-weaning stages of production; in addition, the same review found that specific farm characteristics (such as the density of pigs) influence the use of antibiotics [16]. Apart from the factors associated with pig production, knowledge and understanding of antibiotics among farmers are also important. A number of studies found that farmers may have limited knowledge of the names of antibiotics and their correct usage [10, 12]. For example, a study in China found an association between poor knowledge of antibiotics and inappropriate use in the farms [11]. Findings about the impact of legislation and government policies on antibiotic use have been mixed. In five European countries, farmers were worried about the implications of legal provisions to reduce antibiotic use, particularly their impact on farm maintenance and costs [13]. In two other surveys in Europe, legislation regarding veterinary drugs was perceived to influence prescribing practices more than the price of antibiotics, market demand or clinical guidelines [14, 15].

Despite these studies, our knowledge of practices influencing the agricultural use of antibiotics is still scarce, especially in countries where resources to conduct research and evaluation are more limited. Considering this gap in knowledge, this article reports findings from a study which aimed to explore the experiences and views of key *actors* associated with the use of antibiotics for pig farming in Thailand, from local farmers to officers in central government institutions. After a description of the study context, methods, and the presentation of findings, implications of the study for the design and implementation of action plans on AMR are discussed.

Materials and methods

Study context

The Thai agricultural sector accounts for approximately 10% of GDP (USD 42 billion in 2018) with livestock production, including pigs, contributing around USD 400 million [17]. In 2017, nearly 19.5 million pigs were raised and slaughtered, mainly for the domestic market [18, 19]. Since the 1960s, pig production in the country has increasingly shifted from smallholder farming for household consumption to intensive commercial production for the growing urban markets. The pig sector is dominated by a small number of large agro-industrial conglomerates although a diversity of production systems coexist [20], characterised by different levels of bio-security [21]. In smallholder farms, pigs receive a variety of feed including leftover food and vegetables. Such farms have often limited access to veterinary services and antibiotics, while in commercial farms antibiotics are usually applied to whole groups of pigs through medicated feed, either commercial or mixed in the farm. In 2017, it was estimated that about 3,690 tonnes of antibiotics were given to food-producing animals, of which about 50% belonged to the CIA group [19]. To improve farm management, the Thai Department of Livestock Development (DLD) grants Good Agriculture Practices (GAP) certificates to farms which comply with standards of animal husbandry [22]. GAP-certified farms are required to have designated veterinarians to supervise the control, prevention and treatment of animal diseases, including the use of antibiotics. GAP certification is voluntary.

Study design

This qualitative study was conducted between March 2018 and January 2019 in a province in the central region of Thailand, which accounts for about 20% of annual domestic pig production and hosts different production systems, from smallholders to large industrial farms. The study was part of a larger project which included a cross-sectional survey of antibiotic use among pig farmers in six sub-districts with the highest number of pig farms in the same province [23]. The research design for the qualitative study was meant to capture the diversity of actors in the pig farming sector that may influence antibiotic use at different level of analysis, from disease prevention and control in the farms to the wider regulatory environment. In practice, data collection primarily involved interviews with farmers to explore their views and practices related to antibiotic use. In parallel with the interviews with farmers, observations were conducted to gain a better understanding of management practices in the same farms. In order to capture the diversity of perspectives, interests, and incentives which may influence antibiotic use, veterinarians, drug retailers, industry representatives, and government officers were also interviewed.

Participant selection

Participants in this study were recruited from the larger sample of 84 farmers included in the cross-sectional survey [23]. In total, 11 out of the 84 farmers agreed to participate in the study reported here. Two farmers who did not use antibiotics were purposively selected through a snowball sampling technique. In addition, informants who could provide further insight into the use of antibiotics for pig production were approached at relevant organisations, including government offices, the Thai Feed Mill Association, and associations of human and animal health professionals. The first author contacted potential informants to ask if they were able and willing to participate in the study.

Data collection

Drawing from previous studies [10, 24], the guidelines for the interviews with farmers covered: (a) animal health and farm management, (b) pig production and market demand, (c) relationships with other farmers, veterinarians, pharmaceutical companies, and (d) regulation and policy on antibiotic use (see Additional file 1). Interviews with other categories of participants were tailored to their role and the expertise they could bring to this study. Interviews were conducted face-to-face by the first author and lightly structured to let participants express their own views. Interviews were conducted either in the farms or the offices or shops of key informants. On average, interviews lasted two hours. Written field notes were taken and, where permission was given, the interview was audio-recorded. After the interviews with pig farmers, the researcher sought permission to conduct observations in their farm. During the observations, the researcher examined activities of farm workers, the feed labels, the medicines used in the farm, and general sanitation and farm management practices. In addition, the researcher walked through the farms and engaged in casual conversations with farmers and farm workers. To prevent cross-infection between farms, farm visits were restricted to no more than one a week.

Data processing and analysis

The interview audio recordings were transcribed verbatim and anonymised by the researcher (AL). Data were imported into the software NVivo 12 for qualitative analysis. The researcher (AL) generated initial codes after iterative reading of the transcripts. The field notes were reviewed in parallel with the transcripts. Then two researchers (AL and VT) identified and organised themes and sub-themes. To reduce subjective bias, the researchers (AL, ML, SY and VT) discussed emerging findings and their interpretation throughout the process of analysis. In qualitative data analysis, themes are considered robust when they are cohesive and meaningful within the entire data set [25]. Thus, consistency both within the individual interviews and across respondents by triangulation was assessed.

Results

Profiles of participants and studied farms

Table 1 shows the profiles of the 31 participants interviewed, which consisted of farmers, animal drug retailers, veterinarians, and informants at government offices or relevant professional associations. Table 2 shows the characteristics of the 13 farms, which ranged from a smallholder farm with only one sow and five piglets to a large commercial farm with more than 10,000 pigs and a monthly income of more than US$15,900. Six farms were DLD GAP-certified, one was a contracted farm and five farms were members of a cooperative. Three were fattening farms and ten were farrow-to-finish farms. Two farms were antibiotic-free. Research observations were allowed in six farms with variable characteristics, including "backyard" production and large commercial farms.

Use of antibiotics in pig production: views and experiences of different actors

The analysis of the interviews revealed diverse and at times competing views of different actors in the agricultural sector about antibiotic use – the pig farmers, health professionals, and the pharmaceutical industry, considered in turn in the sections below.

Pig farmers

Perceived health benefits and economic value of antibiotics

All the pig farmers interviewed believed that some form of medication, including antibiotics, was necessary to maintain animal health, and control and prevent disease.

> *Medicines are really important in my farm. Without medicines, my pigs would be very ill. Antibiotics protect my pigs from becoming worse. [Fs02, female, > 40 years old, non-GAP farm]*

Table 1 Respondents' profile

	Total	Gender		Age (years; mean, range)	Work experience (years; mean, range)
		Male	Female		
1. Pig farmers	13	10	3	47.9 (35–66)	22.7 (5–50)
2. Animal drug retailers	5	3	2	40.8 (30–48)	15.1 (3.5–24)
3. Veterinarians	8	5	3	49 (31–61)	22.8 (5–37)
4. Government officers	3	2	1	37.3 (31–50)	10 (4–20)
5. Representatives of health and animal professional associations	2	1	1	62.5 (60–65)	10 (8–12)
Total	31	21	10	47.8 (30–66)	16.1 (3.5–50)

Table 2 Farm characteristics

	Size of farm	Number of pigs		GAP farm	Contracted farm	Member of cooperative	Type of farm	Income from selling pigs per month (US$ 1 = 31.5 THB)	Use of antibiotics	Farm visit
		Number of sows	Number of other pigs							
1	Smallholder	1	5	N	N	N	FtoF	< US$317	Y	Y
2	Smallholder	5	25	N	N	N	FtoF	< US$317	Y	N
3	Smallholder	4	12	N	N	N	FtoF	< US$317	Y	N
4	Commercial (S)	0	60	N	Y	N	Fattening	US$317–1590	Y	Y
5	Commercial (S)	10	90	N	N	N	FtoF	US$3,170–15,900	Y	N
6	Commercial (S)	40	195	N	N	Y	FtoF	Not willing to respond	Y	N
7	Commercial (S)	0	500	Y	N	Y	Fattening	Not willing to respond	Y	N
8	Commercial (S)	50	200	Y	N	N	FtoF	US$3,170–15,900	N	Y
9	Commercial (M)	140	600	Y	N	N	FtoF	US$3,170–15,900	Y	Y
10	Commercial (M)	600	3000	Y	N	Y	FtoF	US$3170–15,900	Y	N
11	Commercial (M)	0	5000	Y	N	N	Fattening	US$3170–15,900	N	Y
12	Commercial (L)	2000	> 10,000	N	N	Y	FtoF	> US$15,900	Y	Y
13	Commercial (L)	2500	> 10,000	Y	N	Y	FtoF	> US$15,900	Y	N

GAP good agriculture practice, *FtoF* farrow-to-finish fa m

At the suckling and nursery stages, the piglets are so vulnerable. I usually apply antibiotics to 100% of them. Whether or not they are sick, I must use antibiotics for prevention... [Fc07, male, > 50 years old, GAP-certified farm]

Many farmers explained that antibiotics are an affordable approach to reduce pig mortality. One farmer estimated that medicated feed cost only 2.7% more than non-medicated feed and administering antibiotics to the whole herd via medicated feed was less labour intensive than individual treatment.

I think that antibiotic use is a cheap solution... and affordable... The cost of production is not really different whether we add medicine [antibiotics] or not. For example, now the cheapest medicine is chlortetracycline. For nursery pigs, the feed mixed with chlortetracycline is baht 22.60 compared with baht 22 per kilogram of regular feed [without antibiotics]. It doesn't add much to my budget. [Fc12, male, > 30 years old, non-GAP farm]

Pig farmers' knowledge of antibiotics and awareness of AMR

Knowledge of antibiotics differed greatly amongst pig farmers. None of the three smallholder farmers understood the word "antibiotics" *(yaa-pati-cheewana)* while commercial farmers could generally differentiate between antibiotics and other medicines. Most farmers who understood the meaning of antibiotics said they used them according to the indications on the package labels or following the recommendations of pharmacists. However, some farmers routinely used high potency antibiotics without clinical justification:

For the treatment of common diseases, I apply a broad-spectrum antibiotic such as amoxycillin. If there is no improvement, I will change to cepha(losporin), cefo(xamine) or enrofloxacin... I believe in higher potency antibiotics. If there is no price difference, I always select higher potency antibiotics [Fc12, male, > 30 years old, non-GAP certified farm]

Commercial farmers also understood the concept of antibiotic resistance but they were elusive when the researcher raised the issue that excessive antibiotic use in the farm was an important contributing factor:

Our pigs are good, clean. I know resistant pathogens, but I don't think that we (farmers) are involved in it. [Fs03, male, > 40 years old, non-GAP certified farm]

Farm management

All interviewed farmers agreed that sound farm management was key to animal health and consequently to reducing the need for antibiotics.

I give more attention to prevention than treatment. Water quality, low pig density and good air ventilation are essential for healthy pigs.... When the pigs are healthy, I don't need to use antibiotics. [Fc09, female, 45 years old, GAP farm]

The government officers in this study also believed that GAP certification contributes to the optimised use of antibiotics. Indeed, the antibiotic-free farms in our study were GAP-certified farms with bio-security measures such as change of clothing and boots and disinfection of all vehicles before entering the farm (Fig. 1). However, only six of the farms in the study were GAP certified. Some farmers were concerned that improving infrastructure and biosecurity to meet GAP standards would require large financial investments.

A closed system housing of 300 m^2 costs more than 1 million THB (US$ 31,700) ...the closed system would improve the health of my pigs and minimise the introduction of pathogens in the farm... so it would reduce the need for antibiotics. But this adds to the production cost. I can't afford it. [Fc06, male, 40 years old, non-GAP-certified farm]

Limited availability of farm veterinarians and gaps in the monitoring system were seen as further challenges to the implementation of GAP requirements.

The GAP criteria are quite strict. They require a farm veterinarian to monitor antibiotic use in the farm. If antibiotic residue is found in pork products, the farm veterinarian must take responsibility. When the farm veterinarian is not available, farmers often give antibiotics to their animals without prescription. [GO3, male, 31 years old].
With the GAP certification, the farmer must report on administrative records all medicines used in the farm and declare they were prescribed by the farm veterinarian. However, farmers may choose to not follow veterinarian's prescription. We cannot really monitor this. [GO2, female, 50 years old]

Fig. 1 Pigs in the outdoor area at the antibiotic free farm

Textbox 1: antibiotic-free farm

The antibiotic-free farm A was a 5000-fattener farm covering 8,000 m^2. Eight barns were lined up in an east–west direction to minimize direct sunlight. Each barn had an indoor area of 400 m^2, with access to an outdoor area of 800 m^2 for two to three hours during the day, allowing the pigs to move in and out freely. There were no inside partitions, so all 400 pigs (per barn) could live together. The barn floors were made of concrete and cleaned daily by farm workers. Weaning pigs were sourced from another farm, located 17 kms away and owned by the same farmer. If sick pigs were found, they were isolated for treatment or culling.

Observations found that all barns were clean. The researchers also observed pigs roaming around, digging up the ground in search for roots, and also eating fruits from trees that the farmer grew outside the barn. The owner said this farming concept was intended to raise "happy and healthy pigs" because the animals could express their natural behaviour and were not stressed. He said this was a feasible alternative to using antibiotics. The farm received many visitors, with walls lined with photos of international guests and actors.

Lack of market demand and production facilities for antibiotic-free pork

The owner of an antibiotic-free farm expressed concerns that market demand for antibiotic-free pork was still low. Another participant pointed out that antibiotic-free standards cannot be fully met in Thailand since most slaughterhouses do not have facilities to separate antibiotic-free pork and medicated pork, causing possible contamination. However, a farmer explained that large companies would not face this problem since they usually control the whole supply chain, including the farm, the slaughterhouse and the retail outlet.

Health professionals

Veterinary services

Antibiotics and other medicines used in the farms were provided by different categories of actors working in the agricultural sector, including veterinary practitioners, veterinarians in pharmacies, representatives of pharmaceutical companies and animal husbandry specialists. Most farmers in our sample relied on the advice of veterinarians regarding the selection and use of antibiotics. However, only one out of 13 farms hired a full-time licensed veterinarian, while the others hired "farm consultants" who were academics, reportedly tied to pharmaceutical companies. Smallholder farmers had limited access to veterinary services, due to lack of public veterinary health facilities and district veterinarians, while most animal clinics served companion animals only. All smallholder farmers received advice on antibiotic use from other farmers or the pharmacies where they purchased antibiotics.

Training

Interviews with key informants from the veterinary and pharmacy councils confirmed that courses on the prudent use of antibiotics were not included in the veterinary and animal husbandry curriculum, while the pharmacy curriculum did not cover use of antibiotics in animals. A key informant from a veterinary association mentioned that their association provided in-service training and clinical practice guidelines for disease management. However, veterinarians expressed concern over lack of clinical guidelines, lack of protocols for sample collection, difficulties in laboratory sample transportation, delays in receiving lab results and high cost of bacterial culture and drug sensitivity testing.

Awareness of AMR

Most veterinarians were aware of government policy on reducing the use of antibiotics. However, some of them became defensive when the researcher raised the issue of AMR. They said antibiotics were used only when necessary, and not indiscriminately as perceived by the public.

> *Of course, we use a large amount of antibiotics in livestock, but I believe that other sectors such as doctors, pharmacists and orchards use more. Patients who don't take the full dose are the cause of the resistant bacteria ... I don't believe that people will die from AMR transmitted by animals. [V07, male, 52 years old]]*

The pharmaceutical industry

Antibiotic sales and advertisement

Commercial farmers explained they could buy antibiotics easily at pharmacies or from representatives of pharmaceutical companies who visited their farms. Respondents from the three commercial farms also reported that representatives of pharmaceutical companies encouraged the purchase of antibiotics and other medicines through discounts and gifts such as leisure travel.

> *All pharmaceutical companies offer sales promotions. You can choose either 10% discount or international leisure travel awards. In previous years, I have*

> *travelled to the US, Iceland, Spain, Japan. I feel like I have to order more medicines to gain the award. [Fc13, male, >40 years old, GAP certified farm]*

> *Representatives of pharmaceutical companies offered me a dinner or presents such as a liquor... and they asked me to help them achieve their sales target... [Fc10, male, >40 years old, GAP certified farm]*

In addition, government officers noted that indiscriminate sales were difficult to control due to lack of sufficient human resources.

> *We have only a few inspectors. We cannot inspect all pharmacies in our catchment area, particularly the animal pharmacies. It is not our priority as the governor gives priority to the control of illegal drugs [GO1, male, 37 years old]*

Relationship between pharmaceutical companies, farmers, and academia

Farmers who hired academic lecturers as farm consultants felt "obligated" to follow their recommendations on various aspects of farm mangement, including advice on the choice of antibiotics. Two farmers believed that academic consultants would receive gifts from the pharmaceutical companies they recommended, such as equipment for their faculty or honoraria.

> *Most lecturers are linked with pharmaceutical companies. They support lecturers by providing equipment to their university (...) When these lecturers come here and recommend to purchase the antibiotics from a company, it is difficult to deny their advice. [Fc10, male, >40 years old, GAP certified farm]*

Discussion

This qualitative study aimed to deepen understanding of the complex set of factors influencing the use of antibiotics for pig farming in a particular context of livestock production. As described above and summarised in Fig. 2, the findings highlight the multi-faceted nature of antibiotic use and the complexity of influencing factors, ranging from perceptions (and misunderstandings) about the health benefits of antibiotics to the various interests of the multiple actors involved. A remarkable finding from this study is that many farmers recognised that good farm management practices (such as safe and clean housing and routine vaccination) could greatly reduce disease prevalence and therefore the need for antibiotics. However, only a few farmers could afford the capital investment that is needed to build and maintain an antibiotic-free farm. By contrast, from a farmer's perspective, intensive use of antibiotics provides a reliable and cost-effective solution to protect animal health and maximise profit. In line with our study, a survey of pig production

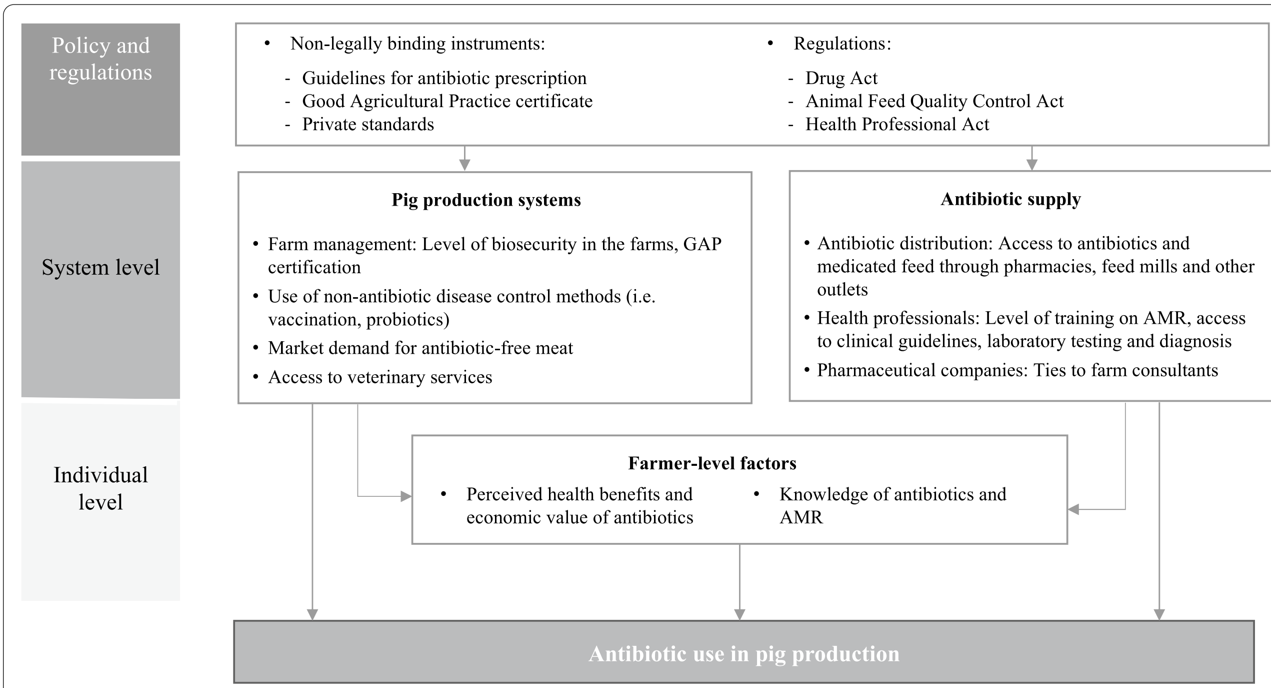

Fig. 2 Factors related to the use of antibiotics for pig production in the study locations

costs in Spain found that the cost of drugs and vaccines was less than 4.2% of the total [26].

Our findings also showed that farmers, particularly smallholders, may have inadequate understanding of antibiotics and antibiotic resistance. As emerged in some interviews, this can partly be explained by the existence of different ways to refer to "antibiotics" in Thai, including *yaa-kha-chue* ("drug that kills germs"), *yaa-khae-akseab* ("anti-inflammatory drug") and *yaa-pati-cheewana* ("drug that fights microbes"). The term *yaa-kha-chue* is particularly confusing since it can also be used to indicate other types of drugs such as antifungal, anthelmintic, and antiprotozoal drugs. In addition, *yaa-pati-cheewana* is a technical term which is often used in AMR campaigns but is not commonly understood by lay people as we found in our study. That said, we should bear in mind that a good understanding of antibiotics does not necessarily translate into appropriate use. For example, a study in Lithuania found no correlation between knowledge of antibiotics and their use for self-medication [27]. The cross-sectional survey of 84 pig farmers we conducted as part of this project also found no association between antibiotic understanding and use [23].

Further considering our findings, we can draw some lessons on policy and regulatory issues that need to be addressed to improve antibiotic use in the pig sector. In most countries, it is recognised that veterinarians and animal health authorities should play a key role in providing information about antibiotics and their appropriate use [24, 28]. In Thailand, the Department of Livestock Development (DLD) is mandated to prevent and control animal disease, enforce legal provisions and promote good practices in livestock production [29]. To this end, the DLD relies on a network of farm veterinarians and officers. However, our study suggests that the availability of veterinary services may be insufficient due to gaps in human resources, particularly for smallholders [30]. In addition, lack of effective surveillance systems for infectious diseases in livestock and limited AMR information were perceived to hamper appropriate dispensing of antibiotics by veterinarians. Similarly, a study in European countries found that veterinarians seldom used sensitivity tests to inform decisions about antibiotic use due to the excessive time lag between testing and results [15]. Veterinarians were also found to have business concerns. such as the need to maintain good relationships with clients and the cost of laboratory diagnosis [31], which are not conducive to appropriate antibiotic dispensing [24, 31–33]. These problems are also apparent in the human health sector, where conflicts of interest between healthcare providers and pharmaceutical companies may lead to inappropriate prescribing behaviour and create negative public perceptions towards health professionals [34–37].

Lastly, the role of pharmaceutical companies and market incentives to promote antibiotic use, including the provisions of gifts and other rewards, deserves particular attention [36–38]. In some countries, codes of conduct and ethical guidelines to regulate the behaviour of pharmaceutical companies are in place [39, 40]. In the UK, for example, the Code of Practice for the Promotion of Animal Medicine restricts the advertisement of animal medicines [41]. In Thailand, the production and use of certain veterinary antibiotics was regulated in 2019. Specifically, farmers need a veterinary prescription to produce farm-mixed medicated feed and to use other types of antibiotics in their farms such as injections or medicated water with quinolones and derivatives, cephalosporins, macrolides or polymyxins [42]. However, implementation of this regulation has been slow and compliance is not yet monitored. In addition, there are no codes of conduct or ethical guidelines to regulate advertisement and marketing practices.

In the future, rules on market access could help increase safety standards for the production, processing and sale of pig products [43, 44]. In recent years, private food safety standards have been implemented in Thailand, including those related to antibiotic residue testing in food products and antibiotic-free pork production, particularly in large commercial farms. By law, animals that are given antibiotics cannot be slaughtered until the withdrawal period ends [45] and the maximum residue limit of veterinary drugs in food is set by the Food and Drug Administration [46]. When residue violations are detected, the Thai-FDA or DLD must take legal action against violators and remove the contaminated products from the market.

Yet tighter restrictions on the use of antibiotics may have a negative impact on the financial viability of smallholders. First, a large farm has higher capacity to replace antibiotic use with other preventive measures such as vaccination and improved infrastructure, while smallholders may not be able to afford these additional costs. Second, as we have seen, the pig production and supply chain in Thailand is structured in a way that limits access of smallholder farmers to the premium markets of antibiotic-free products. Large farm owners can produce antibiotic-free pork in their own farms, process the meat in their slaughterhouses and pack the final product in their retail shops, ensuring supply to premium markets from the farm to the fork. In contrast, interviews with farmers revealed that antibiotic-free pork and other pork are not processed and packed separately at external slaughterhouses. As a result, those who cannot afford the maintenance of a slaughterhouse may find it difficult to produce antibiotic-free meat.

Study limitations

To our knowledge, this is the first qualitative investigation of factors influencing the use of antibiotics in pig production in a middle-income country. The study aimed to unpack the complexity of interactions among actors involved in antibiotic use, in the wider policy and regulatory context. However, limitations should be noted. Since AMR is a sensitive issue in Thailand, the number of farmers who agreed to participate in the study was rather small. In addition, findings cannot be generalised widely although we hope this study can provide useful insights to better understand antibiotic use in many other settings with similar livestock production systems, markets and regulatory environments.

Policy recommendations

Our study highlights the need to improve antibiotic use for pig production in Thailand. Given that farmers had limited knowledge and awareness of antibiotics and AMR, access to veterinary services and reliable information about animal health needs to be improved, particularly for smallholder farmers. Innovative low-cost investment in biosecurity could result in better farm management leading to effective disease control, improved animal health and decreased reliance on antibiotics. Poor antibiotic prescribing could be addressed through continued professional development and training, stronger undergraduate curricula, and monitoring adherence to clinical guidelines. Controlling the commercial interests of the industry and health professionals in promoting antibiotics will also require the establishment, enforcement and monitoring of a code of conduct. Finally, the combination of private market access rules and control through regulations could be another effective instrument to govern the use of antibiotics where other approaches are ineffective.

Supplementary Information

The online version contains supplementary material available at https://doi.org/10.1186/s13756-020-00865-9.

Additional file 1. Factors influencing the use of antibiotics for pig production in Thailand: Interview guide.

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Authors' contributions

AL, SY, VT and ML contributed to the design of the study. AM and JR provided conceptual and technical support in the study design and data interpretation phases. AL, VT and ML conducted the analysis and developed the initial draft of the manuscript. All authors substantively reviewed and revised successive drafts and approved the final manuscript.

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Ethics approval and consent to participate

Ethical approval for this study was granted by the Institute for the Development of Human Research Protection at the Ministry of Public Health, Thailand (Ref: IHRP2018007) and the London School of Hygiene and Tropical Medicine (Ref: 14860). Informed consent was obtained for all interviews. No names or affiliations of the respondents are reported in the presentation of findings.

Consent for publication

The manuscript is not under consideration for publication in another journal and will not be submitted elsewhere until the BMC Antimicrobial Resistance and Infection Control process is completed.

Availability of data and material

The datasets generated during and/or analysed during the current study are available from the corresponding author upon reasonable request.

Competing interests

The authors declare that they have no competing interests.

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Publisher's Note

SECTION C: DISCUSSION AND CONCLUSION

Chapter 7 Conclusions and Reflections

Conclusions

This thesis set out to investigate the patterns of antibiotic use and determinants influencing antibiotic use for pig production in Thailand in order to contribute to the development of policies aimed at optimising the use of antibiotics in pig production. The thesis has four main objectives:

1) To critically review the literature on the use of antibiotics in pigs, and to identify the methods and measurements used to quantify antibiotic use in pigs;
2) To describe the patterns of antibiotic use and estimate the total amount of antibiotics used in pig production in Thailand;
3) To explore the practices and views of pig farmers and other stakeholders about determinants influencing antibiotic use in pig production in Thailand; and
4) To identify potentially effective policy options to optimise the use of antibiotics in pig production.

This PhD comprised the following: two systematic reviews on antibiotic use in pig production and its associations; and methods and measurements for quantification of antibiotic usage in pig production (objective 1); a mixed-methods study using questionnaire surveys of pig farmers and feed mills, and interviews with veterinarians in the feed industry to describe the patterns of antibiotic use and estimate the total amount of antibiotics used in pig production in Thailand (objective 2); and a qualitative study to explore the practices and views of pig farmers and other actors about determinants influencing antibiotic use in pig production in Thailand (objective 3). Evidence generated from the above is synthesized to identify relevant policies and interventions to optimise the use of antibiotics in pig production (objective 4).

This chapter is divided into three parts. The chapter begins with a discussion on the limitations of the scope of the thesis and the methodological approach (section 1). Following this, section 2 describes a summary of the key findings of the thesis based on objectives 1-3. The present investigation is concerned with how and why are antibiotics used in pig production. Therefore, these areas are addressed in section 3 which discusses practices of different actors associated with the use of antibiotics in pig production, and the complex determinants of antibiotic use in pig production through interconnections across different levels of factors. The discussion regarding objective 4 on the policy and other implications of the study are presented in chapter 8.

7.1 Limitations of the thesis

Some limitations should be considered in regard to the scope of the thesis, the outcome investigated, and the methods used, which are described below.

7.1.1 Scope of the thesis

Although there have been many studies exploring the both the positive and negative associations between antibiotic use and AMR in food-producing animals (126). The scope of this thesis was limited to the use of antibiotics in pigs, excluding AMR. As research in Thailand on the use of antibiotics in the context of AMR in pig farms is a sensitive subject. When the Thai government introduced the AMR policy in 2016, there were widespread mass media reports about the use of antibiotics in pigs, in particular, reports that colistin resistant bacteria had been found in pigs in three provinces of Thailand (97). Concerns were highlighted about the possibility of AMR transmission from pigs to humans, leading to panic among the general public about AMR in the food chain (Figure 7.1). Unfortunately, this thesis did not explore AMR situation of pigs in Thailand.

สยองสูตรอาหาร ผสม'โคลิสติน'

ยาเถื่อนฟาร์มหมู

โลกผวาตัวแพร่ยีนดื้อยาสายพันธุ์ใหม่

คม·ชัด·ลึก

ปีที่ 16 ฉบับที่ 5574 วันจันทร์ที่ 23 มกราคม พ.ศ.2560 • 10 บาท •

ตะลึง! พบยา "โคลิสตินเถื่อน" ในฟาร์มหมูไทย สยองสูตรอาหารผสมผงโคลิสติน ขี้ตัวแพร่ "เอ็มซีอาร์-วัน" ยีนดื้อยาสายพันธุ์ใหม่ แพทย์ทั่วโลกผวา ไม่มียารักษา

แผนที่ประเมินผู้เสียชีวิตจากเชื้อดื้อยาทั่วโลก 2050

ที่มา : Review on Antimicrobial Resistance 2014

'ฟาร์มหมู' ภัยเสี่ยง

'ยีนดื้อยาสายพันธุ์ใหม่'

หน้า 3

ทาบหมอประเวศ ดึงร่วมทีมป.ย.ป.

สุวิทย์ย้ำไม่คุยนิรโทษ-ปชป.ค้านปรองดองวาระชาติ

ผ่า 'โรดแม็พปรองดอง' เงื่อนไขไม่ใช่แค่...ฝ่ายการเมือง หน้า 5

ศรีเมืองไผ่ ได้ยก4 ชนะ ราฟฟี่ บาดลอย

จุฬาฯตรวจแหล่งเลี้ยงหมูใหญ่สุดของประเทศ

ดื้อยาโผล่3จว.

นครปฐม-ราชบุรี-ชลบุรี ผงะพบยีนอันตราย50% จี้ปศุสัตว์ลุยฟาร์มใหญ่ นายกฯสั่งเช็กบิล

"บิ๊กตู่" สั่งไล่บี้ฟาร์มหมูใช้ยาปฏิชีวนะรุนแรง ทีมวิจัยสัตวแพทย์จุฬาฯ พบ "เอ็มซีอาร์-1" ยีนดื้อยาสายพันธุ์ใหม่ 50% ในฟาร์มหมู นครปฐม ราชบุรี ชลบุรี สุ่มตรวจ 3 ปี พบดื้อยาโคลิสติน 100% วอนปศุสัตว์ตรวจฟาร์มใหญ่ทั่วประเทศ

คม·ชัด·ลึก

ปีที่ 16 ฉบับที่ 5576 วันพุธที่ 25 มกราคม พ.ศ.2560 • 10 บาท •

วิจัยพบ "ยีนดื้อยา" (เอ็มซีอาร์-1)

"ฟาร์มหมู" 3 จังหวัด 2012-2014

จังหวัด	ปี	จำนวนฟาร์ม (100%)	ดื้อยาโคลิสติน (Colistin)	ยีนดื้อยา เอ็มซีอาร์-1 (MCR-1)
นครปฐม	2012	5	2 (40%)	1 (20%)
	2013	4	4 (100%)	2 (50%)
ราชบุรี	2014	5	4 (80%)	2 (40%)
ชลบุรี	2013	3	3 (100%)	2 (66%)

อาหารหมูกระทบถึงคน

คุมเข้ม ยาโคลิสติน หน้า 10

ที่มา : วารสารสัตวแพทยศาสตร์ ก.ค. 2559 The Thai Journal of Veterinary Medicine.Vol46.2016

มะกันส่งข้อมูลถึงไทย 'สินบนโรลส์-รอยซ์'

ป.ป.ช.ตั้งคณะกรรมการ มท.สั่งสอบสาย2ไฟฟ้า คอตช.จ่อคุ้ย2ปมทุจริต

มหากาพย์ สินบนข้ามชาติ

สายสัมพันธ์ที่ไม่ธรรมดา

ก่อสร้างรถไฟฟ้าสีเขียว ทำรารา รัชโยธินป่วน

Figure 7.1 Cover page of the newspaper on 23 January 2017 (left) and 25 January 2017 (right).

Translated as "Terror of 'Colistin' added in pig feed. Illegal drug used in pig farms. The world is in fear that new drug resistant genes will spread" (23 January 2017); and "The Plasmid-mediated Colistin Resistance Genes (mcr-1) in commensal *Escherichia coli* from Fattening Pigs was found in three provinces of Thailand" (25 January 2017).

7.1.2 Methodological limitations

Systematic reviews: lack of data from LMICs

In the systematic review of the 36 studies which documented patterns of antibiotic use in global pig production, most of the studies were conducted in Europe and North America, particularly in HICs where there are higher research capacities and data availability. Only two studies in LMICs, Vietnam and Sudan, were available for inclusion in this review. This limits the relevance of the findings to which may have very different and highly diverse pig production systems and regulations regarding antibiotics across countries. Moreover, there were different approaches for data collection in different countries. In HICs, veterinary prescription records or antibiotic application records are commonly available to provide data on antibiotic consumption in farm animals either from veterinary medicine authorities or at the farm level. These data provide accurate information on the type of medicine, indication, dose, duration, and the number of animals being treated. However, in LMICs settings, this is generally not the case.

Lack of sampling frame

One of the main limitations in conducting the empirical research was that farm-level data collection was conducted in only one province in Thailand, and the selection of farms was not done at random. Due to budgetary and time constraints, it was only possible to include one province with the highest pig population accounting for about 20% of Thailand's annual pig production and hosts different production systems, from smallholders to large agro-industrial conglomerate farms. Random sampling was not possible because I could not access the lists of pig farmers in the study area to create a sampling frame. The DLD has authority over livestock production in Thailand and has lists of livestock farms and farmers in the study area. Initially, I sent an official letter to the DLD asking for their support to provide lists of pig farmers and farms in the study area however they made it a prerequisite that they review the study findings prior to submission for any publication.

I therefore decided not to receive the lists from the DLD as the International Ethical Guidelines for Health-Related Research Involving Humans states clearly that, "Researchers must not enter into agreements that interfere unduly with their access to the data or their ability to analyse the data independently, prepare manuscripts, or publish them" (127)[6]. The process for seeking DLD support for data collection delayed the study by about four months.

Consequently, the selection of the pig farmers was not done using a systematic random approach but instead relied on the purposive sampling of districts and sub-districts. I contacted the provincial health office and asked the district-level public health staff to identify the three districts and two sub-districts with the highest amount of pig production. Therefore, the study may be subject to selection bias and generalization to the rest of the province and beyond needs to be done cautiously.

Lack of on-farm records on the use of antibiotics

The lack of availability of data on actual antibiotic use on farms in Thailand was a great challenge. I had initially planned to collect data to measure the volume of antibiotics on farms from any of three potential sources at farm level: antibiotic prescription records, treatment records or antibiotic invoices, whichever were available. However, I realised that no data were available from these three potential sources. As mentioned earlier in the findings from the systematic review, no prescription is required for antibiotics in Thailand, therefore data on antibiotic prescription were not available for analysis. There was no system for recording the use or purchase of antibiotics at the farm level and I felt that there was too much potential for recall bias if I relied solely on interviews with farmers.

Several attempts to estimate antibiotic use in animals have been reported in LMICs. In Vietnam, the "bin collection" method was applied in which farmers were asked to retain antimicrobial packaging over a six-week period in order to calculate the volume of antibiotic use at farm through discarded antimicrobial packaging (128). Another approach was through data collected from internet-based survey of sales data of commercial feed products in Vietnamese pig and chicken production (129). However, I could not apply these approaches in this study because the commercial medicated feed did not include information on the antibiotic content on the feed labels. In addition, the lists of animal commercial feed products

[6] The International Ethical Guidelines for Health-related Research Involving Humans of the Council for International Organization of Medical Science states that "Sponsors must not prevent researchers from publishing unwelcome findings that restrict their freedom of publication. As the persons directly responsible for their work. Researchers must not enter into agreements that interfere unduly with their access to the data or their ability to analyse the data independently, prepare manuscripts, or publish them."

destined for livestock as listed in the Animal Feed Quality Control Act did not cover information about the ingredients of feed (whether it contains antibiotics or not, type or concentration of antibiotics. Moreover, the previous study showed that the bin collection method was an inefficient method of collecting quantitative antibiotic use data on farm. There was poor understanding of the methodology by many participants and, consequently, few farms retained antibiotic packaging for the full six-week study (128)

According to my systematic review (130), several studies reported that more than 90% of antimicrobial substances given to pigs are administered orally as medicated feed or water (70,71,131). Therefore, analysis of data from a survey of feed mills is used in this study to estimate the total volume of antibiotics used in pig production in Thailand. The data used in this study have substantial limitations. For example, the resulting estimates tend to underestimate the total volume of antibiotics used in Thailand because they cannot capture antibiotics in other pharmaceutical dosage forms such as powder for use in drinking water. Moreover, they do not include data on medicated feed mixed in-house by farmers who prefer not to purchase commercial medicated feed.

In addition, data from feed mill survey was not able to capture data on dose, duration and indications of medicated feed. To gain more of an understanding about the use of medicated feed I conducted supplementary interviews with veterinarians working in the animal feed industry, focusing on questions about: 1) the common diseases and conditions which require antibiotics in pig production; 2) the common antibiotics used for each clinical condition; and 3) the dose and duration of each antibiotic used at different production stages.

Willingness of respondents to participate in the study

Due to concerns about the possibility of AMR transmission from pigs to humans, it has potentially affected the willingness of farmers to participate in the study. A further problem that affected the willingness of farmers and government officers to participate in the study was the outbreak of African Swine Fever in neighbouring countries during the study's data collection period (January 2018 - January 2019) (132). When I contacted the provincial farmer cooperative in the study province, they did not give any positive signals about participating in the study. They were sensitive to the possibility that the research would report high levels of antibiotic consumption in pig production and that as a consequence there would be a negative impact on the sales of livestock products.

Position of the researcher in data collection process

Gill Walt et al. (133) advised that we need to reflect on the positionality of researchers when conducting health policy analysis, given its implications for access to data and the construction of knowledge. In this regard, the connection with my background is worth discussing. In the farmer survey, the health centre staff introduced me to the participants as a research fellow with a veterinary background. Therefore, most farmers in the study perceived that I was an animal health professional who could provide information about animal care. The farmers' expectations of me being able to give animal health advice created a tension between my clinical duty in response to animal health demands and my role as a researcher. For example, some farmers sought my advice on the use of antibiotics on their farms, particularly smallholder farmers who had limited access to animal health services. Some farmers asked for my comments and suggestions on whether their practices were good or not when I asked about their practices on pig health management and antibiotic use. My positionality could also trigger a dual-role confusion both internally (feelings of conflict between different roles) and externally (clarifying my role to others) (134). Therefore, my positionality and how it may influence data collection and interpretation needs to be considered.

In addition, it was challenging to conduct interviews with veterinarians since I was perceived as a Ministry of Public Health staff member who may be involved with the regulation of antibiotics. This became particularly clear when I raised the issue of AMR in animals and the potential effects on human health. Most veterinarians became quite defensive of their practice saying that antibiotics were used more in other sectors such as by doctors, and pharmacists, for which the Ministry of Public Health should be responsible. Building rapport and establishing comfortable and natural interactions were very important in the interviews with key informants. I approached the respondents with an open and curious attitude, stating specifically why I was interested in a specific point of view. The interview aimed to explore their views and pass no judgment or opinion about whether their practices were right or wrong. I enhanced this sense of rapport with them and built considerable relationships and a sense of mutual trust.

Outcome investigated: lack of measurement of appropriate antibiotic use and agreed metrics to measure the use of antibiotics

As revealed in the literature review, there is a lack of a universal standard about what constitutes 'appropriate' use of antibiotics in livestock production. This presented a significant challenge to the interpretation of the study findings. Efforts to define the term 'appropriate use' are complicated by the array of scenarios for which antibiotics are given. According to the OIE's guidelines, 'prudent use' of antibiotics in livestock is promoted with the purpose of optimising both their efficacy and safety (135,136). In the human sector, the term 'rational use' of medicines used to be used quite commonly. It was endorsed by resolution WHA54.11 on the medicines strategy in 2011. The WHO definition of rational medicine use is: "*Medicine use is rational (appropriate, proper, correct) when patients receive the appropriate medicines, in doses that meet their own individual requirements, for an adequate period of time, and at the lowest cost both to them and the community. Irrational (inappropriate, improper, incorrect) use of medicines is when one or more of these conditions is not met.*" (137).

Therefore, in this thesis, I chose to focus on the practices associated with antibiotic use in pig production, which may contribute to the emergence and threat of AMR to people, particularly the use of antibiotics for disease prevention and antibiotics in the CIA category. Although most international organisations recommend the avoidance of certain uses of antibiotics in livestock the specific uses (51,138,139). The WHO states that the use of any class of antibiotics for disease prevention and the use of highest priority CIA for treatment should be avoided in livestock production (51). The FAO recommended that antibiotics should not replace good husbandry, including hygiene and biosecurity measures for disease prevention (139).

Moreover, as found in the systematic review of the methodological approaches for measuring antibiotic use in animals, there is a lack of standard measurements which hampers cross-study comparisons. In this study, antibiotic used was reported in total volume of active ingredients. However, it should be noted that the unit of measurement of volume of active ingredients does not take into account the number of animals in a population; therefore, it might give a false interpretation.

7.2 Key findings of the thesis

7.2.1 Objective 1: To critically review the literature on the use of antibiotics in pigs and to identify the methods and measurements used to quantify antibiotic use in pigs.

I first conducted a systematic review on the patterns of antibiotic use in global pig production (140); the review assessed the evidence for patterns of antibiotic use in pigs on the basis of papers published in peer-reviewed journals in English between 2000 and 2017. The result of the quality assessment of 36 studies showed that 21 (58%) and 15 (42%) of studies are of high and medium quality respectively. The majority of studies were conducted between 2010 and 2017. Most of the studies were conducted in Europe and North America.

Penicillin and Tetracycline groups were the most commonly used antibiotics in many countries. The most commonly used antibiotics in the CIA category were the following: macrolide: tylosin, tilmicosin; polymyxin: colistin; cephalosporins: 3rd and 4th generation cephalosporins; and fluoroquinolones: enrofloxacin (130). Several studiers reported a positive correlation between antibiotic use and farm characteristics such as a large size of farm (111,118,119,141), high pig density in the farm (111,118) and an industrial production system (141). Good farm biosecurity was identified as common practice in farms with low antibiotic use (120).

For the second review on the methods for quantification of the use of antimicrobials in global pig production, a total of 25 studies were included based on the eligibility criteria. The majority of the studies (20/25) were conducted in European countries. The two main sources of antimicrobial use data were farm surveys and national sales data of antibiotics. The review indicates that there is no harmonised approach for measuring antibiotic use in animals. Ten different units of measurement were identified in the review (140) because of different approaches between studies and different data recording systems. Global consumption of antibiotics in food animal production was estimated at 63.1 million kilograms, which average annual consumption of antimicrobials per kilogram of pig produced was 172 $mg \cdot kg^{-1}$ in 2010 (62).

7.2.2 Objective 2: To describe the pattern of antibiotic use in pig farms and estimate the total amount of antibiotics used in pig production in Thailand.

The findings from the questionnaire survey of 84 pig farmers indicated that 73.8% (62/84) used antibiotics, of which 57.1% of farmers (48/84) reported the use of antibiotics for the prevention of disease. Amoxicillin was the most commonly used antibiotic for disease prevention on farms. Antibiotics in the CIA category were commonly used, reported in one-third of farmers (31%).

The feed mill survey data showed that the estimated total amount of active ingredients of antibiotics mixed into medicated feed for pigs for the whole country was estimated at 843 tonnes (842,571.7 kilograms) in 2017. Among these, the top three active ingredients were amoxicillin, contained in almost half of feeds, then halquinol and tiamulin. Nearly two-thirds of antibiotics (64.3%) contained in medicated feed were in the CIA category.

Based on the analysis of feed industry veterinarian interviews, amoxicillin and tiamulin were commonly recommended for use at all stages; the dose range was between 300 and 400 ppm and 150 and 200 ppm, respectively. Halquinol and colistin were commonly recommended as an addition to medicated feed for suckling piglets and nursery pigs for the prevention of gastrointestinal tract infections. Tylosin, tilmicosin and chlortetracycline were recommended for fatteners.

A number of farmer characteristics were found to be associated with the use of antibiotics in pig production. Farmers appearing to use the greatest levels of antibiotics for disease prevention and antibiotics in the CIA group[7] were those who: received advice on animal health; had higher education levels; were more experienced; belonged to a farm cooperative; had more farm's income [a]; owning commercial farm[a]; and having received GAP certification[a]. There was no correlation between farmers' knowledge about antibiotics and their usage. (This point will be further discussed in section 7.3.2.)

[7] The analysis on the use of antibiotics in CIA category was presented in the American Society Tropical Medicine and Hygiene Annual Meeting 2019, USA, entitled "The use of "Critically Important Antimicrobials" in Thai pig production: survey of 84 pig farms and 31 feed mills" (Appendix 6.4); [a]: variable that had positive association with CIA use only.

7.2.3 Objective 3: To explore the practices and views of pig farmers and other relevant stakeholders associated with the use of antibiotics in pig production in Thailand.

This study explores the practices and views of pig farmers and other stakeholders regarding antibiotic use in pig production in Thailand through semi-structured interviews (31 key informants) and direct observations in six pig farms. Thematic analysis based on practices, views and interests of stakeholders showed that many factors seemed to be associated with antibiotic use including lack of knowledge and awareness about antibiotics and AMR; economic incentives; and loose regulatory frameworks. This information seems to contradict the findings of the farmer survey (The discussion is in the section 7.3.2). Farmers considered that using antibiotics was a worthwhile investment in pig production. Veterinarians stated that they faced challenges in diagnosis and lacked antibiotic prescribing guidelines. Pharmaceutical companies used promotion strategies to increase sales.

7.3 Reflections from the thesis

To my knowledge, this is one of the first studies to assess in detail the use of antibiotics during pig production in a LMIC. Evidence generated from the study aims to contribute to the development of policies to optimise the use of antibiotics in pig production. The details of the study findings are discussed focusing on the main research question: how and why are antibiotics used in pig production? In the first section, the discussion focuses on three practices associated with the use of antibiotics in pig production, including: (1) antibiotic use for disease prevention; (2) volume of antibiotics used through medicated feed; and (3) antibiotic use in the CIA category.

The second section discusses determinants of antibiotic use in pig production through interconnections across different levels of factors. Based on the study framework (described in chapter 4), I have categorised the factors into three levels: farmer level; pig production systems and antibiotic supply level; and policy and regulations level. The farmer level includes farmers' attributes such as their educational level; experience in raising pigs; understanding of antibiotics; awareness of AMR; attitudes on antibiotic use; receiving advice on animal health; being members of a farm cooperative; and the income and size of farm. Factors at the level of pig production systems and antibiotic supply include farm management; health status of pigs on farms; farm productivity; and the role of consumers and food retailers; access and availability of antibiotics and roles of relevant stakeholders involved in the supply of antibiotics such as the pharmaceutical industry and veterinarians. Factors in relation to the policy and regulations level (grey shaded box) are presented in chapter 8, in parallel to a discussion on relevant policy recommendations for optimal use of antibiotics in pig production. Figure 7.2 shows the mapping of the study findings based on the study framework.

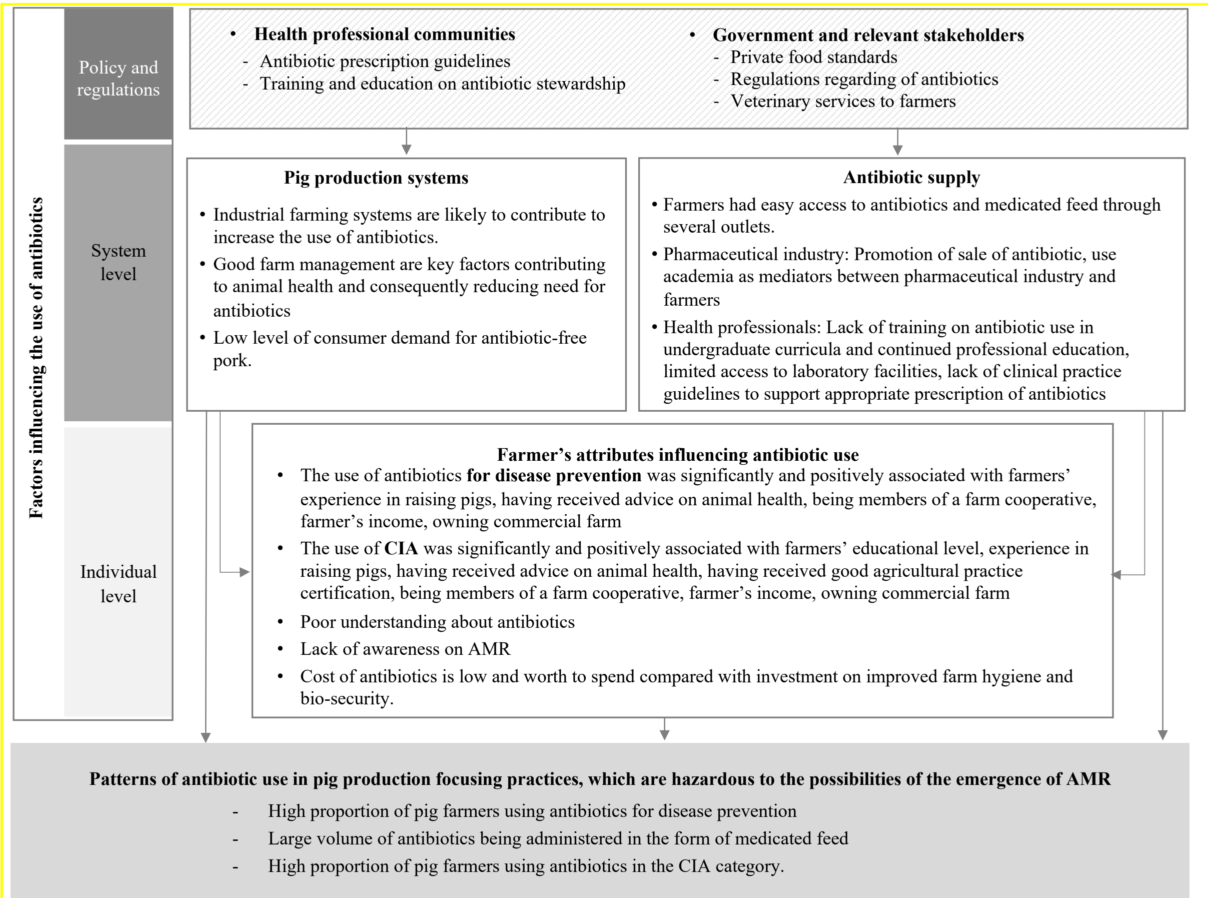

Figure 7.2 Mapping of the study findings

7.3.1 How are antibiotics used in pig production?

My study found several practices associated with antibiotic use in pig production in Thailand, which may contribute to the emergence and threat of AMR to people including a high proportion of pig farmers using antibiotics for disease prevention; a large volume of antibiotics being administered in the form of medicated feed; and a high proportion of antibiotics used in the CIA category.

The survey results of the pig farmers showed that more than half of the pig famers (57.1%; 48/84) reportedly used antibiotics for disease prevention (Chapter 5). This trend reflects findings from my systematic review, which documented a wide use of antibiotics in pig production to prevent and control disease by applying a sub-therapeutic dose (130). Several studies reported that more than 90% of antimicrobial substances were administered for disease prevention in pig production in some European countries (69–71,131). The sub-therapeutic use of antibiotics in agriculture has been a major challenge for decades, as its mechanism is to inhibit the growth of microorganisms, both commensal and pathogenic bacteria, in gastrointestinal tracts (42,43). This leads to selective pressure favouring the survival and growth of resistant bacteria (142). Both WHO and European Union guidelines state that the use of antibiotics for disease prevention should be avoided in livestock production (51,138).

Findings from the survey of pig farmers revealed the significant use of CIA, especially those reserved as a last resort for the most severe human infections such as colistin (Chapter 5). Nearly one-third of farmers (31%; 26/84) reported the use of antibiotics in the CIA group; and of all the antibiotics added to commercial medicated feed, almost two-thirds are classed as CIAs (64.3%; 541,776.9/842,571.7 kilograms), of which 17.3% (145,805.3 kilograms) were in the category of highest priority CIA and 47% (395,971.6 kilograms) in the category of high priority CIA. Similarly, data from the national surveillance of antimicrobial consumption in Thailand (Thailand-SAC) showed that 15.7% of total antibiotic consumption in food-producing animals belonged to the highest priority CIA group (81). Even though it is difficult to compare with other studies, of the total antimicrobials used in food-producing animals in European countries in 2016, 14.9% reportedly belonged to the highest priority CIA group: third- and fourth-generation cephalosporins (0.2 %), quinolones (2.6 %), colistin (5.1 %) and macrolides (7.0 %) (61).

In the analysis of data from the survey of feed mills, I estimated that 842,571.7 kilograms of active ingredients were used through medicated feed for pig production in Thailand in 2017. However, it was difficult to compare data from this study with other sources due to the lack of standardized metrics to quantify antibiotic use in pigs, as found in the systematic review (140). The total annual antibiotic use per year ranged from 15,000 kilograms to 34 million kilograms depending on species included in the study (pigs only or all food producing animals) and studied areas (some farms in country or per country). For example, a study on antibiotic use in Chinese pigs estimated 34 million kilograms of antimicrobials in medicated feed in 2012 due to the massive number of livestock (143), while only 15,000 kg of antimicrobials were used in one year in all animal species in Kenya (144). Therefore, the use of different units of measurement and the unavailability of data by animal species limits the ability to compare studies across settings.

7.3.2 Why are antibiotics used in pig production?

There are various factors influencing the use of antibiotics. This section discusses the three levels of factors: farmers' attributes, pig production systems and antibiotics supply. Factors in relation to the policy and regulations level are presented in chapter 8.

Farmer's attributes influencing antibiotic use

The farmer survey identified a number of characteristics associated with the use of antibiotics in pig production as discussed in the published paper (28) and in Appendix 6.4. For example, farmers appearing to use the greatest quantity of antibiotics for disease prevention were those with more experience. This may be because experienced farmers are more likely to use antibiotics without a detailed examination of their animals' health conditions.

The farmers' motive for making money, and farmers' understanding and awareness about antibiotics and AMR also emerged as important variables in the qualitative study (Chapter 6). Farmers perceived antibiotics as a "worthwhile" and "affordable" investment relative to other interventions, such as high-cost investment in farm biosecurity. For example, findings from the interviews with farmers revealed that the cost of feed only increased by 2.7% when antibiotics were added, compared with regular feed (Chapter 6). Similar to the study in Belgium, farmers perceived antibiotics as cost-effective, therefore they applied antibiotics for disease prevention (68). A study in pig systems in Vietnam also found that farmers agreed that the cost of antimicrobials was low relative to other inputs (128). Analyses of a study in pig farms in Spain showed that the total drug and vaccine cost was less than 4.2% of the total cost per pig (145). While the cost of investing in capital assets such as buildings and farm equipment are larger and often unaffordable, when compared with medicines.

There was some evidence showing the low levels of understanding about antibiotics in farmers. For example, about 40% (33/81) of farmers in this study did not know what an "antibiotic" was; about 80% of farmer respondents incorrectly thought that antibiotics were effective against cold and flu; and more than 70% of farmers wrongly understood that antibiotics can kill viruses (Appendix 7.1 Additional results from the farmer survey). In addition, the qualitative study (Chapter 6) showed that pig farmers, particularly smallholders, have poor understanding about antibiotics.

One reason which contributes to these misunderstandings might be the common use of different Thai words to define "antibiotic". For example, Thai people commonly used a term "*Ya-Khae-Akseab*" (*Ya*=drug, *Khae*=anti, *Akseab*=inflammation) which means drugs that have anti-inflammatory effects to describe an "antibiotic"; this word is similar to anti-inflammatory drugs such as paracetamol. Another term that is used to describe "antibiotics" in Thai is "*Ya-Pati-Cheewana*" (*Ya*=drug, *Pati*=anti, *Cheewana*=microbes) meaning drugs that counter microbes. But "*Pati-Cheewana*" is a medical term which is not commonly used and understood by lay people. Moreover, "antibiotic" can be called as "antiseptic" in Thai (*Ya-Ka-Chua*, *Ya*=drug, *Ka*=kill, *Chua*=microbes).

Another reason contributing to the low level of knowledge about antibiotics among farmers could be that they did not have access to information about antibiotics. A recent study of households in Thailand found that only a small proportion of Thai people (17.8%) had received information about the appropriate use of antibiotics and AMR in the last 12 months (146). Low levels of knowledge related to antibiotics among farmers were common as indicated in other studies. For example, a number of studies found that farmers have limited knowledge of the name of antibiotics or clinical indications for use (115,116). Chen *et al.* found poor knowledge of antibiotics in Chinese farmers, along with a high level of improper use of antibiotics (147).

Although the farmer survey showed no association between the use of antibiotics for prevention and CIA, and farmers' knowledge about antibiotics. This could be because I used a univariate analysis to explore the relationship of each factor to the use of antibiotic due to a low number of samples. Therefore, it was unable to take a relationship between different variable (factor) into account.

Moreover, findings from the interviews with farmers showed that farmers did not consider that their practices on antibiotic use would contribute to AMR (Chapter 6). They doubted public health concerns about the association between the use of antibiotics in livestock production and the emergence of AMR and its potential transmission from animals to humans. In European countries, farmers perceived low to moderate levels of public health risk from antibiotic use, and were significantly more worried about financial issues than AMR (148).

Factors which influence the use of antibiotics in pig production systems

Findings of the farmer survey showed that commercial farms were more likely to use antibiotics for disease prevention (Chapter 5) and to use CIA (Appendix 6.4). The higher use of antibiotics in commercial farms is possibly related to the prevalence of disease on the farms. Particularly in industrial production systems, when pigs catch a disease, it can soon spread to the whole herd leading to mortality, reduced production and economic loss. Kim *et al*. found higher volumes of antibiotics were used for disease prevention in industrial pig farming than on household farms in Vietnam (141). Otte *et al*. explored the linkages between livestock production and global public health where livestock industrial systems with a high concentration of animals of a similar genotype being raised in limited spaces potentially have higher contact rates and pathogen transmission within the herd. He suggested biocontainment measures should be developed for industrial systems to mitigate animal and public health risks. (149). Findings from a study in pig farms in Belgium demonstrated a strong association between biosecurity and the low level of antibiotic use (150). In this study, the disease prevalence at farm was not included in the variables of farm characteristics due to limited information.

Findings from the interview with farmers showed that farmers agreed that good farm management including well-managed housing, and farm sanitation are key factors contributing to animal health and consequently reduce the need for antibiotics. Similarly, one study in Denmark demonstrated that improved farm hygiene contributes to a reduction in antibiotic use (120). However, farmers in this study raised the concern that good farm management requires a large investment to improve infrastructure and biosecurity (Chapter 6).

In Thailand, the DLD established voluntary standards for farm management through the certification of GAP. The standards range from farm infrastructure, animal feed quality, farm management, and animal health management including the use of antibiotics, animal welfare and the environment (151). However, although GAP certification should help to optimise the use of antibiotics on farms, this is not guaranteed; the farmer survey found that GAP-certified farms had a higher chance of using antibiotics in the CIA group than non-GAP-certified farms Appendix 6.4). Compliance might be crucial for the effectiveness of the regulations. Some study demonstrated the low compliance with GAP in some agricultural production. The study of compliance with GAP in Trinidad found that there was low compliance among vegetable farmers with the mean score was 14.4 (a maximum possible GAP compliance score of 42) (152). However, such data are not readily available in Thailand.

Factors which influence antibiotic supply

Findings for the farmer survey showed that most farmers had received advice on animal health and antibiotics from unqualified sources such as relatives, other farmers and lay people and from pharmaceutical companies; and they used the higher levels of antibiotics for disease prevention and antibiotics in the CIA category than farmers who had not received advice on antibiotics (chapter 5, Appendix 6.4). This finding is similar to the study about the antimicrobial use in Vietnamese pig farms which showed that it was driven by response to advice from others (128).

In Thailand, antibiotics do not legally require a prescription but must be dispensed by a licensed pharmacist or veterinarians in licensed pharmacies or pharmaceutical companies. In 2017, a large number of medicine outlets including about 24,000 pharmacies and pharmaceutical companies were licensed for pharmaceutical sales (Appendix 2) (100). Therefore, farmers can buy antibiotics through several channels including distributors, wholesalers, retail pharmacies, or medicated feed from either feed mills or feed. The farmer interviews showed that all farmer respondents had easy access to antibiotics and medicated feed through several outlets (Chapter 6). In most HICs, restriction of access to antibiotics is done through the requirement of prescriptions and regulatory systems involving prescribers (veterinarians) and dispensers/supplier (pharmacists, veterinarians) (153). Pharmaceutical companies commonly promote the sales of medicines, including antibiotics, directly to farmers through different marketing strategies. The farmers' interviews revealed that pharmaceutical companies applied market promotion strategies such as cheaper prices and international leisure travel awards, to increase sales, which are likely to influence farmers' decisions on antibiotic purchases (Chapter 6).

Most Thai veterinarians who work for pharmaceutical companies can play dual roles as drug retailers and health care providers. Their decisions and the information they provide to farmers may be biased in favour of profit-driven sales of pharmaceuticals. In human health, a number of studies showed that the physician can boost a patient's demand for unnecessary use of medications and healthcare through the provision of additional information. Asymmetric information between physicians and patients exists, as patients do not have enough information to determine what health services should be used, which can contribute to a bias of supplier-induced demand (154–156).

Another factor that can potentially influence the use of antibiotics is the relationship between pharmaceutical companies and animal health care providers. Findings from the qualitative study showed that in some situations, pharmaceutical companies used veterinary professors as "academic mediators" to provide advice to farmers on animal health management including the use of antibiotics (their products), while the veterinary professors received honorariums, support for conference participation and laboratory equipment to their faculty in return (Chapter 6). Indeed, many other studies of physicians found that pharmaceutical companies often provide economic incentives such as support for social outings, workshops and conference registration fees, non-educational gifts, reprints of adverts and personal drug samples in order to boost their sale of antibiotics (123,124,157). Support from pharmaceutical companies was found to influence health professionals' decisions on antibiotic prescriptions. A study on factors influencing antibiotic prescription showed that Chinese doctors over-prescribed antibiotics because they earned money through sharing the income and profits made by pharmaceutical companies and hospitals (158). To my knowledge, no study has assessed the influence of the pharmaceutical industry on veterinarians' decision-making.

In terms of limitations of health professionals, findings from the qualitative study shows that the curriculum for pharmacists did not including teaching on veterinary antibiotics despite the fact that pharmacists in Thailand are responsible for both human and animal medicines. Pharmacists therefore may have limited knowledge about pigs' diseases and farm management in order to prescribe appropriate antibiotics to farmers. Furthermore, the rational use of antibiotics is not a topic covered in the curriculum for veterinary and animal husbandry studies, and in the existing in-service trainings. In addition, even though there are guidelines for veterinary clinical practice, they focus on diagnosis and disease management, and do not include the appropriate use of antibiotics (Chapter 6).

Finding from interviews with veterinarians showed limited laboratory facilities to support antibiotic sensitivity testing; a lack of protocols for diagnosis; and a lack of clinical practice guidelines for the appropriate prescription of antibiotics (Chapter 6). It is therefore pragmatic for veterinarians to prescribe antibiotics to pig farmers based on their experience and their understanding of the epidemiological profile of common pathogens for different symptoms, while it is considerably more difficult and costly to undertake laboratory diagnoses and sensitivity testing. Several studies showed that non-clinical factors including time constraints, cost of diagnosis and maintaining a good relationship with clients influence veterinarians' decisions (159–162).

7.4 Summary

This chapter will review the study limitations and discuss its findings. It is clear that there is high use of antibiotics for prevention through medicated feed, and high use of antibiotics in the CIA category in pig production in Thailand, and that this has implications in terms of the emergence and spread of AMR. The use of antibiotics is influenced by some of the complex interactions among stakeholders in the context of policy and regulatory environments including farmer's attributes such as profit motive of antibiotic use, and lack of farmers' understanding and awareness about antibiotics; industrial pig production systems and antibiotics supply. Policy and other implications of the study are considered in the final chapter (Chapter 8)

Chapter 8 Implications for policy and research

Summary

This chapter summarises the implications of the thesis for policy and areas where further research are needed. In the first section, evidence generated from previous chapters is synthesized to discuss the implications for policy and identify relevant policy recommendations for optimal use of antibiotics in pig production. A further section is dedicated to recommendations for research priorities, and the final section looks at the overall conclusions of the thesis.

8.1 Policy implications and recommendations

Antibiotics are common-pool resources. When everyone can gain access to antibiotics and use them inappropriately, it leads to the loss of antibiotic effectiveness through the development of AMR. The control of AMR can be considered a dilemma of a common good as all individuals can benefit in the long-term from collective actions in maintaining the effectiveness of antibiotics (163).

This thesis has contributed to the understanding antibiotic use and determinants influencing antibiotic use in pig production in Thailand. The empirical findings will hopefully be a useful contribution to policy makers in Thailand responsible for making decisions about how to optimise the use of antibiotics in pig production. This study may also have implications for policy in other contexts, particularly LMICs with similar livestock production, market and regulatory environments. The contributions of this thesis are described below.

8.1.1 Policy implications and recommendations for Thailand

In Thailand, the National Strategic Plan on AMR (NSP-AMR) was established and endorsed by a Cabinet resolution in 2016 (Appendix 9). The policy recommendations for optimal use of antibiotics in pig production that are proposed in this thesis are in line with the NSP-AMR focusing on the Strategy 2 Regulation of antimicrobial distribution and Strategy 4 AMR prevention and control, and antibiotic stewardship in agriculture and animals.

Based on the evidence generated from previous chapters, I address implications for policy to guide the optimal use of antibiotics in pig production. There are several interlinking policy interventions and a broad range of instruments for both non-legal norms and regulations to optimise antibiotic use through collective actions of relevant stakeholders. The priority interventions including (1) private standards; (2) monitoring and enforcement of regulations regarding antibiotics; and (3) generating evidence and provision information to relevant stakeholders, are presented in the following section.

8.1.1.1 Private standards in pig production

Private standards have not been set by regulatory authorities, but by non-governmental organisations such as, in the food sector, supermarket chains, retail companies, manufacturers, and producers (164,165). Private food standards have increasingly become an important role in determining market access in food trade through setting the minimum requirements for products, processes or producers. For example, retail corporations such as fast-food companies in the US exerted some leverage over the livestock practices of their suppliers and demanded animal products with fewer antibiotics (166). Another relevant example can be seen in the UK's big supermarket chains which set contractual standards to livestock producers and banned routine preventive use of antibiotics in livestock (167).

In Thailand, some private food standards including antibiotic residue testing in food products and antibiotic-free pork production have been implemented. One of the big supermarkets initiated the 'Big C Farm Fresh Hygienic' program, which set up the standard of livestock production restricting the use of antibiotic as a growth promotor and traceability systems to detect antibiotic residue in livestock products (168). Thailand has a 'Raise Livestock Without Antibiotic Programme', a farm assurance and food labelling scheme set up by the DLD in 2018 (169). Under the programme, animals must be certified that they have not received antibiotics throughout the production, and pig producers were encouraged to apply preventive measures such as vaccination, alternative treatments, and appropriate animal husbandry to maintain the health of the animals. However, there were only five large agro-industrial livestock producers with 144 pig farms who participated in the Raise Livestock Without Antibiotic Programme (169).

The findings from this study revealed that the Thai pig production supply chain potentially limits access of individual farmers, particularly smallholder farmers to antibiotic-free pork markets and food safety program of big supermarkets. The food industries, in cooperation with DLD should apply the market access rules to control the use of antibiotic in pig production, to produce meat which is either free from antibiotic or antibiotic residue. The DLD should consider scaling up the 'Raise Livestock Without Antibiotic Programme, particularly increase enrolment of small farms or farms outside the large company chain which are eligible to produce antibiotic-free pork to become involved in the programme.

8.1.1.2 Monitoring and enforcement of regulations regarding antibiotics

Enforce the regulations in supplement with the private standards

A combination of market access rules by the private sector and control through regulation could be an effective instrument to govern the use of antibiotic in livestock production.

As mentioned in the previous section about private standards on antibiotic residue testing in pig products, the Notification of the Thai-FDA has set the maximum level limit of veterinary drugs residue in foods (170). In addition, the DLD is charged with enforcing the Animal Feed Quality Control Act, animals given an antibiotic should not be slaughtered until the withdrawal period ends (105). When residue violations are detected, Thai-FDA or DLD will take legal action against violators and exclude the contaminated products from the market.

Establish veterinary antibiotic prescriptions monitoring systems

Findings from this study demonstrated that the availability and easy access to affordable antibiotics including CIAs at pharmacies or on-site sales by pharmaceutical detailers potentially contributed to high antibiotic use. Restrictions for veterinary antibiotics have been recently introduced in Thailand under the Drug Act. In 2019, pharmacies and pharmaceutical companies needed medicine prescription for the sale of four groups of veterinary antibiotics: quinolones and derivatives, cephalosporins, macrolides and polymyxins (104). However, implementation is still at an early phase and is not being monitored. To assess the effectiveness of regulatory implementation, Thai-FDA should establish a prescription system to monitor and audit these groups of veterinary antibiotic prescriptions in pharmacies and pharmaceutical companies. The prescription monitoring system should be established in consultation with relevant stakeholders.

In addition, in 2018 the Animal Feed Quality Control Act mandated that veterinary prescription is needed for feed mills before medicated feed production, and for farmers who produce farm-mixed medicated feed on farms (105). Well-designed electronic antibiotic prescription and submission from feed mills and farms could help facilitate timely monitoring and remedial actions. The DLD should accelerate the implementation of this prescription system, and in addition, Thai FDA and the DLD should synchronise or integrate their monitoring systems.

Limit the pharmaceutical industry's influence on the farmers' and veterinarians' decision on the use of antibiotics.

Despite continuing concerns regarding the influence of pharmaceutical companies on the decisions of farmers and veterinarians over the use of antibiotics, the findings of this study clearly showed some evidence of lack of control of pharmaceutical companies regarding the sale of antibiotics in Thailand. There is currently no regulation requiring veterinarians and pharmacists to reveal financial connections to pharmaceutical companies.

In European countries, the European Parliament has discussed the possibility of "decoupling" which separates the right to prescribe from the right to sell antimicrobials in EU member states, thereby eradicating economic incentives for prescribing veterinary medicines (171). The Dutch government implemented a regulation decoupling the functions of prescription from the selling of drugs by veterinarians along with other interventions; this has been shown to be effective with a 56% reduction in antimicrobial use in farm animals between 2007 and 2012 (172). This approach should be applied to Thailand. The government should intervene in the phenomenon of profit-led prescription and sales of antibiotics by the pharmaceutical industry. First, Thai-FDA and the DLD should decouple the prescription of antibiotics from their sale (delivery) to farmers. Secondly, the Thai-FDA and the DLD may consider standardising the conditions of prescription of antibiotics. For example, veterinarians (and/or pharmacists) should not be authorised to prescribe antibiotics without clinical examination or having visited the farm.

8.1.1.3 Generating evidence and provision of information to relevant stakeholders

Farmers: strengthening knowledge about farm management and antibiotic use

Providing correct knowledge and information to farmers help them make better decisions regarding the use of medicine. However, findings from the farmer survey showed that most farmers had received advice on animal health and antibiotics from unqualified sources or from pharmaceutical companies; and they used higher levels of antibiotics for disease prevention and antibiotics in the CIA category than farmers who had not received advice on antibiotics. Moreover, the survey also demonstrated that veterinarians from DLD were reportedly the least frequent source of advice on animal health and use of antibiotics. Farmers, particularly smallholder farmers, reported they had difficulty seeking professional advice.

The DLD should improve access to reliable information about antibiotic use for farmers. Veterinary professionals can also be effective in disseminating information to farmers. Health professionals including doctors, health workers, and pharmacists played a major role contributing about 80% of sources of information on appropriate use of antibiotics and AMR for Thai people (146). The DLD is a livestock health authority with a broad mission covering prevention and control of animal diseases, enforcement of law related to livestock industries and increasing the quantity and quality of animal products (173). The ambition of the mission is not matched by the available resources. There are few veterinarians at the provincial level and veterinarians are lacking in the district livestock development offices (83). Moreover, DLD veterinary laboratories are located at regional level and in the study, farmers and veterinarians expressed concerns over difficulties in laboratory sample transportation and delays in receiving lab results. An evaluation of the performance of veterinary services in Thailand in 2012 reported the lack of personnel and skills of veterinary officers at district level, as well as no veterinarian supervising and providing advice on the use of medicines to farmers (174). One study on the veterinary workforce in Thailand showed the lack of veterinarians working in the government sector; just 10.2% of the total veterinarians working in Thailand (175).

There is an urgent need to reconsider the role of government to respond to demands for veterinary services including the quality and coverage of services provided to livestock farmers focusing on animal health management, disease surveillance and laboratories. Strengthening the role of public veterinary services requires clear, strong and sustainable policies on the veterinary workforce and services in the agricultural sector.

Apart from veterinary service, having relevant knowledge is important but insufficient for behaviour change, as discussed in chapter 7. Specific messages should be targeted such as the consequence of AMR to animal production and public health to create an awareness on AMR. This recommendation is in line with the recommendation in objective 1 of the GAP-AMR which aims to improve awareness and understanding of antimicrobial resistance through effective communication, education and training (176).

Although all farmer respondents in this study agreed that good farm management and biosecurity contribute to animal health and reduce the need for antibiotics, however the findings of this study offer some evidence of the limitations of farmers to improve farm management, due to the need to make large investments in infrastructure and biosecurity. The DLD should consider providing financial and technical support to farmers to improve farm management and biosecurity standards with an affordable cost of investment. For example, DLD could provide essential veterinary products, vaccines in particular, at low prices or indeed free of charge to farmers, as alternatives to antibiotics. It would be beneficial to farmers if the government provides technical support to build cheaper affordable housing units with high biosecurity for livestock production.

Health professionals: antibiotic prescription guidelines and data of antibiotic consumption and AMR in pig production

Findings from the interviews with veterinarians revealed that there is a lack of antibiotic prescribing guidelines. There are very little teachings about AMR and the appropriate use of antibiotics in animals. The topics are not covered in the curriculum for veterinary, pharmacy or animal husbandry studies, nor included in the existing in-service training. In order to optimise antibiotic use in animal health, adding teachings on AMR and antibiotic stewardship into a core component of professional education, training, certification, continuing education and development in the veterinary sector and agricultural practice will help to ensure proper understanding and awareness among professionals.

In the health care of humans, clinical practice guidelines can contribute to the reduction of unnecessary use of antibiotics in humans and are an important tool in antibiotic stewardship (177). However, based on an OIE survey in 2018, most countries outside the EU including Thailand have not established guidelines on the use of antibiotics in food producing animals (178). The Thai-veterinary professional communities should urgently develop guidelines for antibiotic prescription in livestock including pigs through collaborative work between veterinary professional councils and relevant partners. The guidelines should be in line with recommendations of international organisations on the use of antibiotics in food-producing animals. For example, Food and Agriculture Organization of the United Nations (FAO) suggested that antibiotic use for disease prevention should be applied only in exceptional situations, such as when a few animals in a group have been diagnosed with an infection that has probably already sub-clinically infected other animals. Mass treatment of groups of animals should be avoided, and treatment and care targeted to single or small groups of infected pigs in separate pens should be the goal (139). WHO recommends an overall reduction in use of all classes of medically important antimicrobials (MIA) and complete restriction of routine use of MIA for prevention of infectious diseases that have not yet been clinically diagnosed in food-producing animals (51). Ideally, the use of antibiotics in the CIA category should be limited to treatment, with specific indications and only when there is no lower tier alternative. Where possible non-WHO CIA list antibiotics should be recommended, and where this is not possible then antibiotics in the lower tiers on this list should be recommended first.

In addition, guidelines should be based on local microbiological surveillance data. The surveillance data can help guide veterinary decisions on antibiotic prescription. Currently, there is no existing analysis of the potential association between antibiotic use in animals, and AMR in animals and humans. The government should support this analysis, in particular for the CIA group of common pathogens. National guidelines on antimicrobial use and antimicrobial stewardship need to be developed based on evidence of antibiotic sensitivity testing.

Key policy recommendations for the government:

1. *The food industries, in cooperation with DLD and Thai-FDA should apply a combination of market access rules and regulations to control the use of antibiotics in pig production.*
2. *The DLD should consider scaling up the 'Raise Livestock Without Antibiotic Programme.*
3. *The Thai-FDA should establish a prescription for certain groups of veterinary antibiotics in pharmacies and pharmaceutical companies.*
4. *The DLD should accelerate the implementation of the prescription system for medicated feed production at feed mills and on farms.*
5. *The Thai-FDA in cooperation with DLD should decouple the prescription and sale (delivery) of antibiotics to farmers.*
6. *The DLD should improve farmers' access to information about antibiotics and create specific messages to create an awareness on AMR*
7. *The DLD should strengthen animal health systems through providing public veterinary services including animal health management, disease surveillance and laboratories.*
8. *The DLD should consider providing financial and technical support to farmers to improve farm management and biosecurity standards with an affordable cost of investment.*

Key policy recommendations for veterinary communities

1. *The veterinary professionals' councils should urgently develop guidelines for antibiotic prescription in livestock including pigs through collaboration with relevant partners.*
2. *The health professionals' councils including both veterinarians and pharmacists should support training and education on antibiotic stewardship as a mandatory requirement in continuing professional development and relicensing of professional practice.*

These policy recommendations are in line with the GAP-AMR which all countries adopted through decisions taken at the World Health Assembly, the Food and Agricultural Organization Governing Conference and the World Assembly of World Organisation for Animal Health Delegates (176). Optimising the use of antimicrobials in livestock production is one of the GAP-AMR key recommendations. There are several interventions such as strengthening agricultural practices, conducting research to identify alternatives to nontherapeutic uses of antimicrobial agents in agriculture, promoting vaccination as a method of reducing infections in food animals, and effective and enforceable regulation and governance for licensing, distribution, use and quality assurance of antibiotics (176). Given the possibility of applying evidence from this study to other contexts, the next section considers the potential policy implications for other countries and global actors, which are in compliance with GAP-AMR.

8.1.2 Possible policy implications and recommendations for other countries and global actors

8.1.2.1 Promoting good animal production and hygiene practices among farmers, and other stakeholders in the animal sector

As discussed in policy implications for Thailand, improving farm management and standards of biosecurity contributes to optimising the use of antibiotics in pig production. I strongly agree with three measures including good animal husbandry, effective biosecurity and vaccination to prevent infectious diseases without using antibiotics recommended by the Food and Agricultural Organization recommendation (139) to be promoted among animal producers, and other stakeholders in the food and agriculture sectors. Good animal husbandry includes, for instance, safe and clean housing; manure management; good hygiene practices; adequate amount and nutrient content of feed; and regular veterinary advice on disease prevention and animal health programmes. Effective biosecurity covers both actions taken to prevent the introduction of infectious diseases onto the farm such as quarantining all new animals; and actions taken to prevent the spread of infections within the farm including cleaning and disinfecting tools and equipment when moving between animal groups. Routine vaccination programmes should be adapted to the diseases circulating in each country. However, the guideline should be widely disseminated to relevant stakeholders such as farmers, veterinarians and policy makers at all levels.

8.1.2.2 Investing in the research and development of alternatives to antibiotics

Alternatives to antibiotics such as probiotics or prebiotics could help replace the use of antibiotics on farms; however, farmers in the study raised concerns that they were found to increase the cost of production. The replacement of antibiotics with cost-effective solutions should be explored to the benefit of farmers and reduction in the use of antibiotics. Investigating these alternatives requires collaborative work with partner organisations and the research community for the development and evaluation of new tools. A number of studies have proposed a range of potential immuno-stimulant alternatives to antibiotics including probiotics, prebiotics, and plant-derived or crude plant extracts (179–181).

The development of alternatives to antibiotics requires substantial time and resource investments for research undertaken by global collective efforts. Research regarding alternatives to antibiotics should be prioritized to ensure limited public resources are invested first to areas with potentially maximum impact. This recommendation, in line with the OIE strategies on prudent antibiotic use, is to support research into alternatives to using antibiotics (182).

8.1.2.3 Strengthening the knowledge and evidence base through surveillance and research

Quantifying antibiotic use is important to understand the magnitude and profile of antibiotic usage in countries. In order to guide the strengthening of existing antibiotic use monitoring systems and the development of new ones to facilitate cross-country comparisons, OIE, supported by FAO and WHO within the tripartite collaboration, should support countries, in particular LMICs, to develop antibiotic use monitoring systems and integrate them into a global database on the use of antibiotics in animals. Data on the quantity of antimicrobial consumption should be classified into different types of indication (therapeutic use or growth promotion), different animal species group and different routes of administration (183).

While there has been progress in the monitoring of antibiotic consumption in animals, action regarding AMR monitoring in animals has lagged behind. Data on AMR in animals can also be used to investigate the association between the use of specific antibiotics and resistant bacteria in animals and meat products (184,185). This will help identify the risks between the use of antibiotic in animals, and AMR in animals and humans. For the next step, OIE should support countries to build up an AMR surveillance system and also include AMR information in the global database. In the human sector, WHO supports Member States to participate the Global AMR Surveillance System (GLASS) in which GLASS promotes and supports standardized national AMR surveillance systems.

Key policy recommendations:

1. *Intergovernmental organizations, including FAO, OIE, and civil society organizations should promote good animal production and hygiene practices among animal producers, and other stakeholders in the food and agriculture sectors.*
2. *The research community should invest in the research and development of alternatives to antibiotics with cost-effective solutions.*
3. *The OIE, supported by FAO and WHO within the tripartite collaboration, should support countries, in particular LMICs, to develop antibiotic use and AMR monitoring systems.*

8.2 Recommendations for research priorities

This thesis identifies research gaps related to antibiotic use in pig production and suggests future avenues of research for achieving optimal antibiotic use across different settings.

8.2.1 Examining the association between antibiotic use and AMR in food-producing animals and humans

Findings from the interviews with farmers showed that farmers did not consider that their practices on antibiotic use would contribute to AMR (Chapter 6). They doubted public health concerns about the association between the use of antibiotics in livestock production and the emergence of AMR and its potential transmission from animals to humans. However, the scope of the thesis does not cover information of AMR in pigs.

Previous studies exploring the associations between antibiotic use and AMR in food-producing animals resulted in inconclusive outcomes, having both negative and positive associations (186–188). Burow et al. (186) conducted the systematic review of 36 different trials and found that a majority of the identified studies showed effects of orally administered drugs on AMR in *E. coli* from pigs; whereas the study of pig farms in Vietnam demonstrated that there were no significant correlation between total use of antimicrobials at the farm level and AMR in pigs (188).

Moreover, there have been many studies exploring the associations between antibiotic use in food-producing animals and AMR in humans. Some studies have found a positive association between antimicrobial consumption in animals and resistance in bacteria in humans. A 2013 study by the European Centre of Disease Prevention and Control, showed significant positive associations between the consumption of tetracyclines in animals and resistance in isolates of *Salmonella* spp. from humans (189). In addition, possible relationships between the occurrence of resistance in *Campylobacter coli* and *Campylobacter jejuni* isolates from humans and the total consumption of macrolides in food-producing animals were observed in 2013-2014.

However, most studies have relied on indirect relationships or molecular microbiology techniques, which may not have sufficient capacity to provide evidence of the use of antibiotic and an emergence of resistant bacteria in animals and humans. For example, one study showed the shared genes between pigs and humans. One study of isolates of patients and poultry workers demonstrated significantly higher resistance rates of chicken *E. coli* to common antibiotics used in poultry, such as ampicillin and spectinomycin, than antibiotics not used in poultry, such as amoxicillin clavulanate and ceftazidime (190). People who had direct contact with pigs which were detected as carrying ESBL-producing *E. coli,* had significantly higher ESBL-producing *E. coli* in their stools compared with people who had contact with pigs which were not detected as carrying ESBL-producing *E. coli* (191).

This highlights the urgent need for epidemiological evidence to confirm and characterise the relationship between antibiotic use and AMR in livestock and humans. This includes confirmation of the association between the emergence of AMR in animals and the use of antibiotics on the identified farm, and that infections caused by drug resistant bacteria in humans have been transmitted from animals raised in the identified farm using certain antibiotics. The molecular approach, including targeted and whole-genome sequencing methods, should be added to epidemiological studies to examine the evolutionary origins of pathogens in both humans and animals. Such research could also facilitate identification of high-risk populations (both humans and animals) for AMR transmission, and provide specific measures for prevention and treatment in these groups and for veterinary antibiotic practices.

8.2.2 Evaluating the effectiveness and cost-benefit of alternatives to antibiotics

As discussed earlier, intergovernmental organizations and other partners should support investment in the research and development of alternatives to antibiotics. However, interview with farmers has revealed that the high costs of these new alternatives might be a major barrier to rapid uptake by farmers. The challenge for supporting alternative use in animals is to prove not only the effectiveness but also the cost-effectiveness of alternatives to antibiotics. Future research should cover a cost-benefit analysis of these alternatives, by comparing the following: costs of alternatives; cost saving from not using antibiotics; economic gains from premium grade antibiotic free pork compared with normal pork; and comparing outcomes in term of mortality and productivity such as feed conversion ratio between pigs which received antibiotics compared with alternatives. Such research will assist policy makers in targeting alternatives to antibiotics and reduce antibiotic use in livestock. The beneficial effects of many alternatives to antibiotics have been demonstrated but are so far unorganised and scattered. A systematic review of effectiveness of alternatives, particularly in LMICs settings, should be conducted to identify the effective alternatives to antibiotics.

At the macro level, prospective studies to compare the benefits of antibiotic use in animals and the cost of antibiotics are needed to guide the use of antibiotics in animal farming. The financial cost of antibiotics should not only reflect production and marketing costs, but should cover both the cost of antibiotic development and the externalities of AMR (192). One relevant study on the cost-effectiveness of antibiotic use proposed a framework to analyse the costs of antibiotic use through a marginal abatement cost theory, which is derived from the economics of pollution control (193). The study applied the approach to compare different interventions with the amount of antibiotic use reduction according to the intervention, and the implicit mitigation cost. The study also presented interventions to modify the use of antibiotics in animals including vaccines, disease eradication, husbandry and restrictions on highly critical antibiotics.

8.2.3 Exploring consumers' demand for and willingness to pay for antibiotics-free animal products

Changes in consumer attitudes and meat consumption preference can have a significant influence over the practice of livestock production. One relevant study in the US showed that American consumers were willing to pay an additional price for growth-hormone-free animal products, and premium prices for safer food and products with quality assurance (194). The European Food Safety Authority conducted a survey in farmers, veterinarians and consumers which showed that consumer willingness to pay an increased price for antibiotic-free products would relieve farmers of some of the economic pressure to use antibiotics (195). But the market demand for antibiotic-free pork in Thailand is still limited, as shown by the findings of the qualitative study. Further studies are needed to identify context-specific measures to stimulate consumer preference, consumer demand for antibiotic-free pork products, and their willingness to pay for premium products in Thailand.

8.3 Concluding remarks

The work presented in this thesis has fulfilled the aim of the thesis to investigate patterns of antibiotic use and determinants influencing antibiotic use in pig production in Thailand in order to contribute to the development of policies aimed at optimising the use of antibiotics in pig production. Evidence showed several practices, which may contribute to the emergence and spread of AMR associated with the use of antibiotics in pig production including: (1) a high proportion of pig farmers using antibiotics for disease prevention; (2) a large volume of antibiotics used in medicated feed; and (3) a high proportion of the CIA group usage. Factors influencing antibiotic use in pig production were the complex interactions among actors involved in antibiotic use including farmers, veterinarians, pharmaceutical industry, pork retailers and consumers, operating in the context of policy and regulatory environments.

Collective and synergistic actions towards optimising the use of antibiotics in livestock should involve a broad range of strategies to target actors including farmers, veterinarians and authorities; and system-oriented approaches to address private standards and voluntary measures, monitoring and enforcement of regulations regarding antibiotics, and provision of information.

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APPENDICES TO THESIS

Appendix 1 Antibiotic distribution in Thailand: manuscript published in the Bulletin of the World Health Organization

I conducted this study in parallel to my PhD research between 2016 and 2017. The aim of the study was to analyse how antibiotics are imported, manufactured, distributed and regulated in Thailand. The manuscript entitled ‘Antibiotic distribution channels in Thailand: results of key-informant interviews, reviews of drug regulations and database searches’ has been published in the Bulletin of the World Health Organization. I am the first author (My maiden name is Angkana Sommanustweechai).

Sommanustweechai A, Chanvatik S, Sermsinsiri V, Sivilaikul S, Patcharanarumol W, Yeung S, and Tangcharoensathien V. Antibiotic distribution channels in Thailand: results of key-informant interviews, reviews of drug regulations and database searches. Bulletin of the World Health Organization 2018;96:101-9.

(Cover sheet on next page)

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SECTION A – Student Details

Student	Angkana Lekagul
Principal Supervisor	Professor Shunmay Yeung
Thesis Title	Understanding the use of antibiotics in pig production in Thailand

If the Research Paper has previously been published please complete Section B, if not please move to Section C

SECTION B – Paper already published

Where was the work published?	Bulletin of the World Health Organization		
When was the work published?	Jan 2018		
If the work was published prior to registration for your research degree, give a brief rationale for its inclusion			
Have you retained the copyright for the work?*	**No** Open Access CC-BY	Was the work subject to academic peer review?	**Yes**

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For multi-authored work, give full details of your role in the research included in the paper and in the preparation of the paper. (Attach a further sheet if necessary)	

Student Signature: ______________________ **Date:** 31 August 2020

Supervisor Signature: ______________________ **Date:** 31 August 2020

Antibiotic distribution channels in Thailand: results of key-informant interviews, reviews of drug regulations and database searches

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Objective To analyse how antibiotics are imported, manufactured, distributed and regulated in Thailand.

Methods We gathered information, on antibiotic distribution in Thailand, in in-depth interviews – with 43 key informants from farms, health facilities, pharmaceutical and animal feed industries, private pharmacies and regulators– and in database and literature searches.

Findings In 2016–2017, licensed antibiotic distribution in Thailand involves over 700 importers and about 24 000 distributors – e.g. retail pharmacies and wholesalers. Thailand imports antibiotics and active pharmaceutical ingredients. There is no system for monitoring the distribution of active ingredients, some of which are used directly on farms, without being processed. Most antibiotics can be bought from pharmacies, for home or farm use, without a prescription. Although the 1987 Drug Act classified most antibiotics as "dangerous drugs", it only classified a few of them as prescription-only medicines and placed no restrictions on the quantities of antibiotics that could be sold to any individual. Pharmacists working in pharmacies are covered by some of the Act's regulations, but the quality of their dispensing and prescribing appears to be largely reliant on their competences.

Conclusion In Thailand, most antibiotics are easily and widely available from retail pharmacies, without a prescription. If the inappropriate use of active pharmaceutical ingredients and antibiotics is to be reduced, we need to reclassify and restrict access to certain antibiotics and to develop systems to audit the dispensing of antibiotics in the retail sector and track the movements of active ingredients.

Abstracts in عربي, 中文, Français, Русский and Español at the end of each article.

Introduction

To address antimicrobial resistance, antibiotics should be used appropriately in human medicine. Patients should receive antibiotics "appropriate to their clinical needs, in doses that meet their own individual requirements, for an adequate period of time".[4] Similar rules apply to the prudent use of antibiotics by all of the relevant stakeholders involved in veterinary medicine.[5]

The inappropriate use of antibiotics may involve the use of antibiotics for a health problem for which antibiotics are not indicated or the rational use of antibiotics either in doses that are inadequate or in the correct doses, but for an inadequate duration. As exposure of susceptible bacteria to low doses of antibiotics can lead to the selection of resistance,[1] there is a strong association between antimicrobial resistance and inappropriate use of antibiotics at both individual and population levels.[2,3]

In most developing countries, many antibiotics can be easily bought without prescription and self-medication with antibiotics, mostly bought from drugstores or pharmacies or left over from previous treatments, is common.[6,7] Such self-medication is also found in some high-income countries.[8]

A major aim of the pharmaceutical market is to respond to increased demand. As the number of retail pharmacies and other outlets for the distribution of antibiotics increases, antibiotics become more widely and easily available. Health professionals may also be persuaded to over-prescribe antibiotics by financial incentives.[9]

In low- and middle-income countries most drug regulation is focussed on the quality of drugs and the process of licensing; relatively little attention is given to distribution, price and other aspects of market control. Furthermore, in such countries, the enforcement of the drug regulations that do exist is often poor and the sale of substandard over-the-counter antibiotics and weak pharmaco-vigilance are often common.[10–12]

One of the main aims of the Global Action Plan on Antimicrobial Resistance, which was adopted by the World Health Assembly in 2015, was to optimize the use of antibiotics in human and veterinary medicine.[13] A key goal of Thailand's subsequent National Action Plan on Antimicrobial Resistance, which was developed and endorsed by the Thai Cabinet in 2016, was to reduce antibiotic consumption, by 20% in human medicine and by 30% in veterinary medicine by 2021.

In 2009, the value of the antibiotics imported into Thailand or manufactured in the country was about 315 million United States dollars and this value represented about 10% of the total value of the medicines consumed in the country.[15] There appears to be widespread and often unregulated use of antibiotics, not only for human and pet health, but also for the treatment of livestock both on farms and in household settings.

In 2016, we decided to investigate Thailand's importation, manufacture, distribution and regulation of antibiotics. In interviews with key informants, we investigated the multiple channels for the distribution of antibiotics, from import and manufacture to retail sale, and the various issues that probably contribute to the inappropriate use of antibiotics.

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Methods

We investigated antibiotic distribution and regulation in Thailand using a combination of key-informant interviews, a review of the relevant drug regulations and database searches.

Interviews

Between the July and November of 2016, we conducted in-depth interviews, lasting a mean of 90 minutes, with 43 key informants. Each interviewee had been selected using a purposive sampling technique in which relevant associations, i.e. Thailand's Animal Health Products, Animal Feed Mill, Community Pharmacy and Pharmaceutical Manufacturers Associations, were asked to propose lists of their members who could provide information about antibiotic distribution. Each potential informant identified was asked if they were able and willing to participate in the study and, if so, they were asked to give their written informed consent. Our initial aim was to recruit at least three consenting informants from each of six main stakeholder groups, i.e. animal feed industries, farms, government authorities in the fields of human and animal health, health facilities, pharmaceutical industries and pharmacies. However, using the snowball technique, more key informants were interviewed until our data became saturated and no new information emerged (Table 1). To ensure consistency, the same individual (AS) interviewed each key informant.

All of the interviews were conducted face-to-face, in Thai. They were semi-structured, but based on open-ended questions. The informants were asked about the processes of antibiotic import, manufacturing, distribution, dispensing, prescription and use. For example, they were asked about the sources of active pharmaceutical ingredients used in the manufacture of finished products and about their sale patterns. All of the interviewees were asked about the licensing process and requirements for each distributor, the registration of medicines and the factors that might contribute to the excessive and inappropriate use of antibiotics. The informants representing the farming industry or health facilities were asked about their sources of antibiotics and the processes they followed to purchase such drugs or active pharmaceutical ingredients. The data recorded in each interview were kept confidential.

Table 1. **Types, ages and years in relevant work of the 43 key informants, Thailand, 2016**

Type	No. of informants	Ages (years)	Relevant work experience (years)[a]	
			Mean	Range
Regulator	13	35–59	15.9	0.5–32.0
Representative of pharmaceutical company[b]	14	35–65	17.1	3.0–40.0
Representative of animal feed company[c]	5	30–61	18.5	3.5–37.0
Health professional from human or animal health facility	4	35–54	14.3	1.0–31.0
Wholesaler or owner of retail drug store	4	36–70	25.5	11.0–42.5
Farmer	3	37–52	16.6	13.0–19.0
Total	43	30–70	17.2	0.5–42.5

[a] Recorded after rounding to the nearest half year.
[b] Involved in the import, manufacturer and/or distribution of antibiotics.
[c] Running a feed mill or feed store.

Database searches

We estimated the numbers of licensees involved in antibiotic distribution in the Thai market and in the regulation of such distribution by analysing the relevant databases held by the Thai Food and Drug Administration[32] and the Thai Department of Livestock Development.[14]

Drug regulations

We reviewed all of the regulations promulgated by both of the Acts that, in 2016, regulated the use of antibiotics and medicated feed through inspection, licensing and marketing: the 1987 Drug Act[30] and the 2015 Animal Feed Quality Control Act.[31] The 1987 Drug Act, enforced by the Food and Drug Administration of the Thai Ministry of Public Health, regulates the finished products used in human and veterinary medicine and active pharmaceutical ingredients. The 2015 Animal Feed Quality Control Act is enforced by the Department of Livestock Development of the Thai Ministry of Agriculture and Cooperatives.

Data analysis

The data obtained from the key-informant interviews and document reviews were summarized to provide an overview of the distribution of antibiotics and identify weaknesses that could contribute to the inappropriate use of antibiotics. To assess the accuracy of the interview data, we used triangulation across the 43 interviewees. If information from one interviewee differed substantially from, and contradicted, the corresponding information from another interviewee, both pieces of information were ignored. Thailand's antibiotic distribution channels were summarized as a system flowchart. The provincial numbers of licensed private pharmacies per 100 000 population were mapped using ArcGIS software (Esri, Redlands, United States of America).

Ethics

The study protocol was approved by the Research Ethics Committee at the Thai Ministry of Public Health's Institute for Development of Human Research. Interviewees gave their written informed consent. Strict confidentiality was observed and interviewees could opt out from the interviews at any time.

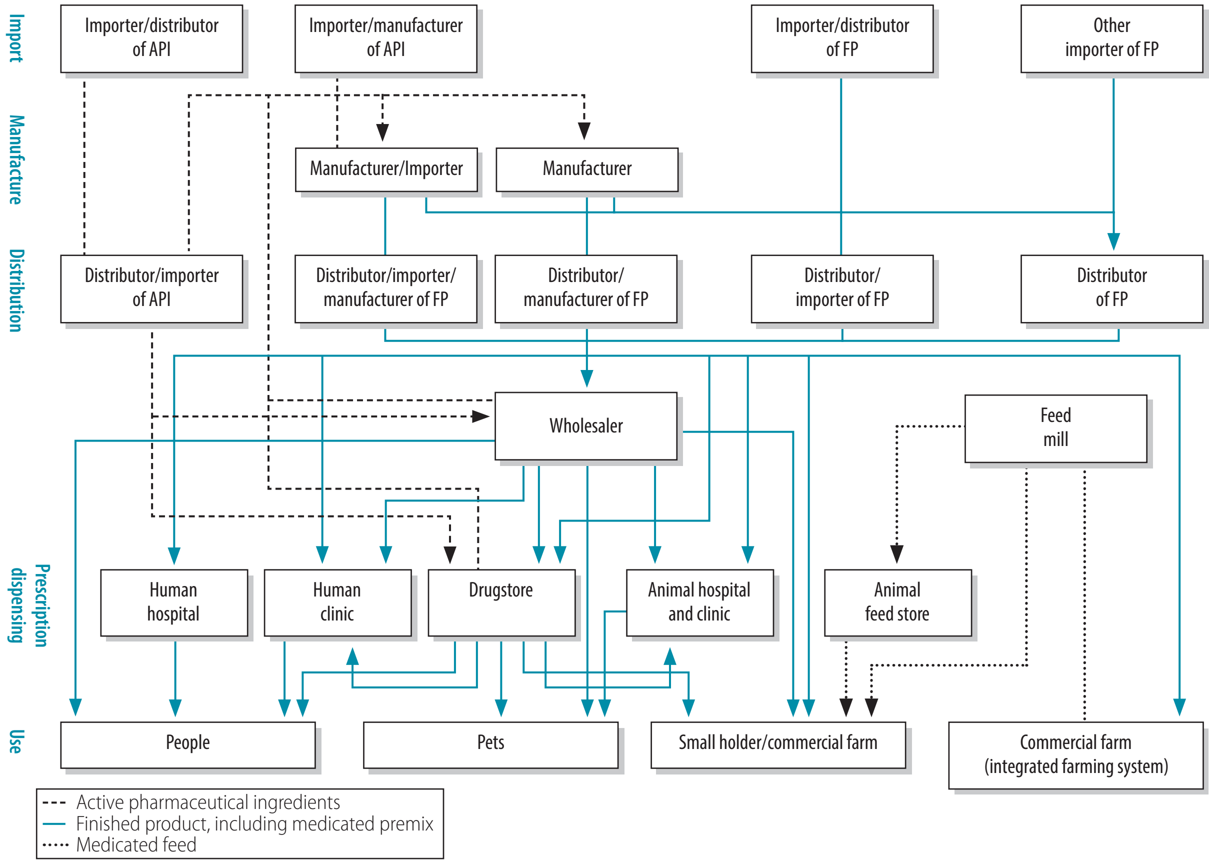
Results

We created a flowchart, based on data from the key-informant interviews and reviews of the 1987 Drug Act and the 2015 Animal Feed Quality Control Act, to summarize the antibiotic distribution channels (Fig. 1). It illustrates the complexity of the distribution, of active pharmaceutical ingredients, finished products and medicated feed, from the importers and local manufacturers to final consumption by humans, livestock or pets.

Import, manufacture and distribution

Thailand imported active pharmaceutical ingredients, for local manufacturing into finished products. It also imported medicated premix for the manufacture

Fig. 1. **Antibiotic distribution channels, Thailand, 2016**



API: active pharmaceutical ingredients; FP: finished product.
Note: An integrated farming system covers all aspects of the commercial production of livestock, including breeding, feeding, processing and marketing.

of medicated feed by feed mills. Active pharmaceutical ingredients were imported either by manufacturers or by licensed importers that then sold the ingredients to manufacturers. Most of the manufacturers either purchased active pharmaceutical ingredients from licensed importers or imported such ingredients themselves – rather than buying them, at a greater cost, from drugstores. The antibiotics produced by the manufacturers were sold to distributors, retail outlets and/or wholesalers. The imported finished products were distributed, by importers who were licensed to distribute or by distributors, to drugstores, farms, feed mills, health facilities, veterinary facilities and/or wholesalers. Our data indicated that the import and manufacture of human medicines were very similar to those of veterinary medicines, because the Thai Food and Drug Administration regulated all of these processes.

Several interviewees, representing regulators, retailers and wholesalers, described the illegal distribution of both finished products and certain active pharmaceutical ingredients. The 1987 Drug Act stipulates that all active pharmaceutical ingredients must be used by manufacturers to produce finished products. However, a few informants reported how drug inspectors had confiscated active pharmaceutical ingredients that were being used directly on livestock in farms. The interviewees that represented the farming industry reported how the high cost of buying medicated feed had persuaded some farmers to mix active pharmaceutical ingredients into their animal feed. The farmers who produced their own medicated feed did not have quality control and, in the interviewees' opinion, the feed they produced was unlikely to have an even distribution of active pharmaceutical ingredients. Although the 2015 Animal Feed Quality Control Act prohibited such direct use of active pharmaceutical ingredients in animal feed, inadequate inspection allowed farmers to purchase such ingredients from drugstores or wholesalers.

According to the various ministerial notifications and regulations promulgated by the 1987 Drug Act, most antibiotics are classified as "dangerous drugs" that can only be dispensed by licensed pharmacists in pharmacies, but can be obtained, legally, without a prescription. Only a few antibiotics, e.g. betalactamase inhibitor, carbapenems and fosfomycin, are classified as special-control drugs because of the high prevalence of resistance to them. Such drugs cannot be obtained, legally, without a prescription and are reserved for hospital use.

According to our interviews with key informants representing the country's health providers, every private and public clinic and hospital had a pharmacy section in which antibiotics were dispensed to inpatients and outpatients according to the prescriptions of doctors. Although most of these prescriptions were not required by law, the routine issuing of prescriptions, even for drugs that were not, legally, prescription-only, had become the tradition of most health facilities. Antibiotics were also dispensed directly to consumers and pet owners by licensed pharmacists in wholesalers or drugstores.

Informants representing animal feed companies reported how feed mills mostly purchased medicated premix, from importers, manufacturers or distributors, to produce medicated feed that was then sold to farms either directly or via feed stores. According to the key informants from the farming industry, most of the antibiotics that farmers used were given to livestock in medicated feed, either for treatment or for prophylaxis during periods of increased vulnerability, e.g. when livestock were transferred to new environments.

The large number of licensed individuals involved in the antibiotic supply chains can be categorized according to the type of license granted to them under the 1987 Drug Act or 2015 Animal Feed Quality Control Act. According to the licenses issued in 2016–2017, these chains involved 793 drug importers, 187 drug manufacturers, 323 animal feed importers, 299 animal feed mills, 27 165 feed stores and about 24 000 other individuals who were distributors, wholesalers or retail pharmacies (Table 2). Of the 793 importers involved in antibiotic distribution, 675 (85%) were located in Bangkok, the capital city where the main air and sea ports are located.[32] From Bangkok, many medicines, including antibiotics, are distributed throughout the country by importers, manufacturers and wholesalers, with sales driven, as usual, by market forces. In 2016, the provinces of Bangkok, Chonburi and Phuket had more than 61 licensed private pharmacies per 100 000 population (Fig. 2).

Our database searches revealed how, in 2015, about 3.1 million Thai households raised chickens ($n = 2.4$ million), ducks ($n = 0.4$ million), buffalo ($n = 0.2$ million) and/or pigs ($n = 0.2$ million).[14]

Market authorization and licensing

Overall, 5371 antibiotics were registered in the Thai Food and Drug Administration's database for 2016.[34] Of these, 3371 (63%) were registered for human use and the rest for use on livestock and pets, some as medicated premix. The database records did not distinguish between imported antibiotics and those produced in Thailand.

The importation of any drugs must be registered and pre-approved by the Thai Food and Drug Administration. By law, active pharmaceutical ingredients must only be sold by licensed importers and manufacturers. At customs, the licensed importers of active pharmaceutical ingredients are required to notify the Thai Food and Drug Administration before gaining approval for imports.

The 1987 Drug Act regulates pharmacists working in pharmacies, on aspects such as working hours and the dispensing of special-control drugs. However, most of the dispensing of antibiotics classified as dangerous drugs is not legally regulated and the quality of dispensing is largely reliant on the competences of the doctors, pharmacists and veterinarians involved. Historically, there have been no legal requirements for the keeping of records on the types and quantities of antibiotics dispensed within the retail sector. At the time of our study, prescriptions were routinely issued in hospitals, but no prescription audits were required.

Table 2. **The types and numbers of individuals involved in the distribution of antibiotics and other medicines, Thailand, 2016–2017**

Type	License held	No. of individuals
Licensed providers		
Medicine importers	Pharmaceutical import	793[a]
Medicine manufacturers	Pharmaceutical manufacture	187[a]
Medicine distributors	Pharmaceutical sales	NA[a]
Medicine wholesalers	Pharmaceutical sales	NA[a]
Retail drug stores or pharmacies		
Selling all medicines	Pharmaceutical sales	NA[a]
Selling only ready-packed medicines	Pharmaceutical sales – ready-packed medicines only	3164[a]
Selling only ready-packed medicines for animals	Pharmaceutical sales – ready-packed medicines for animals only	763[a]
Human health facilities	Health facility	11 560[b]
Importers of animal feed	Animal feed import	323[c]
Animal feed mills	Animal feed manufacture	299[c]
Animal feed stores	Animal feed sales	27 165[c]
Animal health facilities	Animal health facility	2058[d]
Unlicensed individuals		
Households involved in the rearing of livestock	None	3 102 530[e]

NA: not available.
[a] In 2017, according to the Thai Food and Drug Administration's records, there were 19 934 individuals holding full pharmaceutical sales licenses in Thailand.[32]
[b] Data from the Thai Ministry of Public Health's records for 2016.[33]
[c] Data from the Thai Department of Livestock Development's records for 2016.[35]
[d] Data from the Thai Department of Livestock Development's records for 2016.[36]
[e] The estimated number of households involved in the rearing of livestock.[14]

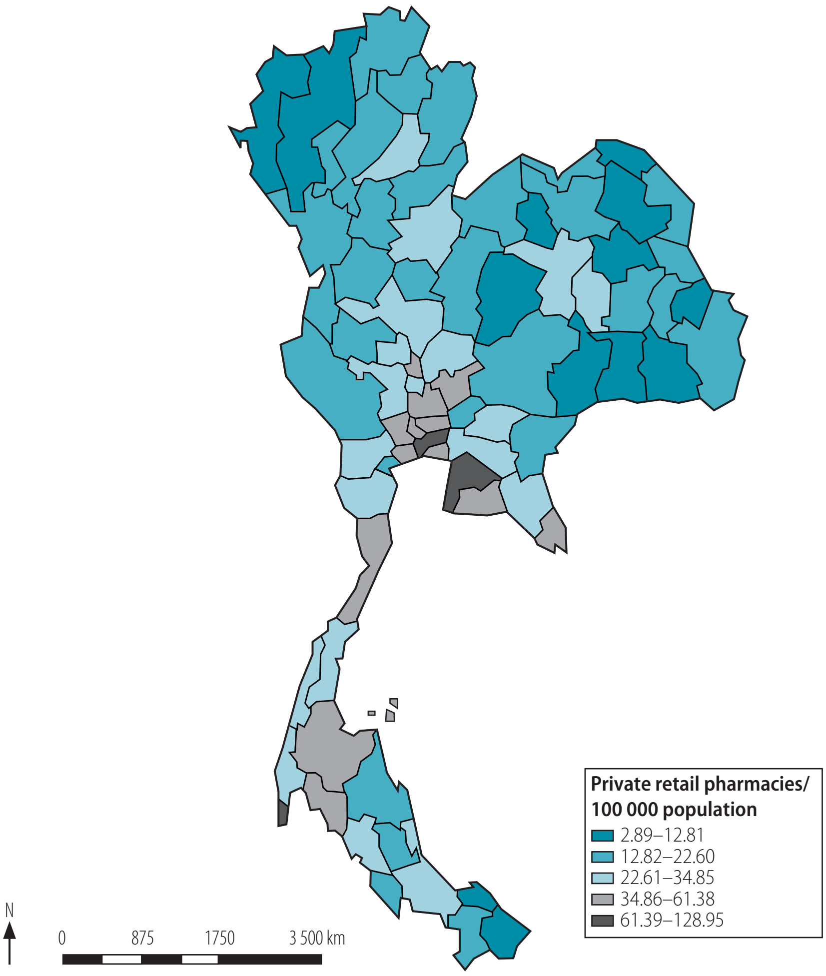
Discussion

Our study was triggered by the Global Action Plan on Antimicrobial Resistance. In this study, we identified a few key challenges, on both the demand and supply sides of the market as well as in health facilities and the regulatory environment, that perhaps made access to antibiotics too easy (Fig. 3).

Demand by patients and farmers

Self-medication with antibiotics obtained without a prescription is a common practice in most developing countries.[16] Although such self-medication may appear to be a relatively cheap option for the sick and their household carers, the societal cost of such treatment, often associated with inappropriate drugs or appropriate drugs in inadequate or suboptimal doses, and with a lack of counselling by the drug provider, can be relatively high. In China and Viet Nam, inadequate knowledge and lack of awareness of antimicrobial resistance, in both patients and providers, were recognized as important factors contributing to the irrational use of antibiotics.[17] Inadequate regulation of drug distribution and sales may result in easy access, especially when, as is often

Fig. 2. **Provincial numbers of private licensed retail pharmacies per 100 000 population, Thailand, 2016**



Source: Based on data from the Thai Food and Drug Administration's records for 2017.[32]

the case in Thailand, prescriptions are not required. In turn, easy access may boost the inappropriate use of drugs by households.[18,19]

Supply problems

Any economic incentives offered by pharmaceutical companies to boost their market share may contribute to the excessive provision of antibiotics.[17] Some pharmaceutical companies support clinicians by sponsoring continuing professional education, financing international travel for conferences and leisure or offering generous speaking fees.[20–22] In an attempt to break the link between such incentives and the preferential dispensing of drugs produced by the company providing the incentives, Denmark has decoupled the prescribing and dispensing of medicines by veterinarians.[23] Almost all medicines used in the livestock sector in Denmark are now sold directly to the farmers by pharmacies.[23]

In much of Asia, the quality of the pharmaceutical services provided by retail pharmacies is often poor. The staff in such pharmacies may offer no counselling or history taking and may recommend inappropriate presumptive treatments, e.g. antibiotics for the treatment of the symptoms of a common cold or influenza, or appropriate drugs in suboptimal doses.[24] Suboptimal doses may be all that the patient can afford. In Peru and central Thailand, private retail pharmacies, where dispensing could not be guided by the antibiotic-resistance profiles of the causative agents, were found to be the most common source of antibiotics for the treatment of sexually transmitted diseases.[25,26]

In Thailand, we identified about 24 000 distributors, retailers and wholesalers who were fully licensed for pharmaceutical sales in 2017. At the time of our study, the records of the Thai Food and Drug Administration did not differentiate between such licensed distributors, retailers and wholesalers. In consequence, there was no easy way to monitor or control the sale of large quantities of antibiotics to individual patients or farmers. We found that, if they could afford it, Thai farmers could easily buy very large amounts of finished products and active pharmaceutical ingredients from drug retailers or wholesalers.

Regulatory environment

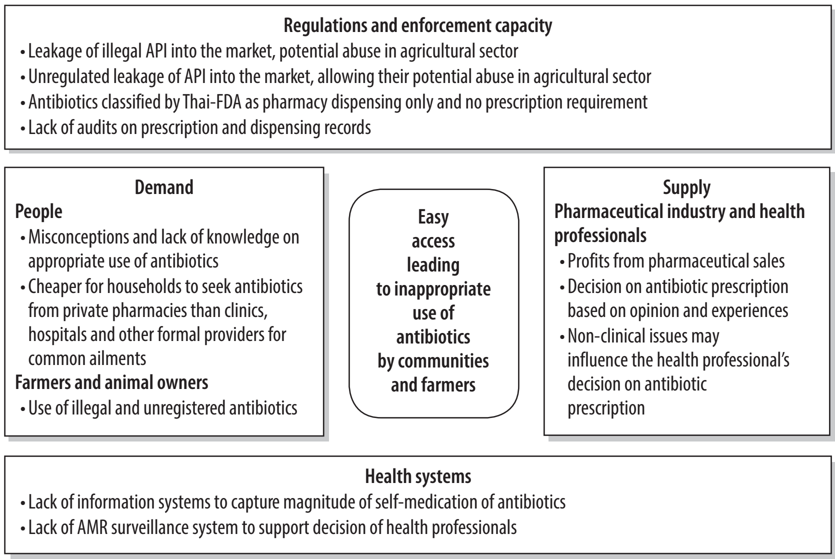
The focus of drug regulation in low- and middle-income countries, e.g. Ethiopia, Thailand, the United Republic of Tanzania and Zimbabwe, is on drug quality and licensing rather than availability and distribution channels.[10–12]

In Thailand, the 1987 Drug Act did attempt to regulate the availability of some antibiotics, by dividing antibiotics into a large group of "dangerous drugs not requiring prescriptions" and a much smaller group of "special-control drugs requiring prescriptions".[30] This categorization meant that most antibiotics could be dispensed, by licensed pharmacists in retail pharmacies, without a prescription. Furthermore, the Act made no attempt to regulate the quantity of antibiotics that could be distributed to any individual or to control the excessive use of antibiotics in livestock. Later, the 2015 Animal Feed Quality Control Act prohibited direct use of active pharmaceutical ingredient in the animal feeds. However, our interviews indicated that, many Thai farmers were, illegally, adding active pharmaceutical ingredients to animal feeds, probably as a cost-saving measure.

Following a series of public consultations, the Thai Food and Drug Administration is working on a reclassification of antibiotics in which a larger proportion of the drugs will be categorized as special-control/prescription-only, in line with the recommendations made by the World Health Organization in its 20th Model List of Essential Medicines.[27]

Compared with access to antibiotics, access to active pharmaceutical ingredients appears to be less well regulated, leading to inappropriate use by farmers. In Thailand, all drugs have to be registered with the Food and Drug Administration before production or importation. There is, however, no corresponding requirement for the

Fig. 3. **Factors potentially contributing to the excessive and/or inappropriate use of antibiotics, Thailand, 2016**



AMR: antimicrobial resistance; API: active pharmaceutical ingredients; FDA: Food and Drug Administration.

registration of active pharmaceutical ingredients. Drug distributors and retailers can only sell active pharmaceutical ingredients legally to manufacturers. However, a lack of monitoring and tracking of active pharmaceutical ingredients and inadequate inspections at the drug distributors and retailers mean that this legal restriction is generally ignored.

One limitation of our study is that the data maintained by the Thai Food and Drug Administration do not allow any estimation of the national consumption of each major class of antibiotics in terms of, for example, the defined daily dose per 1000 inhabitants per day. The Thai Working Group on the Surveillance of Antimicrobial Consumption is working on the development of a sustainable system to monitor annual antimicrobial consumption.[28]

In conclusion, this study appears to be the first published study in Thailand to investigate antibiotic distribution, for human and animal health. The thousands of drug distributors, drug wholesalers, retail pharmacies and animal feed stores that have arisen in the country, as a result of market forces, and the small number of antibiotics that are classified as special-control/prescription-only make most antibiotics easily and widely available in both the human and animal health sectors. Such wide availability probably leads to frequent inappropriate use. A general lack of enforcement of the legislation covering the distribution of active pharmaceutical ingredients facilitates the direct use of such ingredients on farms.

The unnecessary and inappropriate use of antibiotics will probably lead to an increase in the problem posed by antimicrobial resistance in Thailand. A system for recording antibiotic dispensing at retail pharmacies should be established[29] and then carefully audited by pharmacists. The continued professional education of retail pharmacists should be promoted, as a means of reducing the inappropriate use of antibiotics, and other drugs. The sales of large quantities of antibiotics to individuals need to be restricted by differentiating wholesalers from retailers in the licensing system. This includes prohibiting wholesalers from selling large quantities of antibiotics to farmers, or others who are not licensed retail outlets, and carefully restricting the sale by retailers of large quantities of such drugs to individuals. The ongoing policy to reclassify more antibiotics as special-control/prescription-only drugs in Thailand should be rapidly implemented. A national system for tracking active pharmaceutical ingredients should be established immediately, to prevent the direct use of such ingredients on farms. ■

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ملخص

قنوات توزيع المضادات الحيوية في تايلند: نتائج المقابلات مع المبلغين الرئيسين ومراجعات اللوائح التنظيمية للعقاقير وعمليات البحث في قاعدة البيانات

الغرض تحليل كيفية استيراد المضادات الحيوية وتصنيعها وتوزيعها وتنظيمها في تايلند.

الطريقة قمنا بجمع معلومات حول توزيع المضادات الحيوية في تايلند في مقابلات متعمقة مع 43 من المبلغين الرئيسين من المزارع والمنشآت الصحية وصناعات المنتجات الدوائية وعلف الحيوانات والصيدليات الخاصة ومنظمين، وكذلك في قاعدة البيانات وأبحاث المؤلفات.

النتائج في عام 2016–2017 تضمن التوزيع المرخص للمضادات الحيوية في تايلند أكثر من 700 مستورد وحوالي 24 ألف موزع مثل الصيدليات التي تبيع بالتجزئة للجمهور وبائعي الجملة. تستورد تايلند المضادات الحيوية والمكونات الدوائية النشطة دون وجودِ نظام لمراقبة توزيع المكونات النشطة، والتي يُستخدم بعضها مباشرةً في المزارع دون خضوعها للمعالجة. ومن الممكن شراء معظم المضادات الحيوية من الصيدليات لاستخدامها في المنازل أو المزارع دون وصفة طبية. وعلى الرغم من أن قانون العقاقير لعام

1987 جاء ليصنف أغلب المضادات الحيوية "كعقاقير خطيرة"، فقد صنف فقط القليل منها كعقاقير لا تُصرف إلا بأمر الطبيب، دون أن يفرض أي قيود علي كميات المضادات الحيوية المصرّح ببيعها لأي فرد. وهناك بعضٌ من اللوائح التنفيذية للقانون التي تغطي الصيادلة العاملين في الصيدليات إلا أنه يبدو أن جودة وصفهم للأدوية وصرفها تتوقف بشكل كبير على مستوى كفاءتهم.

الاستنتاج تتوفر معظم المضادات الحيوية في تايلند بسهولة وعلى نطاق واسع لدى الصيدليات التي تبيع للجمهور دون وصفة طبية. وإذا كان من المعتزم الحد من الاستخدام غير الأمثل للمكونات الدوائية النشطة والمضادات الحيوية، فسوف يلزمنا إعادة تصنيف مضادات حيوية معينة وفرض قيود على صرفها، فضلاً عن وضع أنظمة لمراجعة صرف المضادات الحيوية في قطاع البيع بالتجزئة، وتتبع أوجه استخدام المكونات النشطة.

摘要

泰国的抗生素销售渠道：关键知情人访谈结果、药品监管审查和数据库检索

目的 分析泰国的抗生素是如何进口、加工、销售和监管的。

方法 我们收集了泰国的抗生素销售信息，深入采访了来自农场、医疗机构、制药和动物饲料行业、私人药店和监管机构的 43 名关键知情人，并进行了数据库和文献检索。

结果 2016-2017 年，泰国获得许可的抗生素销售涉及 700 多家进口和 24000 家分销商——例如零售药店和批发商。泰国进口抗生素和活性药物成分。目前还没有用于监测活性成分的分配的系统，其中一些未经过处理而直接在农场使用。大多数抗生素可以从药店购买，供家庭或农场使用，无需处方。尽管 1987 年的《药品法》将大多数抗生素列为“危险药物”，但它只将其中少量的抗生素列为处方类药物，并未对可以出售给任何个人的抗生素的数量加以限制。药店工作的药剂师受该法案中的某些条例的监管，但是其配药和开药的质量似乎在很大程度上依赖于他们的能力。

结论 在泰国，大多数抗生素很容易从零售药店买到，无需处方。如要减少对活性药物成分和抗生素的不当使用，我们需要对某些抗生素进行重新分类和限制销售，并开发相应系统审核零售部门的抗生素分配和追踪活性成分的流通。

Résumé

Les circuits de distribution des antibiotiques en Thaïlande: résultats d'entretiens avec des informateurs clés, de revues de la réglementation sur les médicaments et de recherches dans des bases de données

Objectif Analyser l'importation, la fabrication, la distribution et la réglementation des antibiotiques en Thaïlande.

Méthodes Nous avons rassemblé des informations sur la distribution des antibiotiques en Thaïlande à partir d'entretiens approfondis avec 43 informateurs clés –provenant d'exploitations agricoles, d'établissements de soins, du secteur pharmaceutique et de la production d'aliments pour animaux, de pharmacies et d'organismes de réglementation privés– et de recherches dans des publications et des bases de données.

Résultats En 2016-2017, la distribution d'antibiotiques autorisés en Thaïlande a fait intervenir plus de 700 importateurs et environ 24 000 distributeurs, comme les pharmacies d'officine et les grossistes. La Thaïlande importe des antibiotiques et des principes actifs pharmaceutiques. Elle n'a pas de système de contrôle de la distribution des principes actifs, dont certains sont utilisés directement dans les exploitations agricoles, sans traitement préalable. La plupart des antibiotiques sont en vente dans les pharmacies, pour usage domestique ou agricole, sans ordonnance. Bien que la Loi sur les médicaments de 1987 ait classé la plupart des antibiotiques comme «médicaments dangereux», elle n'en a classé qu'une petite partie en tant que médicaments soumis à ordonnance et n'impose aucune restriction sur la quantité d'antibiotiques qui peut être vendue à une personne. Certaines dispositions de cette Loi s'appliquent aux pharmaciens qui travaillent dans des pharmacies, mais il apparaît que la qualité de leur délivrance et de leur prescription dépend fortement de leurs compétences.

Conclusion En Thaïlande, la plupart des antibiotiques sont très facilement accessibles dans les pharmacies d'officine, sans ordonnance. Si l'on veut réduire l'usage inapproprié des principes actifs pharmaceutiques et des antibiotiques, il faudra reclasser certains antibiotiques et en limiter l'accès, mettre au point des systèmes pour contrôler la délivrance d'antibiotiques dans les officines et contrôler les mouvements des principes actifs.

Резюме

Каналы распространения антибиотиков в Таиланде: результаты интервью с ключевыми информантами, обзоры правового регулирования оборота лекарственных средств и поиск в базах данных

Цель Выяснить, каким образом происходит импорт, производство, распространение и контроль антибиотиков в Таиланде.

Методы Мы собрали информацию о распространении антибиотиков в Таиланде с помощью углубленных интервью с 43 ключевыми информантами — представителями фермерских хозяйств, медицинских учреждений, фармацевтической и комбикормовой промышленности, частных аптек и регулирующих органов, а также путем поисках в базах данных и научной литературе.

Результаты В 2016–2017 гг. сеть лицензированного распространения антибиотиков в Таиланде включала более 700 импортеров и около 24 000 дистрибьюторов, таких как розничные аптеки и организации оптовой торговли. Таиланд импортирует антибиотики и активные фармацевтические ингредиенты. При этом в Таиланде отсутствует система мониторинга распространения активных ингредиентов, некоторые из которых в исходном виде используются непосредственно на фермах. Большинство антибиотиков можно купить для домашнего или фермерского использования в аптеках без рецепта. Хотя в Законе о продаже рецептурных лекарственных средств (Prescription Drug Marketing Act) от 1987 года большинство антибиотиков классифицированы как сильнодействующие лекарственные средства, в то же время в этом документе лишь некоторые из них классифицированы как лекарственные средства, отпускаемые по рецепту, и отсутствуют ограничения по количеству антибиотиков, в котором они могут быть отпущены одному лицу. Некоторые положения закона распространяются на фармацевтов, работающих в аптеках, но качество их назначения и отпуска лекарственных средств, по-видимому, в значительной степени зависит от их компетенции.

Вывод В Таиланде большинство антибиотиков легко и широко доступны в розничных аптеках, где их можно приобрести без рецепта. Чтобы сократить ненадлежащее использование активных фармацевтических ингредиентов и антибиотиков, необходимо повторно их классифицировать, ограничить доступ к определенным антибиотикам и разработать системы контроля отпуска антибиотиков в розничном секторе и отслеживания движения активных ингредиентов.

Resumen

Canales de distribución de antibióticos en Tailandia: resultados de entrevistas con informantes clave, revisiones de regulaciones de medicamentos y búsquedas en bases de datos

Objetivo Analizar cómo se importan, fabrican, distribuyen y regulan los antibióticos en Tailandia.

Métodos Recopilamos información sobre la distribución de antibióticos en Tailandia, en entrevistas en profundidad, con 43 informadores clave de granjas, centros de salud, la industria farmacéutica y alimentación animal, farmacias privadas y reguladores, y en búsquedas de bases de datos y bibliografía.

Resultados En 2016-2017, en la distribución autorizada de antibióticos en Tailandia participan más de 700 importadores y alrededor de 24 000 distribuidores, p.e. farmacias minoristas y mayoristas. Tailandia importa antibióticos y sustancias farmacéuticas activas. No existe un sistema para controlar la distribución de los ingredientes activos, algunos de los cuales se usan directamente en las granjas, sin ser procesados. La mayoría de los antibióticos se pueden comprar en farmacias, para uso doméstico o agrícola, sin receta médica. Aunque la Ley de Medicamentos de 1987 clasificó la mayoría de los antibióticos como "drogas peligrosas", solo clasificó algunos de ellos como medicamentos de venta con receta y no restringió las cantidades de antibióticos que podrían venderse a cada persona. Los farmacéuticos que trabajan en farmacias están cubiertos por algunas de las normas de la Ley, pero la calidad de su dispensación y prescripción parece depender en gran medida de sus competencias.

Conclusión En Tailandia, la mayoría de los antibióticos están disponibles de forma fácil y general en farmacias minoristas, sin receta médica. Para reducir el uso inapropiado de sustancias farmacéuticas activas y antibióticos, debemos volver a clasificar y restringir el acceso a ciertos antibióticos y desarrollar sistemas para auditar la dispensación de antibióticos en el sector minorista y llevar a cabo un seguimiento de los movimientos de los ingredientes activos.

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Appendix 2 System analysis of antimicrobial utilization in humans and animals: International Health Policy Program Working Paper

I have reviewed laws and regulations, and assessed the enforcement capacities of the antimicrobial distribution reporting system in Thailand. It was reported in Part 1: Regulation and regulatory enforcement, 'System analysis of antimicrobial utilization in humans and animals: actors and legal framework'. Two main regulations were examined in the report:

1. Drug Act, BE 2530 (1987), BE 2530 (1987)
2. Animal Feed Quality Control Act, BE 2558 (2015)

The full report is in the next page.

System analysis of antimicrobial utilization in humans and animals: actors and legal framework

iHPP Thailand

System analysis of antimicrobial utilization
in humans and animals: actors and legal framework

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Acronym

AFVC	Animal Feed and Veterinary Products Control
AMR	Antimicrobial Resistance
AMU	Antimicrobial Use
API	Active Pharmaceutical Ingredient
B.E.	Buddhist Era
DLD	Department of Livestock Development
FAO	Food and Agricultural Organization
FDA	Food and Drug Administration
FP	Finish Product
GDP	Gross Domestic product
GMP	Good Manufacturing Practice
GPP	Good Pharmacy Practice
ISO	International Organization for Standardization
MoAC	Ministry of Agriculture and Cooperatives
MoPH	Ministry of Public Health
OIE	World Organization for Animal Health
PIC/S	Pharmaceutical Inspection Co-operation Scheme
PHO	Provincial Health Office
SMP	Safety Monitoring Program
Thai-SAC	Thai Surveillance of Antimicrobial Consumption
WHO	World Health Organization

A. Background

Antimicrobial Resistance (AMR) has recently been recognized as a major threat to global health; its increased prevalence and spread of resistant microorganisms affect humans and animals throughout the world [1]. Worldwide, AMR claims 700,000 human deaths annually; unless effective interventions are installed, AMR will claim ten million deaths by 2050 and cost the world up to US$ 100 trillion, equivalent to 2% - 3.5% of Gross Domestic Product (GDP) [2].

Antibiotic use is a critical factor in the emergence of resistant bacteria, as irrational use of antibiotics can speed up the resistance [3]. Currently in the world, drug supplies and drug distribution channels are dramatically increasing which improves access to medicines. However, equally important parallel interventions to support the rational use of medicines are not increasing at the same rate. In developed countries, drug prescriptions are under authorization by licensing prescribers. The mandatory prescription system can easily track the distribution of drugs and facilitate audits which may redress the irrational use of antibiotics.

However, in developing countries including Thailand, there is no such monitoring. Moreover, people's easy access to antimicrobials without prescription (through dispensing and purchasing of antibiotics) is common at private pharmacies. At the farm level, active pharmaceutical ingredients and medicated premix can be used without professional supervision.

In May 2015, the World Health Assembly adopted a Global Action Plan on Antimicrobial Resistance, calling on member states to develop a national action plan within two years [4]. The World Organisation for Animal Health (OIE) and the Food and Agricultural Organization (FAO) also adopted AMR resolutions in 2015, fostering tripartite collaboration. Thailand developed a national AMR strategy, endorsed by the Cabinet in August 2018, which has gained legitimacy and facilitated multi-sectoral collaboration. One of the five indicators of the National Strategic Plan is the establishment of the Antimicrobial Use (AMU) monitoring system. Antimicrobial consumption monitoring is a key instrument for monitoring trends and evaluating the outcomes of interventions which strengthen antimicrobial stewardship. It generates evidence on the magnitude and profiles of antimicrobial consumption. It can provide entry points for evidence-based policy actions to reduce antimicrobial use in the country [5, 6].

The system analysis of antimicrobial utilization - including marketing, distribution, prescription and use - supports the development of AMU monitoring systems and contributes to the design of effective policy control levers at different levels of the distributional channel.

B. Objective

The overall objective of this study is to describe and analyse the system of antimicrobial utilization in humans and animals, the actions of key actors involved in distribution channels and the legal frameworks governing distribution and regulatory capacities.

Specific objectives:

- To review laws and regulations and assess the enforcement capacities of the antimicrobial distribution reporting system
- To describe the system and process of antimicrobial utilization in humans and animals
- To identify key actors and their roles in antimicrobial utilization.

C. Methods

Framework of the study

Key terms and explanations included in this study are defined as follows:

Antimicrobials: An antimicrobial is considered as a naturally occurring, semi-synthetic or synthetic substance that exhibits antimicrobial activity (to kill or inhibit the growth of micro-organisms) at concentrations attainable in vivo. Anti-helminthic and substances classed as disinfectants or antiseptics are excluded from this definition [7]. In this study, it focuses on antibiotics.

Drug utilization: Drug utilization research is defined by WHO as the marketing, distribution, prescription and use of drugs in a society with special emphasis on the resulting medical, social and economic consequences [8]. In this study, we focus on distribution as it is governed by two relevant Acts responsible by FDA and DLD.

We began by reviewing what regulations and the processes under which they are enforced mean. The research team proposed assessing the regulatory framework and the process of enforcement with the application of Kumaranayake [9]. Although there are different regulatory goals such as product quality, quantity, price and distribution, this study focuses on antimicrobial distribution.

Regulating quality and quantity is implicitly linked with regulating distribution. For example, restricting the number of drug stores in some geographical areas by setting standards and quality assurance, or the licensing of medicines to ensure their safety, contribute to the number of providers and the quality of products.

Relevant key actors involved in antimicrobial distribution are also fully covered by this study. There are many types of regulatory instruments to control and monitor drug utilization such as legislation, incentives and codes of conduct. This study focused on two main pieces of legislation covering pharmaceutical products including medicated feed. The two Acts are Drug Act BE 2530 (1987) and the Animal Feed Quality Control Act BE 2558 (2015).

Figure 1. The four regulatory questions captured by this study: what to regulate, who is regulated, how to regulate and at what level? Target variables can be applied at different levels. This study considered antibiotics and organization levels such as the licensing of operators and health facilities. Licensing and regulating individual health professionals by related professional councils are beyond the scope of this study.

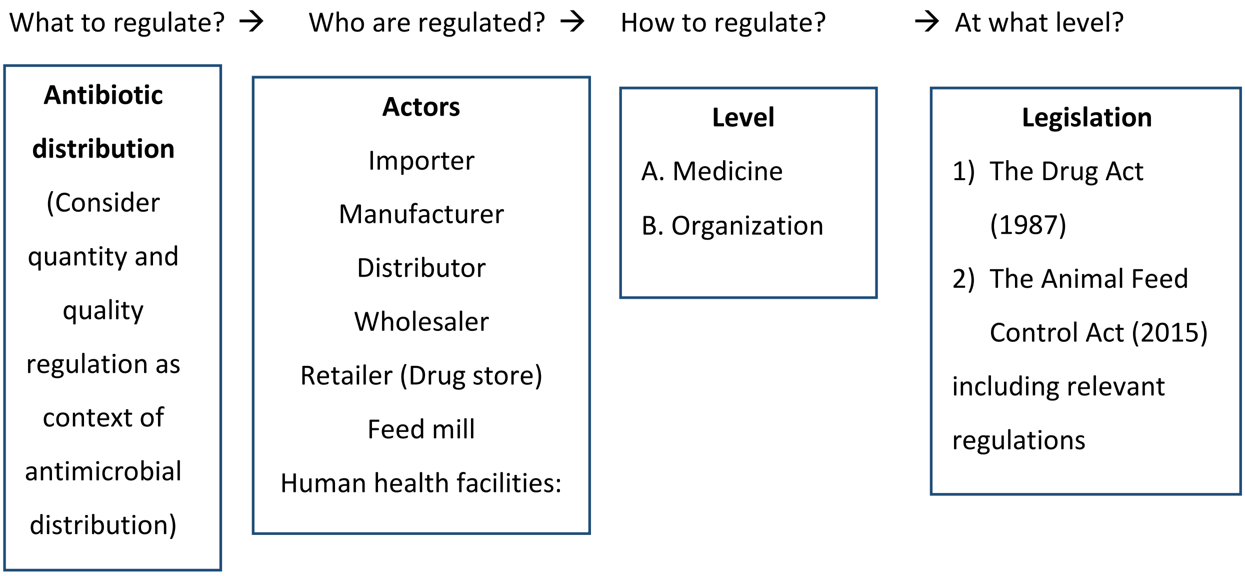

Figure 1 Scope of regulating antimicrobial distribution captured by this study

In terms of the system and process of antibiotic utilization, the study covered importation, manufacturing, and distribution by operators, dispensing and prescription by professionals. The study covered numerous actors such as: importers, manufacturers, distributors, wholesalers, retailers, feed mills, feed stores and animal health facilities and human health facilities including public hospitals, private hospitals, clinics, farmers, and pet owners.

Data collection and analysis

Mixed methods were applied. This included reviews of relevant literature and in-depth interviews with key informants.

Key document reviews included official papers on licensing operators, medicine marketing authorization and inspection under the two Acts which control antibiotic and medicated feed (medicine for feed medication used in animals). Firstly, the Drug Act (1987) is responsible by the Thai Food and Drug Administration (FDA) of the Ministry of Public Health (MoPH). This Act controls both human and veterinary medicine finished products and Active Pharmaceutical Ingredients (API). Secondly, the Animal Feed Quality Control Act BE (2015), the responsibility of the Department of

Livestock Development, Ministry of Agriculture and Cooperatives (MoAC), which controls medicated feed. This study reviewed the total 45 relevant laws and regulations ranging from the Act itself and accompanying regulations, notifications, and rules (Table 1).

Table 1 Number of documents related to regulations reviewed by this study

	MoPH	**MoA**
Act	**The Drug Act (1987)**	**The Animal Feed Control Act (2015)**
Ministerial regulation	8	2
Notification of ministry	18	5
Notification of the responsible organization (FDA, DLD)	9	1
Rule of the organization	1	-
Total documents reviewed	36	9

The reviews of regulation were supplemented by data gathered through semi-structured interviews with 13 regulators; this gained additional information about the legal resources and how regulatory enforcement was interpreted and implemented. The regulators are government officers in MoPH: FDA, the Bureau of Drug, Rural and Local Consumer Health Products Promotion and Protection Division, Provincial Health Office; MoAC: Animal Feed and Veterinary Products Control (AFVC), and Provincial Livestock Office. Interviews with regulators focused on existing antibiotics regulations and enforcement, according to the conceptual framework of the study. On the effectiveness of regulation, the study analyzed the content of regulation, and real-life enforcement and regulatory capacity. The practices and challenges of regulatory enforcement also covered two levels - national and provincial - as certain regulations were devolved to provincial offices.

Further, this study covered a total of 30 key informant interviews including pharmaceutical companies, animal feed companies, health professionals, wholesalers, drug stores and farmers, and others from the association in accordance with pharmaceutical production and sale (Table 2). The key informants have experience in their respective areas, with an average of 17 years (range 0.5 to 43). The purpose of the in-depth interviews was to understand how regulation was enforced in real-life and the extent of their capacity to so. Interviews with key informants who are operators focused on the insights of drug distribution though the supply chain and how they are regulated in real life.

The interviewees were asked about their roles on drug distribution channels. The interview allowed investigators to explore new and other open-ended themes surrounding antimicrobial distribution which may be overlooked by the conceptual framework. Themes covered by the interviews included: (1) regulations in relation to antimicrobial distribution: (2) its enforcement: responsible organization, capacity of organization in term of resources and infrastructure, regulatory activity and outcomes; (3) cooperation between these regulatory organizations at different levels and with other regulation enforcement agencies; (4) distribution process of antimicrobials; and (5) roles of operator in the distribution.

Table 2 Number and profiles of key informants covered by the study

Key informants	Total number	Age (range; year)	Work experience in the organization (mean, range; year)
Regulator	13	(35-59)	(15.88, 0.5-32)
Pharmaceutical company (importer, manufacturer, distributor)	14	(35-65)	(17.07,3-40)
Animal feed company	5	(30-61)	(18.5, 3.5-37)
Health professional from human and animal health facility	4	(35-54)	(14.25, 1-31)
Wholesaler, drug store (retailer)	4	(36-70)	(25.5, 11-42.5)
Farmer	3	(37-52)	(16.6, 13-19)
Total	43	(30-70)	(17.17,0.5-42.5)

The data extracted from document reviews and transcripts of the key informant's interviews were summarized, analyzed and presented according to the study framework. The antimicrobial distribution in line with roles of key actors was mapped into the system flow chart.

Consultative meeting

A consultative meeting took place after initial data sets were analyzed. Its aim was to present the preliminary findings and invite workshop participants to review, verify, discuss and propose policy recommendations on antibiotic distribution and related regulatory enforcement.

The workshop participants were invited from the following groups: governmental officers at national and provincial level, academia from the faculty of medicine, pharmacy and veterinary science, and relevant associations.

Before the meeting, a draft document and a brief summary of the document were circulated to participants for advance review. The meeting started with a presentation by the research team and opened for multi-stakeholder discussion in order to identify certain policy recommendations and improve the study report. Afterwards, participants were encouraged to submit their written comments within 30 days following the meeting. The report was revised, taking into account comments by participants, in order to get final approval.

D. Findings

Findings consist of three parts: the first starts with the regulatory environment of antimicrobial distributions. The second part concerns actors involved in the distribution channels until antibiotic use by consumers and animals. Finally, in part three, reveals the complexity of distribution channels and concerned actors.

PART I: Regulation and regulatory enforcement

Two laws govern antibiotic use in human and livestock: the Drug Act BE 2530 (1987) and the Animal Feed Quality Control Act BE 2558 (2015). FDA and DLD are the custodies of these laws respectively. However, the authority of law enforcement on the operators operating outside Bangkok was delegated to the Provincial Health Office (PHO) and Provincial Livestock Office (PLO) respectively. Details are discussed in the supply chain inspection section.

The Drug Act, BE 2530 (1987)

The Drug Act BE 2510 (1967) was first legislated in 1967; it has been amended four times in 1975, 1979, 1984 and the last revision in 1987. The current version is the Drug Act BE 2530 (1987). The aim of the law is to assure safety, efficacy and quality of medicines.

- **Regulatory authority**

The FDA was established in 1922; it was the Narcotics Division under the Public Health Department, Ministry of the Interior in 1922 and then transformed to assume the functions of the current FDA. Currently, it is the responsible agency under the MoPH with a statutory duty to protect consumers' health through ensuring the safety, quality and efficacy of all consumable health products that have implications on health of the population. The portfolio of health products responsible by the FDA are: foods, drugs, psychotropic substances, narcotics, medical devices, volatile substances, cosmetics and hazardous substances. Each product is governed by specific law.

There are eight laws relating to health products, for which the FDA has responsibility. These are:

1) Drug Act, B.E. 2510 (1967) and amendment No. 2 (1975), No. 3 (1979), No. 4 (1985) and No. 5 (1987),
2) Psychotropic Substance Act B.E. 2518 (1975) and amendment No. 2 (1985), No. 3 (1992) and No. 4 (2000)
3) Food Act, B.E. 2522 (1979)

4) Narcotic Act, B.E. 2522 (1979) and amendment No. 2 (1985), No. 3 (1987) and No. 4 (2000)
5) The Emergency Decree on the Prevention of Abuse of Volatile Substances, B.E. 2533 (1990) and amendment No. 2 (2000)
6) Hazardous Substance Act, B.E. 2535 (1992)
7) Medical Device Act, B.E. 2551 (2008)
8) Cosmetic Act, B.E. 2558 (2015)

The FDA is responsible for four international agreements: 1) the Single Convention on Narcotic drug 1961; 2) The Convention on Psychotropic Substance 1971; 3) the International Code of Marketing of Breast Milk Substitute 1981; and 4) The United Nation Convention Against Illicit Traffic in Narcotic Drugs and Psychotropic Substances 1988.

- **Definition and classification of medicines**

In line with the fifth revision of the Drug Act (1987), the FDA is responsible for regulating all pharmaceutical products, as defined in Section 4 of the Drug Act.

Drugs are defined as:

(1) Substances recognized by pharmacopoeias as notified by the Minister;

(2) Substances intended for use for the diagnosis, treatment, relief, cure or prevention of human or animal disease or illness;

(3) Substances which are pharmaceutical chemicals or semi–processed pharma chemicals; and

(4) Substances intended to affect the health, structure or function of the human or animal body.

Substances under (1) (2) or (4) shall not include:

(a) Those intended for use in agriculture or industry as notified by the Minister;

(b) Those intended for use as food for human, sport and medical apparatus, cosmetics or device for use in the practice of medicine and a component thereof;

(c) Those intended for use in science laboratory for research, analysis or verification of disease, which is not directly done to human body.

The Drug Act also classifies drugs into different categories; this includes:

“Modern drug” meaning a drug intended for use in the practice of modern medicine or the cure of an animal disease;

“Dangerous drug” meaning a modern of traditional drug notified by the Minister as a dangerous drug;

“Special-controlled drug” meaning a modern or traditional drug notified by the Minister requiring a specific control mechanism on its distribution and use;

“External drug” meaning a modern or traditional drug intended for external use.

“Specific local application drug” meaning a modern or traditional drug intended for use in specific areas of human body such as drugs for ears, eyes, nose, mouth, anus, vagina or urinary tracks.

“Household drug” means a modern or traditional drug which is notified by the Minister as a household drug;

“Ready – packed drug” means a modern drug manufactured in a pharmaceutical from, which is packed in a closed or sealed package which has all the label as required by this Act.

It is noted that drugs cover finished products: human medicines, veterinary medicines including medicated premix (medicine for animal feed mixing only), and API. The medicated feed (medicine for feed medication) is regulated by the Animal Feed Quality Control 2015 responsible by Department of Livestock Development, which will be discussed later in Part 1.

- **Instruments for regulating antibiotic distribution**

To regulate antibiotic distribution, sale and access by the population, the Drug Act (1987) classified medicines into two main groups; modern and traditional medicines. All types of antibiotics are defined as modern medicine and are classified into four categories including:

1) Household drug, which does not require a license to sell. There are currently 52 items of all household drugs according the MoPH notification, and two items are antibiotics:
    - Sulfacetamide sodium 10% (eye drops)
    - Silver Sulfadiazine 1% (topical use)
2) Dangerous drug (pharmacy dispensing only). This group of antibiotics can be sold without prescription but must be dispensed by pharmacists in licensed pharmacies. On the front of the package, there is a red font label with the words “dangerous drug”. There are more than 78 items on the list, according the last MoPH notification. All antibiotics are classified as dangerous drugs except the following:
    - All specific local application drugs, with the exception of Penicillin

- Special-controlled substance drug: Sulfonamides PO, Chloramphenicol for children use, for animal registered medicine, for adult (systematic use))
- Household drug (Sulfacetamide sodium 10% (eye drop), Silver Sulfadiazine 1% (topical use))
- Penicillin V Potassium (dry syrup)
- Phenylsulphathiazole 500 mg (tablet)
- Sulfamethoxazone 400 mg + Sulfa-trimethoprim 80 mg (tablet/capsule)
- Sulfadoxine 500 mg + Pyrimethamine 25 mg (tablet)
- Anti-tuberculosis, anti-malaria, antiprotozoal, anti-virus (except specific local application drug), anti-fungus (except specific place drug).

3) Special-controlled drug, which requires prescription and can only be used in hospitals or sold to doctors, dentists, veterinary professionals and drug wholesale licensees. On the front of the package, there is a red font label with the words “special-controlled drug”. There are 83 items of medicines on these lists according the MoPH notification. The special-controlled antibiotics are:
   - Sulfonamide PO
   - Chloramphenicol for children use, for animal registered medicine, and for adults (internal use)
   - New drug (registered under conditional approval); these can be used by hospitals under the Safety Monitoring Program (SMP) for at least two years, where the SMP is managed by FDA.
4) Non-dangerous and non-special controlled drugs (ready-packed drugs), which can be sold by health professionals. None of the existing registered antibiotics are categorized as this group.

In summary, the Drug Act regulates antibiotic distribution by classifying all types of antibiotics into groups, and specifies which outlets can patients access.

- **Market authorization**

According to section 79 of the 1987 Drug Act, any person licensed to produce or import drugs who wishes to produce or import drugs is required to apply to the competent officer for registration of the formula. Upon receipt of certificate of medicine registration, the drug could be produced or imported.

As of 2016, FDA registered approximately 5,371 antibiotics; 3,371 drugs (63%) were for human use and about 2,000 were veterinary antibiotics including medicated premix. However, data does not allow differentiation between imported and locally-produced antibiotics.

Section 79 states that it does not cover API control. Under the MoPH notification, the import and manufacture licensees can import and, or produce API on the following conditions 1) use for their own production of finished products, 2) sell to drug sale or manufacture licensees, 3) export to overseas. The law stipulates that API must be distributed to the production of finished products only; it cannot be used directly in humans and animals due to its high concentration. At customs, licensed importers are required to notify FDA before API importation. Notification is much weaker than registration. In addition, notifications are not kept and reported in the FDA statistics. The regulation gaps result in API leakage for direct use in animal and plant sectors, which will be addressed later in the Section discussion.

- **Licensing**

All operators should be licensed by the Drug Act 1987. There are six types of licensing which cover importation, manufacture and sale. In terms of sale, it can be divided into four sub-categories including sales of modern medicines, wholesale, sale of ready-packed modern drugs which are not dangerous or special-controlled drugs and sale of ready-packed modern drugs for veterinary use.

Section 12 stipulates that no persons shall produce or sell a modern drug or import or order a modern drug into the Kingdom, unless they obtained a license from the licensing authority, —the FDA. The application for and grant of a license shall be in accordance with the rules, procedures and conditions prescribed in the Ministerial Regulation. Section 15 clarifies license categories for modern drugs are as follows:

(1) a license to produce modern drugs;
(2) a license to sell modern drugs;
(3) a license for modern drug wholesale;
(4) a license to sell ready-packed modern drugs which are not dangerous or special-controlled drugs;
(5) a license to sell ready-packed modern drugs for veterinary use;
(6) a license to import or order drugs into Thailand;

Furthermore, there is complexity on cross licensing, as the regulation stipulates that:

A licensee under (1) or (6) shall be also *de facto* deemed to be licensee under (2), authorized to sell the drugs which the licensee produces, imports or orders into the Kingdom where applicable.

A licensee under (3) shall be also *de facto* deemed to be licensed under (4) and (5), namely authorized for retail sales of the ready-packed drugs for human (which are not dangerous or special-controlled), and for veterinary use.

A licensee under (3) shall be also *de facto* deemed to be licensed under (4) and (5) for wholesale only.

- **Supply chain inspection**

FDA and provincial health offices (PHO) are two main authorities responsible for the inspection of the six types of operators licensed above. For all types of licensing including importation, manufacture and sale located in Bangkok, inspections are responsible by FDA. The inspections of operators operated at provincial level are decentralized to the PHO which represents the MoPH in each province. However, operator-held manufacture licenses located in any provinces will be inspected by FDA, due to lack of certain technical capacities in the PHO.

Table 3 Inspection of licenses including importation, manufacture and sale by different geographical areas

Location	Importation Licensee	Manufacture Licensee	Sale Licensee
Bangkok	First inspection for license approval, annual inspection, inspection when complaint: FDA (Post-marketing surveillance division)		
Other provinces	First inspection for license approval: PHO Annual inspection: PHO Inspection in response to complaints: PHO work with Post-marketing control division, Rural and local consumer health products promotion protection division, FDA	First inspection for license approval, annual inspection, inspection when complaint: FDA (Post-marketing surveillance division)	First inspection for license approval: PHO Annual inspection: PHO Inspection in responses to complaints: PHO work with Post-marketing control division, Rural and local consumer health products promotion protection division, FDA

- **Control the quality of the process**

Importation at point of entry:

The FDA designated 40 air, sea and land ports for pharmaceutical products (among these, ten are designated for the regulation of API), which are responsible for inspection and approval of the importation of medicine and API into the country (Table 4). Operators licensed to import drugs shall pass the inspection by officials at these checkpoints. This practice adheres to Ministerial regulations, which appoint official authority and mechanisms to control importation at customs.

Table 4 Regulation at forty points of entry for finished medicine products and API importation

No.	Checkpoints	Province	Superintendent
1	Food and drug checkpoints of Bangkok International Airport divided by the Bangkok International Airport customhouse border*	Bangkok	FDA
2	Food and drug checkpoints of post office divided by customhouse border Bangkok post office*	Bangkok	FDA
3	Food and drug checkpoint of the Actulum private harbor*	Samut Prakan	FDA
4	Food and drug checkpoint of Lardkrabang train station*	Bangkok	FDA
5	Food and drug checkpoints of Bangkok harbor divided by customhouse border Bangkok harbor*	Bangkok	FDA
6	Food and drug checkpoint of private harbor No.10*	Samut Prakan	FDA
7	Food and drug checkpoints of Suvarnabhumi international airport (International passengers, Warehouse*)	Samut Prakan	FDA
8	Food and drug) harbor(checkpoint of Amphoe Phra Samut Chedi *	Samut Prakan	FDA
9	Food and drug checkpoint of Samut Prakan (Uni-Thai) *	Samut Prakan	FDA
10	Food and drug checkpoint of Amphoe Bang Sao Thong	Samut Prakan	FDA
11	Food and drug checkpoint of Chiang rai international airport (Mae fah luang)	Chiang rai	FDA
12	Food and drug checkpoint of Amphoe Chiangsaen (harbor), Chiang rai province	Chiang rai	FDA
13	Food and drug checkpoint of Amphoe Chiangkhong, Chiang rai province	Chiang rai	FDA
14	Food and drug checkpoint of Amphoe Maesai, Chiang rai province	Chiang rai	FDA
15	Food and drug checkpoint of Lamchabung harbor*	Chon buri	FDA
16	Food and drug checkpoint of Amphoe Sadao divided by customhouse Sadao border, Songkhla province	Songkhla	FDA
17	Food and drug checkpoint of Ban Prakob, Songkha province	Songkhla	FDA
18	Food and drug checkpoint of Songklha Port	Songkhla	FDA
19	Food and drug checkpoint of Hatyai international airport	Songkhla	FDA
20	Food and drug checkpoint of Padangbezar city divided by customhouse Padangbezar city border, Malaysia	Songkhla	FDA
21	Food and drug checkpoint of Phuket international airport	Phuket	FDA
22	Food and drug checkpoint of Sumut Sakhon	Sumut Sakhon	PHO

No.	Checkpoints	Province	Superintendent
23	Food and drug checkpoint Amphoe Kantang, Trang province	Trang	PHO
24	Food and drug checkpoint Chongmek border, Ubon Ratchathani province	Ubon Ratchathani	PHO
25	Food and drug checkpoint of Chiangmai international airport	Chiangmai	PHO
26	Food and drug checkpoint of Lampoon province	Lampoon	PHO
27	Food and drug checkpoint Amphoe Maesod, Tak province	Tak	PHO
28	Food and drug checkpoint of Nong Khai province	Nong Khai	PHO
29	Food and drug checkpoint of Ranong province	Ranong	PHO
30	Food and drug checkpoint of Samui international airport, Suratthani province	Suratthani	PHO
31	Food and drug checkpoint of Wangprachan, Satul province	Satul	PHO
32	Food and drug checkpoint of Amphoe Tahlee, Loie province	Loie	PHO
33	Food and drug checkpoint of Amphoe Sungai Kolok, Narathiwas province	Narathiwas	PHO
34	Food and drug checkpoint of Amphoe Tungchang, Nan province	Nan	PHO
35	Food and drug checkpoint of Bungkarn province	Bungkan	PHO
36	Food and drug checkpoint of Nakhon Phanom province	Nakhon Phanom	PHO
37	Food and drug checkpoint of Mookdahan province	Mookdahan	PHO
38	Food and drug checkpoint of Amphoe Aranyaprathet, Srakaew province	Srakaew	PHO
39	Food and drug checkpoint of Choomporn province	Choomporn	PHO
40	Food and drug checkpoint of Krabi international airport	Krabi	PHO

*Ten designated checkpoints for API

Manufacturing:

To ensure the quality of the manufacturing system, the MoPH has issued additional notifications under the Drug Act. The MoPH notification for rules and methods of quality control of medicine production covers the areas of quality management, personnel, facilities and infrastructure, document processing, production operation, quality control, complaint management and recalling unqualified products, and self-evaluation.

In addition, the FDA notification establishes guidelines for licensing manufacturers in accordance with the Good Manufacturing Practice (GMP) based on the Pharmaceutical Inspection Co-operation Scheme (PIC/S) criteria.

Sale at pharmacy:

Pharmacies which hold sale licenses are at the forefront of pharmaceutical services with close interface with communities. They play a critical role in ensuring quality medicines are provided to the population. The MoPH has issued a notification to control the quality of pharmacy premises, service equipment, and Good Pharmacy Practice (GPP) in 2014. This notification contributed significantly to the improvement of the quality of pharmacies in terms of community pharmaco-vigilance practice, equipment used in sales, storage and control of drug quality. In addition, it contributed to the standardization of pharmaceutical services. As a result, it reduced the problem of selling special-controlled drugs without a pharmacist. For example, these pharmacies were evaluated as required by notification before the annual renewal of their license. Passing the annual evaluation is the precondition for a sales license renewal. However, current license holders who were licensed prior to June 25, 2014 have a special provision of "grace period" for the adjustment of standards as required. They are waived the standards of premises, equipment, and compliance with GPP during this grace period of adjustment. All sales licensees shall have to comply with all standards as required by the MoPH notification by 2022, which is eight years grace period since 2014.

- **Monitoring system of distribution and sales of pharmaceutical products**

According to the Drug Act, operators are legally required to send the report to the FDA. The monitoring systems apply to both pharmaceutical products: finished products and API. The mandatory report by import, manufacture and sale licensees are described in table 5.

Finished products

1) A weekly *wholesale* report of five potentially abused medicines (this group does not include antibiotics) i.e. Tramadol, Dextromethorphan, Antihistamine, Corticosteroids and Sildenafil, Tadalafil or Vardenafil by import, produce and sale licensees_through a web-based information system (sometimes, this is called "FDA reporter")
2) A four-monthly report of *importation, manufacture and sale* of four potentially abused medicines (also not include antibiotics), i.e. Tramadol, Dextromethorphan, Antihistamine and Sildenafil, Tadalafil or Vardenafil by import, produce and sale licensees.
3) An annual report of *importation and manufacture* of all pharmaceutical products by import,

produce licensees (which historically does not cover distribution detail).

API

1) A four-monthly report of the *sale* of Corticosteroids, Quinolone and derevatives, Cephalosporins, Macrolide [all bold type are antibiotics] by import, produce licensees through web based information system
2) An annual report of *importation, manufacture and sale* of all pharmaceutical products by import, produce licensees.

Table 5 Mandatory report by import, produce and sale licensees

Report	Drug import licensee	Drug produce licensee	Drug sale licensee	Drug
Finished product				
A weekly report	Wholesale	Wholesale	Wholesale	Tramadol, Dextromethorphan, Antihistamine, Corticosteroids and Sildenafil, Tadalafil or Vardenafil
A four-monthly report	Importation and sale	Manufacture and sale	Sale	Tramadol, Dextromethorphan, Antihistamine and Sildenafil, Tadalafil or Vardenafil
Annual report	Importation	Manufacture	-	All medicines
API				
A four-monthly report	Sale			Corticosteroids, Quinolone and derivatives, Cephalosporins, Macrolides, Polymyxins
Annual report	Importation and sale	Manufacture and sale	-	All medicines

The Animal Feed Quality Control Act, BE 2558 (2015)

The Animal Feed Quality Control Act controls the quality and standard of animal feed including complete animal feed (finished product of animal feed), and regulated by the Department of Livestock Development, Ministry of Agriculture. The FDA recently issued the notification in 2017 to exempt the medicated feed, which was formerly regulated by the Drug Act, to be regulated by the DLD. Consequently, DLD of the MOAC would issue a notification to control the quality and standard of medicated feed. Note that the overlap between "veterinary antibiotics in particular medicated premix" under FDA mandates and "animal feed" under DLD mandates is that the "medicated feed" has now been transferred so that it is regulated by DLD.

In order to control the medicated feed, the law (Animal Feed Quality Control Act) regulates that any operator who wishes to produce special-controlled animal feed must register the “Special-controlled animal feed”. This refers to the animal feeds that have a potential impact on the economy or society or may be harmful to animals or may affect the consumers of animal products. When registration is approved, medicated feed can be produced from the mixture of registered special-controlled animal feed and antibiotics, registered by FDA.

In addition, the Animal Feed Quality Control Act covers licensing and regular inspection of feed mills which produce feed and stores which sell medicated feed. Operators who want to produce, import and sell animal feed should be licensed by DLD. Since the law was newly legislated in 2015, it is under the process of drafting the following notification. In the draft of notification, veterinary prescription and GMP inspection for feed mills are required for controlling the importation, sale, production and use at feed mills and farms. Members of the EU decided to apply a stepwise approach to ban the use of antibiotics as growth promoters before 2000 and implemented a total ban policy in 2006. Thailand, having recognised the importance and urgency of the matter, decided to introduce this policy before 2000 and enforced the total ban policy in 2015. The direct use of API in animal farms is also prohibited and unlawful.

- **Regulatory authority**

The DLD was founded in 1942, and is the National Veterinary Authority of Thailand, responsible for animal health, animal production and livestock development, food safety of animal-derived products, veterinary public health, animal welfare, environmental impact of livestock farms and international animal health matters. DLD is the national counterpart of OIE.

AFVC is a department under DLD. Based on the mandates given by two Acts - the Animal Feed Quality Control Act BE 2558 (2015), and the Hazardous Substance Act BE 2535 (1992) - it regulates the operators to comply with the law on: quality animal feed, veterinary products and use of dangerous substances in animals, monitoring and supervision of operators of animal feed, and veterinary drugs.

- **Definition and classification**

According to the section 4, animal feed and special-controlled animal feed are defined as follows.

"Animal feed" means

(1) materials which are intended for use or feeding animals by eating, drinking, licking or entering into animal bodies by any method or;

(2) materials which are intended for use with or as a mixture in the production of animal feed;

"Special-controlled animal feed" means animal feed that has impact on the economy or society or may be harmful to animals or may affect the consumers of animal products. The production or importation of such animal feed for sale must be registered in accordance with the notifications prescribed by the Minister taking into account the advice of the Animal Feed Quality Control Committee.

Section 4 links with Section 6 of the Act that the Minister shall, with the advice of the Committee, have power to issue notifications on the name, category, type, characteristic, quality and standard of special-controlled animal feed and animal feed as well as the rules, procedures and conditions of the production for sale, importation for sale or the sale of these products.

In the past, no provision in the Drug Act explicitly defined the regulation of medicated feed. As a result of close consultation and collaboration between the two key agencies - FDA and DLD - both finally reached the consensus that the medicated premix should be regulated by FDA through the provisions in the Drug Act, while the medicated feed is regulated by the DLD, under the Animal Feed Quality Control Act.

- **Instrument for regulating antibiotic distribution in animal sector**

The use of antibiotics as growth promoters was totally banned and enforced in 2015. In 2016, the use of pharmaceutical active ingredients in animal farms was also totally prohibited with close vigilance.

In addition, the DLD is in the process of drafting the MoAC notification on the control of the production, import, sales and use of medicated feed according to the Animal Feed Quality Control Act (2015). It is in line with the FDA, which proposes that the Minister of Public Health should sign the notification of the MoPH that animal feed containing antibiotics will be regulated through the Animal Feed Quality Control Act, and responsibility is held by DLD.

The details of the ongoing development of MoAC notification would cover the production, importation and sale of medicated feed. The key contents cover the following:

- Prohibit the manufacture, import, and sale of animal feeds which contain (1) unregistered drug, (2) Polymyxin group, Penicillin Group, Fluoroquinolones, Fosfomycin for the purpose of prophylaxis, or use outside the indications approved by the registration (off-label use), (3) medicine in sub-paragraph (2) with a combination of more than two medicines in the medicated feed, (4) Use of antibiotics mixed in animal feeds in a lower level than that specified in the drug authorization, (5) Cephalosporin group (Draft of MoAC notification, Article 4)
- Prohibit farm mixer systems on the following: a) pig farms having more than 500 pigs, b) broiler farms having more than 5,000 animals, c) layer farms having more than 1,000 animals. Below this benchmark, the farm mixer systems are allowed to produce medicated feeds for their own use but are required to keep the prescription and e-signature by farm veterinarians for three years for the purpose of DLD inspection. Regarding notification and reporting requirements, these farm mixer systems are required to notify the number and names of the farm veterinary doctors or animal husbandry under their supervision including the farm mixing production systems. They are required to produce annual reports to DLD on the total annual production of their medicated feed and laboratory test results of the proof of a) homogeneity of the medicated feed, b) no cross contamination of antibiotics to non-medicated feed production. (Draft of MoAC notification, Article 5). Note that there is a consultation among FDA, DLD and relevant stakeholders to issue the notification to control the use of such antibiotics in the farm mixer systems under veterinary prescription and supervision.
- Medicated feed producers shall meet the requirements for the production quality such as GMP certified manufacture, and production controlled by veterinarians (Draft of MoAC notification, Article 6).
- Prohibit the sale of the following animal feed from mills directly to feed store; these are (1) concentrated medicated feed, (2) animal feed containing Polymyxin group, Penicillin Group, Cephalosporin, Fluoroquinolones, Fosfomycin, (3) medicated feed for fattening pigs weighing 90 kg upwards, last stage of broiler and layer, (4) medicated feed without veterinary prescription (except animal feed for pigs weighing less than 25 kg with no more than two types of antibiotics). (Draft of MoAC notification, Article 7)

- Prohibits the sale of medicated feed by stores to farms without veterinary prescription. (Draft of MoAC notification, Article 8)

- **Market authorization of medicated feed**

According to the chapter four of the Animal Feed Quality Control Act, licensees who wish to produce or import any special-controlled animal feed, must register with competent officials. After a certificate of registration for the animal feed has been granted, they would be able to produce or import special-controlled animal feed. Note that the registration covers all animal feed, not specified medicated feed. The total of registered animal feed formulas was more than 12,000 items.

- **Licensing of special-controlled animal feeds**

The Animal Feed Quality Control Act regulates the operators who produce or import the special-controlled animal feed, in this case, the medicated feed (section 15) and sale (section 17). Three types of license are defined in the section 22 of the Law: production, importation and sale.

- Section 15: Any person, who wishes to produce or import for sale of special-controlled animal feed shall apply for a relevant license and shall produce or import for sale when such license has been granted by the licensor. The application and issuance of a license under paragraph one shall be in accordance with the rules, procedures and conditions prescribed in the Ministerial Regulation (MOAC). The licensee under paragraph one must also comply with the rules, procedures and conditions for the production or importation for sale of the special-controlled animal feed prescribed by the Minister under Section 6.
- Section 17: Any person, who wishes to sell special-controlled animal feed under Section 6 (1), shall apply for a license and shall sell the said special-controlled animal feed only after such sales license has been granted by the licensor. The application and issuance of a license under paragraph one shall be in accordance with the rules, procedures and conditions prescribed in the Ministerial Regulation (MOAC). Licensees under paragraph one must comply with the rules, procedures and conditions for the sale of the special-controlled animal feed prescribed by the Minister under Section 6 (1).
- Section 22 licenses are classified as follows:

(1) license to produce special-controlled animal feed;

(2) license to import special-controlled animal feed;

(3) license to sell special-controlled animal feed.

The licensees under (1), namely license to produce shall also be the licensees under (3) for sale of the special-controlled animal feed that they produce. The licensees under (2) shall also be the licensees under (3) for sales of the special-controlled animal feed that they import.

However certain exceptions remain; section 21 of the Animal Feed Quality Control Act, does not apply to (1) Ministries, Government Departments or State enterprises engaging in the production or importation of special-controlled animal feed for their own uses; (2) the production and importation for sale or the sale of special-controlled animal feed as an samples for academic, for the purpose of registration; (3) legally registered cooperatives or farmers' groups who produce special-controlled animal feed for the uses by their cooperative members or for farmers in their group. The MOAC notification will set up rules, procedures and conditions as well as reporting requirement of these operators.

Furthermore, registration requirement does not apply to the licensed animal feed producer for the production of these animal feed specifically for the use by their own animals. This *de facto* refers to the application of farm mixer for internal use (including in business scale of integrated farming system). The MoAC will also announce the rules, procedures and conditions to control farm mixer to ensure quality of production such as homogeneous distributions of antibiotics in the feed.

- **Supply chain inspection**

There are four possible cases for the inspection of operators licensed to produce and sell animal feed including 1) inspection before licensing approval, 2) annual inspections, 3) inspection before relicensing and 4) inspection in response to complaints.

There are joint inspections by different authorities at national and local levels. The AFVC is responsible for inspection of all types of licensed operator operated in Bangkok. The officers in the regional and provincial livestock development offices are responsible for the inspection for license renewal and annual inspections of operators in provincial level. See summary of inspections in table 6.

Table 6 Inspection of licensee on feed mill and feed store by different areas

Location	Feed mill license	Feed store license
Bangkok	Inspection before licensing approval, Inspection before relicensing, annual inspection, Inspection in response to complaints: AFVC	
Other provinces	Inspection before licensing approval: AFVC and PLO Inspection before relicensing (annual inspection): Regional livestock office and PLO Inspection in responses to complaints: AFVC collaborates with regional livestock office and PLO	Inspection before licensing approval and inspection before relicensing (annual inspection): PLO and district livestock office Inspection in responses to complaints: AFVC collaborates with regional livestock office and PLO

- **Control the quality of the process**

To promote the standard of animal feed mills, the DLD enforces a regulation for establishing a voluntary GMP certification for feed mill; the GMP is granted by DLD. For a GMP certified feed mill, the DLD will inspect the plant not less than twice a year. For a non-GMP certified feed mill, the DLD inspection to the plant is required more frequently, that is three times a year.

Note that GMP certification is mandatory for animal feed mills which produce medicated feed, and it will be named “medicated feed mill” consequently. In addition to GMP by DLD, ISO certification is voluntary for feed mills aiming for export to regional markets.

- **Monitoring system of medicated feed**

Currently, the DLD is working on a draft of MOAC notification to control feed mill licensees and farm mixers which will mandate them to submit the volume of antibiotic used in medicated feed annually. The report of such exemption to the cooperatives will be announced later.

PART II: Key actors and their roles involving in the antimicrobial distribution chain

There are a large number of operators involved in the whole range of supply chains of antibiotics. Actors are categorized by types of license granted according to the Drug Act and the Animal Quality Control Act (Table 7).

Table 7 Number or operators categorized by the licensee (for all drug (not antibiotics)

Actors involved in antibiotics	Type of licensing	Number
1) Importer	Pharmaceutical import license	774[1]
2) Manufacturer	Pharmaceutical manufacture license	184[1]
3) Distributor	Pharmaceutical sale license	(15,359)[2]
4) Wholesaler	Pharmaceutical sale license	(15,359)[2]
5) Drug store		
- Sale medicines	Pharmaceutical sale license	(15,359)[2]
- Sale of package medicines	Pharmaceutical sale license (only for package medicines)	3,164[2]
- Sale of package medicines for animals	Pharmaceutical sale license (only package medicines for animals)	722[2]
6) Human health facility	Health facility license	11,560[3]
7) Importer (animal feed)	Animal feed import license	323[4]
8) Animal feed mill	Animal feed manufacturer license	299[4] (73)*
9) Animal feed store	Animal feed sale license	27,165[4]
10) Animal health facility	Animal health facility license	2,058[4]
11) Livestock farms	-	1,048,614[4]**

***** There are 73 animal feed manufacturer licensees who received the GMP standard, which can produce medicated feed.

**Total livestock farms include the following: broiler chicken 35,371 farms, layer chicken 57,286 farms, pig 191,289 farms and beef cattle 764,668 farms

Sources:

1) FDA 2015
2) FDA 2013
3) Ministry of Public Health 2015
4) Information and Communication Technology Center, DLD 2015

The study identified more than one million livestock farms in Thailand. Of these 1,048,614 farms, there were 35,371 broiler farms (with 1,473,628,997 animals), 57,286 layer farms (with 104,761,215 animals), 191,289 pig farms (with 18,804,487 animals) and 764,668 beef cattle farms (with 4,407,108 animals).

Competitive market and high-profit-margin markets result in a proliferation of multiple actors: 774 importers, 184 manufacturers, 323 animal feed importers, 299 feed mills, 27,165 feed stores and over 15,000 distributors, wholesalers and retailed pharmacies. Of 774 importers, three groups can be identified: 176 importers of finished products, 222 importers of API and 108 of both products, while 268 licensed for imports are inactive in the businesses. From the interviews, it was estimated that more than 95 percent (15,359 operators) of pharmaceutical sale licensed operators sell antibiotics; however, registration records do not support the differentiation between wholesalers and retailers.

Most importers and manufactures are located in Bangkok where main ports (air and sea ports) are located. Medicines including antibiotics are distributed throughout the country through the marketing force by importers, manufactures and wholesalers. The highest density of private pharmacies to population ratio was in Bangkok, Chonburi and Phuket (>61 drug stores/100,000 population). Figure 2 shows density of pharmacies per 100,000 populations by 77 provinces of Thailand. Note that the density is classified by five equal percentiles (quintiles). Note that the provinces with red shade denote highest concentration, while the dark green shade denotes the lowest concentration of pharmacies per 100,000 population.

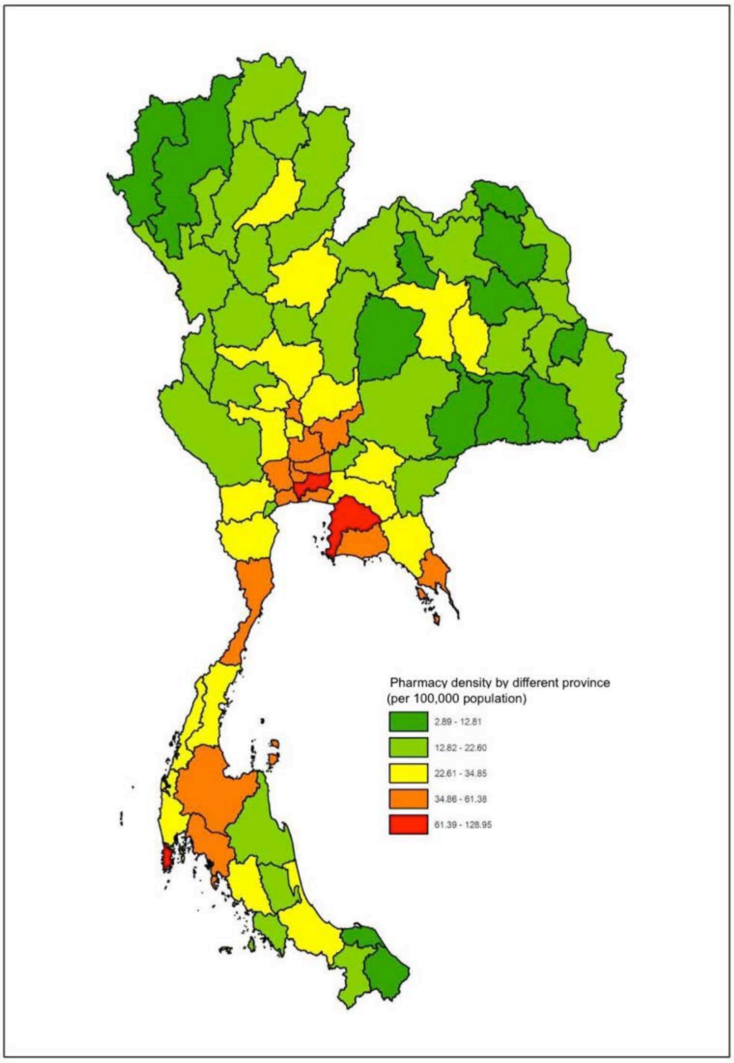

Figure 2 Number of pharmacies per 100,000 populations by provinces, 2016

Source: Thai Food and Drug Administration, 2016

PART III: Antimicrobial distribution

The distributional system of antibiotic is complex. Figure 3 unpacks the complexity of antibiotic distribution including API, finished products and medicated feed from importers and local manufactures to human and animal final consumption; see Figure 3.

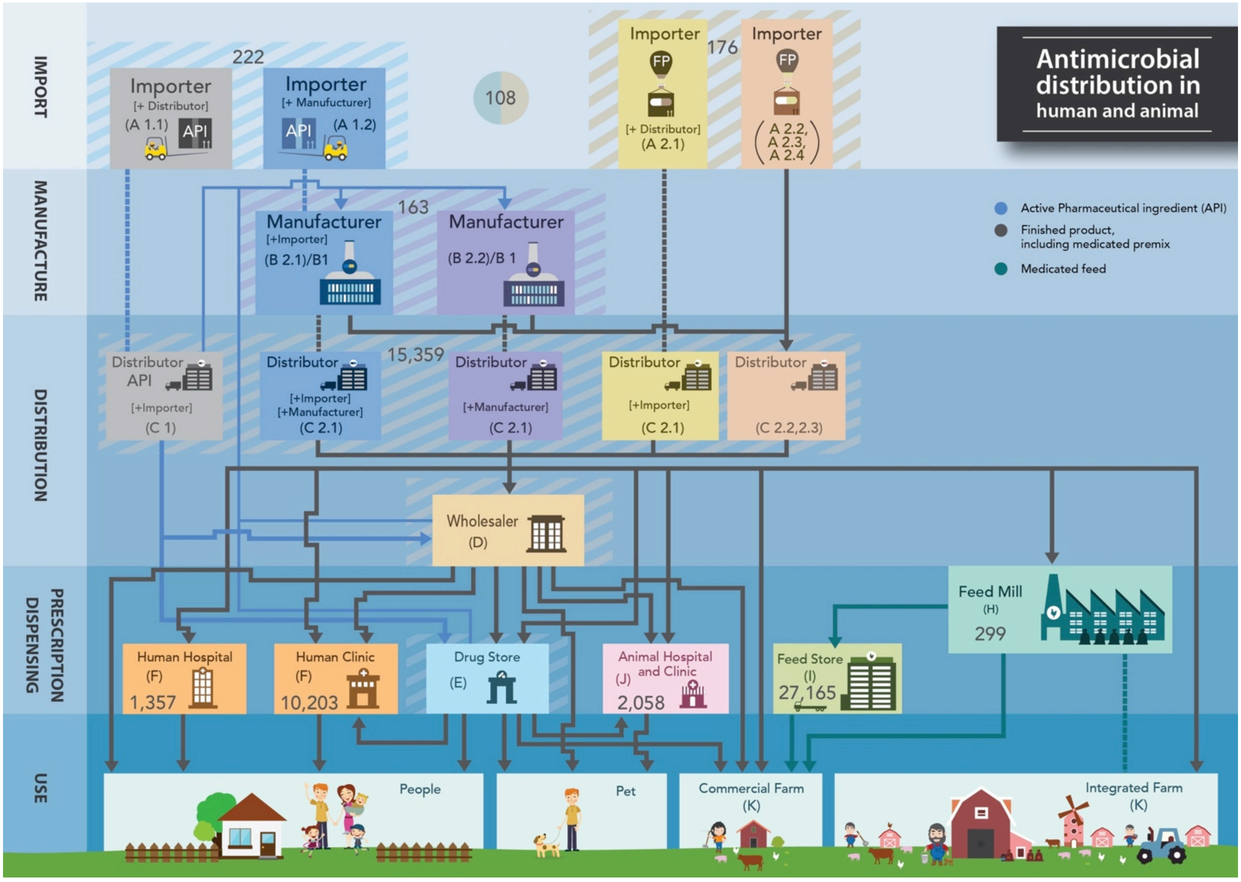

Figure 3 Antibiotic distributional channels: from importation, manufacture to the end users

How are antibiotics imported, manufactured and distributed?

Thailand imports API for local manufacturing and finished products for domestic consumption (including medicated premix for manufacturing of medicated feed by feed mills). Most API was imported for pharmaceutical production, either by manufacturers (A1.2) or by importers (A1.1) who are also licensed as API distributors (C1).

By law, API must be sold by persons who are licensed to produce or import. Most manufactures usually purchase API from importers or import by their own (B2.1 or A1.2). They seldom buy API from drug stores. Once antibiotics were produced by manufacturers (B2.1 and B2.2), the manufacturers can sell these antibiotics directly (C2.1), or distributed through distributors (C2.2 and C2.3). By law API must be used for the manufacture of finished products. API cannot be directly used by humans or animals due to its high concentration. At customs, licensed importers of API are required to notify the FDA before approval for imports.

For finished products, antibiotics can be distributed through importers who are also licensed to distribute (C2.1), by manufacturers (C2.1) and by distributors (C2.2, C2.3) to wholesalers, human health facilities, animal health facilities, drug stores, feed mills and farms. There was no difference between the process of importation and manufacture of human and animal antibiotics.

How are antibiotics dispensed and prescribed?

Most antibiotics are classified as dangerous drugs, which mean "pharmacy dispensing only" medicine. This means antibiotics can be sold in the retail sector without prescription but dispensed by professional pharmacists in licensed pharmacies (mostly private). In practice, pharmacists do not keep dispensing records as this is not required by the Drug Act. Oral form of Sulfonamide (due to its potential complication of Drug Rash with Eosinophilia and Systemic Symptoms Syndrome) and Chloramphenicol (due to severe complications of neutropenia and leukemia) are categorised as "special-controlled drugs", which require prescriptions and can be sold to health professionals only, by licensed pharmacies. Sulfacetamide sodium 10% eye drops and Silver Sulfadiazine 1% for topical use are classified as "household remedies" which do not require sale licenses.

All public and private health facilities (hospitals or clinics) have their own pharmacy sections, which dispense antibiotics based on prescription by doctors for either outpatients or inpatients. Although prescription is not required by law, it has been historically practiced.

At the community level, antibiotics are dispensed by pharmacists either by wholesalers (D) or drug stores (E) to household end users and pet owners. Feed mills (G) produce medicated feed sold to feed stores (H) and animal farms (J).

How are antibiotics used?

At user level, people have easy access to antibiotics. In addition to prescriptions in health facilities, people buy antibiotics from licensed wholesale and retail pharmacies. There is a high level of market penetration of private pharmacies in urban communities. However, rural people also have easy access to pharmacies in the district town centers. Farmers can buy antibiotics through several channels including distributors, wholesalers, drug stores, or medicated feed from either feed mills or feed stores. The regulatory framework and enforcement on the use of antibiotics are outside the scope of this study.

E. Discussion

Table 7 summarizes the way legislation categorizes types of operator for licensing requirements, and types of product for registration and distribution according to the Drug Act and the Animal Feed Quality Control Act.

Table 7 Laws and regulations: operator, product and distribution

	Drug Act	Animal Feed Quality Control Act
1. Operator		
1.1 Level of control	• Import, manufacture, sale at pharmacy • Not cover dispensing by health professionals and use by people	• Import, manufacture, sale, prescription at feed mill and farm, and use at farm • Not cover dispensing and prescription by veterinarian
1.2 Licensing	• Pharmaceutical import license • Pharmaceutical manufacture license • Pharmaceutical sale license	• Animal feed import license • Animal feed manufacture license* • Animal Feed sale license * *Not specific to Medicated feed
1.3 Control quality of the process	• Import: Point of Entry (Finished Products = 40, of which 10 are designated for API) • Manufacture: GMP, PIC/S, post marketing quality surveillance • Sale: Good Pharmaceutical Practice (GPP)	Import: NA Manufacture: GMP, ISO Sale: NA
2. Product		
2.1 Registration	Registration required for all imported and produced medicines (including antibiotics)	Required registration for all imported and manufactured animal feed, but not required for medicated feed
2.2 Classification	All antibiotics are classified as dangerous drugs, except such drugs including household drug (Sulfacetamide sodium 10% (eye drop), Silver Sulfadiazine 1% (topical use)), and special-controlled drug (Sulfanilamide (PO), Chloramphenicol for children, animal and systematic use for adult, new drug (register under conditional approval)), Penicillin, Phenylsulphathiazole, Sulfamethoxazone, anti-tuberculosis, anti-Malaria, antiprotozoal, anti-virus (except specific local application drug), anti-fungus (except specific place drug)	Prohibit the use of Cephalosporin, Polymyxin, Pennicillin, Fluoroquinolones and Fosfomycin for prophylaxis and extra-label use*
2.3 Control of product	Withdraw antibiotics registration of Chloramphenicol and Nitrofuran for animal use	Total ban the use of antibiotic as growth promoter Total ban the direct use of API in the animal feed

	Drug Act	Animal Feed Quality Control Act
3. Distribution		
3.1 Control	• Import, distributor, sale: API can be sold to manufacture license and sale license holders • Import: control import 10 antibiotics, ban import of Chloramphenicol, Nitrofurazone, Furazolidone, Dimetridazole, Ronidazole in animal drug registry	• Prohibit import, manufacture and sale of medicated feed containing Cephalosporin, Polymyxin, Pennicillin, Fluoroquinolones and Fosfomycin; prohibit feed containing antibiotics for fattening pigs, layer and last stage of broiler; prohibit use of medicated feed without veterinary prescription (except for pig<25 kg at feed store) * • Manufacture: prescription only (except for pig<25 kg), Using colistin and Amoxycillin for medicated feed (need drug sensitivity test)* • Sale: prescription only* • Farm • Integrated farm (pig>500, broiler>5,000, layer>1,000): prescription, licensing* • Cooperatives: label and sale animal feed for member only
3.2 Monitoring	• Finished product: annual sale report of production and importation of all pharmaceutical products (including antibiotics). • API: a four-monthly report of sale of Quinolone and derevatives, Cephalosporins, Macrolide by import, produce licensees; annual report of importation, manufacture and sale of all pharmaceutical products by import, produce licensees. *Not included its distribution channel.	At feed mill: annual report the quantity of sale on medicated feed* At farm levels • Farm mixer (for business scale): annual report the quantity of use on medicated feed* • Cooperative: annual report the quantity of use on medicated feed*

*Draft MOAC notification

The Drug Act, BE 2530 (1987)

After the last revision of the Drug Act in 1987, many regulations and ministerial and FDA notifications further contribute to the effective functions of the law. The FDA attempted to revise the Drug Act in 2014 but it was defeated due to major professional conflicts about various dimensions of the amendments and changes of Government.

Drug regulations aim to ensure the safety, efficacy and quality of drugs, which contribute to the health protection of the consumers. Five regulatory functions include market authorization, licensing, inspection, quality control and pharmacovigilance; almost all regulatory measures ensure the quality and efficacy of medicine through licensing operators, quality control of the process and registration.

The Drug Act categorizes types of medicines, including antibiotics, and regulates which channels can be used for distribution. There is no regulation with the objective of containing the quantity of medicines, including antibiotics, distributed to end users. The quantity of drugs distributed through different channels is market oriented, where suppliers are responsive to demand without government interference to the market. Hence there is containment neither of the number of licensed operators, in particular distributors and pharmacies, nor of the quantity of drugs distributed through each channel.

Despite the fact that all drugs must be registered with their formula before production or importation, no registration requirements are enforced for API. Only notification to FDA is needed for import formalities required by customs. (Note there are only ten designated gateways for the importation of API: see table 4). This can potentially lead to the leak of API for direct use in animal farms, while the direct use of API is prohibited. These leakages can be either through legal or illegal importation. Drug inspectors at the DLD provide event reports and have previously confiscated certain API in farms and aquaculture.

The FDA is working on the reclassification of certain preserved antibiotics as prescription-only medicines. In the context of a laissez-faire capitalist economy, policy is not in favour of containing a volume of antibiotic distribution. However, reclassification and differentiation of antibiotics may apply to the three groups as recommended by the 20th edition of the WHO Model List of Essential Medicine, according to local infectious disease profiles [10].

- **Group one** is key access antibiotics (including beta-lactam and other antibacterial). These can be classified as dangerous drugs required for dispensing by a pharmacist, but introducing a policy to keep dispensing records for audits and peer reviews to improve the dispensing performance is likely to be a minor reform; no resistance by pharmacists is forseen as it improves their professional services.
- **Group two** is watch group antibiotics (including Quinolones and Dluoroquinolones, third generation of Cephalosporin, Macrolide, Glycopeptides, Antipseudomonal penicillins and bata-latamase inhibitors, Carbapenems, and Penems); these antibiotic classes have higher resistant potential and are recommended as first or second choice treatment only for a specific limited number of indications. This requires prescription-only medicine and strong pharmaco-vigilance, in relation to the emergence of AMR against these medicines. They

must not be freely available in retail pharmacies. However, efforts should be given to ensure that patients in need have access to these medicines.

- **Group three** is reserved antibiotic (including Aztreonam, 4th generation cephalosporins, polymixins, Fosfomycin, Oxazolidinones, Tigecycline and Daptomycin). These are the last resort options. Use of these medicines should be tailored to highly specific patients and settings, when all alternatives have failed. Undeniably, this antibiotics group should be administered by infections experts with strong monitoring and who are key targets for the national stewardship program.

In veterinary medicine, the OIE also classified antibiotics used by animals into three groups including Veterinary Critically Important Antimicrobials (VCIA), Veterinary Highly Important Antimicrobials (VHIA) and Veterinary Important Antimicrobials (VIA). Specific antibiotics were considered for the treatment of a particular disease for different animal species. The current ongoing reclassification by FDA, under the Drug Act should be aware of the categorization of veterinary important antimicrobial agent as recommended by OIE [11].

Prescription and dispensing antibiotics

Human and animal health facilities are controlled by other Acts such as the Medical Premise Act and the Animal Health Facility Act. The regulations include mandatory licensing of private human health facilities, while public health facilities are outside the licensing requirement. All private animal health facilities are regulated by the Animal Health Facility Act, while public animal health facilities are not covered by this Act.

The prescribing and dispensing of antibiotics in health facilities are the responsibility of professional practitioners such as doctors, pharmacists and veterinarians. Professional councils provide standard guidelines for the rational use of antibiotics, but are not required to report on antibiotics prescription in all settings. Unlike the common practice of high-income countries, the use of antibiotics in the retail sector, primary care facilities (public health centers and private clinics) and hospitals are neither required to keep records of their dispensing or prescribing, nor are subject to audit by regulatory authorities or professional peers. Without such records and stringent audit, the excessive and inappropriate uses of antibiotics remain unknown.

Several non-clinical issues were found to influence the health professional's decision on antibiotic prescription. Economic incentives offered by pharmaceutical companies to boost their market contribute to excessive provision of antibiotics [12]. Demand and influences by clients are common in particular patients in the private sector [13, 14, 15]. A study across 17 European countries shows that a one percent increase in doctor-to-population density is associated with 0.52% to 0.86% increase in outpatient use of antibiotics; fee-for-service incentives lead to a higher use than the capitation payment method [16].

The antimicrobial sensitivity testing is an important tool to identify bacteria and for antibiotic selection. However, practitioners made their decision about antibiotic use based on individual preference and clinical experiences. Some studies show that decision-making by health professionals is based on "expert opinion", other colleagues who are "opinion leaders" or from internet sources, rather than scientific and peer-reviewed data [17].

The poor quality of pharmaceutical services provided by retail pharmacies is commonly reported. This includes: inappropriate presumptive treatment, use of antibiotics for common colds or flu symptoms, insufficient history taking, sale of medicines that are neither clinically appropriate nor proper doses, sale of incomplete courses of treatment, poor or no labeling, and limited provision of counseling [18].

Several interventions can help to improve professional practice. For example, law enforcement which prohibits non-prescription sale of antibiotics, strengthening antimicrobial stewardship programs [19] and audits of dispensing records [20].

In-service training such as thorough continued professional education to pharmacists in the retail sector may improve the quality of pharmaceutical services [21]. However, trainings which are sponsored by the pharmaceutical industry may undermine the integrity of these courses as they may protect the interest of pharmaceutical industry. To redress this challenge, Australia has introduced a self-regulatory Code of Conduct where pharmaceutical companies voluntarily adhere to a set of principles and behavior for ethical marketing and for the promotion of prescription pharmaceutical products [22]. This also requires a strong regulatory environment to shape health professional behavior.

Use of antibiotics by people and farmers

People and farmers can access medicines, including antibiotics from various sources. There were a large number of distributors and retailers for selling medicines resulting from the competitive market of medicines. No prescription requirement results in people having easy access to antibiotics, which they often use inappropriately use due to the lack of understanding in households. On the one hand, availability of medicines supports access to antibiotics, but on the other hand excessive availability can lead to excessive consumption and subsequent pressure on the emergence of AMR. The rational use of antibiotics by the community can be enhanced by the professional and quality services provided by full-time pharmacists in retail pharmacies and through audits of dispensing records. Significantly, there is no special control for wholesalers and people can buy a large quantity of antibiotics from pharmacies. There is no wholesale license authorized by FDA and no foundation for tracking the quantity of total sales by wholesalers.

Obtaining and using antibiotics in the retail sector without prescription are common in developing countries [23]. There is often inadequate regulation on antibiotic distribution and sale [24, 25], and inadequate knowledge and lack of AMR awareness. These were recognized as important factors contributing to the irrational use of antibiotics in China and Vietnam [26]. Therefore, general public knowledge of antibiotic use and awareness on harmful self-medication should be raised. To improve knowledge of antibiotics and public awareness of AMR, it is essential to understand the gaps in understanding about the proper use of antibiotics and AMR awareness in the communities.

The special Euro-barometers 338 and 445 [27, 28] fill these gaps. These surveys contribute to the prevalence of the self-use of antibiotics and sources in the last 12 months, knowledge of antibiotics and awareness of AMR. In Thailand, an AMR module was embedded into the Health and Welfare Survey (HWS) in 2017 conducted by the National Statistical Office. It is a national representative household survey conducted biannually. Evidence from these surveys will support the precision of advocacy messages for effective changes of behaviors. Regular surveys are important to monitor the progress of public campaigns on AMR.

The Animal Feed Quality Control Act, BE 2558 (2015)

As the Animal Feed Quality Control Act was newly legislated in 2015, it is at an early stage of drafting regulations for effective implementation. Literature suggests that pressure from farmers and financial gains from antibiotics use affects prescribing behavior in veterinarians. The Act however does not control dispensing and prescription by veterinarians. In Denmark, interventions that significantly stemmed antibiotic consumption included delinking veterinarian prescribing and dispensing and restricting the maximum profit on antibiotic sales to 5%, down from a 25% markup prior to regulation [29]. As a result, Denmark managed to curb significantly the total consumption of veterinarian antibiotics.

In many countries, there have been attempts to decouple the prescription and dispensing of medicines by veterinarians. Almost all medicines used in the livestock sector in Denmark are now sold directly to the farmers by pharmacies [30]. This should be reflected in a MOAC notification in order to control the use of antibiotics requiring veterinary prescription in feed mills and feed stores

The MOAC Regulation allows cooperatives or farmer groups to produce special-controlled animal feed (medicated feed) for their members. The quality of these local non-GMP productions of medicated feeds - in particular the homogeneity of antibiotics from the mix - which may result in the emergence of AMR pathogens are policy concerns. In such case, the DLD needs to have close vigilance in this area.

The DLD is developing reporting systems for relevant stakeholders including retail medicated feed producers, farm mixers for businesses, co-operatives and farmer groups. The system design should be in line with the recommendation by OIE. Without mandatory reporting systems for medicated feed, there will be a lack of evidence to support monitoring consumption of certain reserved antibiotics in the Thai-SAC.

Literature on medicines regulations [9] in low- and middle-income countries such as Tanzania, Zimbabwe, Ethiopia and Thailand focus more on quality and the process of licensing for entry to the market, but lose sight on controlling the quantity of distribution and price [9, 31, 32]. Failure to address market promotion results in easy access and inappropriate use of antibiotics. The outdated law and lack of functioning regulation in Zimbabwe has led to double problems of poor quality and high price [33].

Regulatory enforcement

Various provisions in the law and regulations do not always guarantee good outcomes as intended; it requires effective enforcement and institutional capacities to regulate the relevant operators who should be guided by M&E evidence in a timely manner. The lack of effective regulatory control can lead to the inappropriate use of antibiotics. Many studies indicate ineffective regulatory functions. A study in Ethiopia reports no inspection of the supply chain with importers and manufacturers [32]. In Zimbabwe, it is indicated that regulators lack significant information about the structure and operation of the private sector [33].

Possible reasons for ineffective law enforcement include the over-centralization of regulation with poor cooperation between the national and local levels [32], a lack of knowledge by patients of their rights [33], inadequate monitoring and information systems [34, 35] and a shortage of qualified and skilled workers for medicine regulation. The latter might be due to low government salaries and that the regulators are subsequently employed by private industries; this presents a clear conflict of interest resulting in regulatory captures [36]. In order to increase the effectiveness of regulation, new approaches are proposed; these include a consumer-oriented approach such as improving information for consumers and a market-oriented approach, such as intervening to change the incentives available to private sectors [37,38].

FDA and DLD devolved by delegating their inspection authority to provincial offices. However, the field observations showed that inspectors are spread too thinly across laws and regulations, and inspections focus on quality as the primary concern, but not on the quantity of distributions. The laws and regulations on antibiotic distribution are not implemented and enforced effectively in the following ways.

Firstly, there are several regulatory authorities at national and local levels such as FDA, PHO, AFVC, and PLO. There are variations in the interpretation of enforcement, intensity and degree of penalty for violations. From the in-depth interviews with the regulatory officers in four selected provinces, in one province there is no annual inspection of animal drug stores. Furthermore, the Drug Act enforcement is decentralized to PHO resulting in non-standardized enforcement on licensing and annual inspection or license renewals. Antibiotics are not a main concern of pharmacists at district hospitals who inspect all drug stores at district levels. Moreover, at a small community level, unavoidably, the relationship between the regulator in district hospitals and the operators may lead to sympathy and relaxation.

Secondly, there is no specific or standard protocol for the inspection of the distribution and use of antibiotics. Antibiotics are likely to be used and controlled in a similar way to other medicines. However, several classes of antibiotics should be reserved for severe illnesses as a last resort to save life. In addition, there are other competing priorities. Interviews with key informants reflect that antibiotics are not a main interest of the regulators compared with GMP inspections. In some provinces, government officers focus on the inspection of potential drug abuses such as tramadol for addiction and the use of beta-agonist group such as Salbutamol as leanness-enhancing agents in food animals. These are the immediate concerns for consumer protection by PHO while antibiotics are overlooked.

Thirdly, across the interviews with regulators, a heavy workload was common. For example, in Bangkok, there were more than 5,000 drug sale license holders and more than 600 import license holders, with only approximately 40 staff members in FDA responsible for annual inspection. At the local level, there were about three to five staff members in PHO who enforce six to seven Acts delegated by the MoPH to the PHO. These include the Food Act, the Medical Device Act and the Cosmetic Act to name a few.

Fourthly, antibiotics classified as dangerous drugs can be dispensed by pharmacists in private pharmacies without prescription. Prescription is the only instrument for auditing inappropriate and excessive use of antibiotics. To overcome prescription issues, continued professional education, legal sanction and prescription audits could be introduced, such as those implemented by the

Swedish Strategic Programme Against Antibiotic Resistance (Strama) in Sweden [39]. Given the current designation of antibiotics as dangerous drugs (except a few special-controlled items for hospital use only), it is technically feasible to require pharmacists to keep electronic dispensing records for audits by regulatory authority or professional peers. This is one of the critical entry points for rational use of antibiotics, in response to the call by Global Action Plan on AMR.

This study identified significant information gaps. For example, the study estimated the number of operators from the license holders at FDA, but this might be outdated. Information gaps are due to the lack of data sharing and timely updating between FDA and provincial health offices responsible for drug store annual relicensing. The study could not differentiate between operators among three groups - distributors, wholesalers and retailers at drug stores - since they hold the same sale license. Interestingly, no operator holds a wholesaler packaged medicine sale license. In addition, this study could not identify the number of feed mills and feed stores who produce and sell medicated feed. For the number of livestock farms, this study could only identify the number of ’standard farms’ registered by the DLD. The number of backyards and small-scale farms which substantially use antibiotics are yet unknown.

This study did not cover an illegal use of unregistered antibiotics and API either through legal imported or smuggling.

Surveillance of antimicrobial consumption

The existing mandatory monitoring system for antibiotics surveillance covers only an annual sale report of the production and importation of all pharmaceutical products (historically FDA has not requested distribution details). This applies for any medicines, including antibiotics. The four-monthly report (FDA reporter) of the sales and distribution of potentially-abused medicines is designed for the tighter control of the distribution of medicines to prevent drug abuse; however, antibiotics are not covered.

Currently, there is no system to monitor the consumption of antimicrobials in Thailand. The Thai Surveillance of Antimicrobial Consumption (Thai-SAC) is currently developed through multi-stakeholder involvement to fill the gap and grants from USAID, WHO and FAO were secured in early 2017. The research team comprises FDA, Department of Livestock Development, universities and the International Health Policy Program of the Ministry of Public Health. All medicines in the FDA registration database are assigned with the ATC classification code for human drugs and ATCvet for veterinary medicinal products. The scope of the surveillance system will cover antimicrobials at least for systemic use, J01 in humans and QJ01 in animals. The Thai-SAC will also cover the optional list such as anti-tuberculosis, anti-malarial and antiviral as recommended by WHO [40].

To facilitate the development of the surveillance system, these two existing reports need to be revised in such a way as to better track the distribution of antimicrobials from production and importation to users. However, the FDA has to issue regulations with reference to provision in the Drug Act, to include reserved or watch group antibiotics, as recommended by the WHO Model List of Essential Medicines, to the four-monthly report. Moreover, for monitoring the total annual sales of the whole set of human and veterinary antibiotics, research and development of the Thai-SAC will have to rely on the mandatory annual report on production and importation of antibiotics, with volumes and values of sales by different distribution channels. This will facilitate monitoring the total consumption of antibiotics: this is in terms of the defined daily dose per 1000 of the population in humans and milligrams of active ingredient per population correcting unit in animals.

F. Conclusion and policy recommendations

In general, the Drug Act regulated market authorization, licensing, inspection, quality control and pharmaco-vigilance. The Act categorizes types of medicines and specific channels that can be used for distribution; but regulation does not aim to contain the quantity of medicines, including antibiotics, distributed to the end users. The quantity of drugs distributed through different channels is market oriented, where suppliers are responsive to demand without government interference to the market.

Prescribing and dispensing of antibiotics in human and animal health facilities are the responsibility of professional practitioners such as doctors, pharmacists and veterinarians, yet these professionals are not regulated by the Drug Act. Professional councils provide standard guidelines for the rational use of antibiotics, but are not required to report on antibiotics prescription in all settings.

No containment of the number of licensed operators - especially distributors and pharmacies in the high profit market - results in a large number of operators who boost their market share. There is easy access of antibiotics by people and farmers.

No systems exist in Thailand to monitor the consumption of antimicrobials and estimate antimicrobial usage trends over time. This type of evidence is important for policy to optimize consumption and minimize the development of antimicrobial resistance.

In the context of significant challenges posed by AMR and a global call for serious remedial actions, dispensing and prescription audits are entry points which can redress the inappropriate and excessive use of antibiotics; these interventions require policy leadership and reform in both human and veterinary antibiotics.

General recommendations are to:

1) Reclassify the antibiotics for humans and animals that have shown high levels of resistance, as special-control drugs and prescription-only medicines with restricted use by specialists;

2) Introduce effective dispensing and prescribing audits in the pharmacies, hospitals, feed mills and farms.

3) Establish the national surveillance of antimicrobial consumption, improve the quality and accuracy of annual mandatory report by operators, and ensure its uses for policy decision.

Specific recommendations for organizations are below.

Recommendations to FDA:

- Accelerate the policy process of re-classification of antibiotics for human consumption according to the WHO Model List of Essential Medicine and the OIE categorization of three levels of veterinary important antimicrobial agents for animal consumption.
- Establish a mandatory dispensing record and auditing system of certain group two antibiotics (watch group antibiotics) and group three (reserved antibiotics) in order to improve the performance of the use of antibiotics at retail sector. Prescription audits in the hospital sector provide evidence for improving antibiotic stewardship through training of professionals and other sanctions as appropriate.
- Strictly control API by revising the regulation in order to track API after importation; this should be made mandatory despite no registration requirements for API. In addition, the sale licensee should provide mandatory annual reports to the FDA on the API sales and distribution channels used.
- Strengthen the collaboration and data-sharing between national and local levels for effective inspection.
- Develop tools and procedures for the audit of dispensing records kept by pharmacists in the retail sector and standard operating procedures for prescription audits in health care facilities. Punitive, education, training and incentive measures should be introduced to change the course of dispensing behaviour at the retail sector and prescription behaviour in hospital settings.
- Establish the Thai-SAC to monitor the annual consumption of antibiotics at national level. It should be measured by DDD per 1000 population-day in humans, and milligram of active ingredient per population correcting unit in animals. This will help measure the impact of policy outcomes on optimizing consumption in both sectors. There is a need to strengthen the quality, accuracy and adequacy of the annual mandatory report by importer and manufacturers to cover antibiotic distribution channels and also to expand the mandatory annual report of antibiotic sales by distributors and wholesalers and their different distributional channels.

Recommendations to DLD

- Accelerate the implementation of the Animal Feed Quality Control Act (2015) and finalize the draft MOAC regulation to be announced and implemented rapidly
- Control the use of antibiotics requiring veterinary prescription in feed mills and feed stores.

- Establish a well-designed monitoring system of medicated feed by distributional channels and animal species, which should be in line with the Thai-SAC. One potential loophole in the quality of medicated feed is the exemption of register requirements for the production of medicated feed by cooperatives and farmer groups, which are not GMP qualified.

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Appendix 3 Supplement study paper 1

A 3.1 Questionnaire (English and Thai)

A 3.2 Table A1 Characteristics of the 84 pig farmers and farms surveyed in the study

Table A2 Source of advice on animal health management, antibiotics and medicated feed from 84 farms

A 3.3 Lists of farms participated in the study

Table S1 Number of farms that farmers agreed to participated and did not participate in the studied area in the farmer survey

วันที่ให้สัมภาษณ์........../.........../.............

รายการที่ 3 แบบสอบถามเพื่อใช้กับเกษตรกรผู้เลี้ยงสุกร

แบบสัมภาษณ์เกษตรกรเกี่ยวกับการใช้ยาปฏิชีวนะในการเลี้ยงสุกร

Interview questionnaire for farmers on antibiotic use in pig production in Thailand

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ชื่อผู้สัมภาษณ์ (Name of interviewer) ....

ชื่อผู้ให้ข้อมูล (Name of respondent) ....

วันที่สัมภาษณ์ (Date) ....

ที่อยู่ผู้ให้สัมภาษณ์ (Address)

บ้านเลขที่ (No).................หมู่ที่ (Moo) .... ตำบล (Sub-district) ....

อำเภอ (District) .... จังหวัดราชบุรี (Ratchaburi)

โทรศัพท์บ้าน (Tel) .... มือถือ (Mobile) ....

คำชี้แจง โปรดทำเครื่องหมาย X ลงในช่อง ☐ หรือเติมข้อความใน (....) ให้สมบูรณ์

Please mark X in ☐ or fill in (....)

ส่วนที่ 1 ข้อมูลทั่วไป (Section A – General)

1.1 ผู้ให้ข้อมูล (respondent profiles)

1. เพศ (gender) ☐1. ชาย (male) ☐2. หญิง (female) ☐ 3. ไม่ระบุ (NA)

2. อายุ (age) .... ปี (year)

3. ระดับการศึกษาขั้นสูงสุด (Educational level)

   ☐ 1. ประถมศึกษา (Primary school)

   ☐ 2. มัธยมศึกษาตอนต้น (Secondary school-grade 9)

   ☐ 3. มัธยมศึกษาตอนปลาย/ปวช. (Secondary school-grade 12/ Por Wor Chor)

   ☐ 4. ปวส. (Por Wor Sor/Diploma)

   ☐ 5. ปริญญาตรีหรือสูงกว่าปริญญาตรี Bachelor degree or higher

   ☐ 6 .อื่นๆ (other) ระบุ (i.e.) ....

4. จำนวนปีที่ทำงานเกี่ยวกับการเลี้ยงสุกร (Years working on the pig farm, in any farm) .... ปี (year)

5. สถานะ (Position)

   ☐ 1. เจ้าของ (owner)

   ☐ 2. ผู้จัดการ (manager)

   ☐ 3. อื่นๆ (ETC) ระบุ (i.e.) ....

1.2 ฟาร์ม (farm characteristics)

6. อายุของฟาร์ม (age of farm) .... ปี (year)
7. จำนวนพนักงานในฟาร์ม <u>(เฉพาะที่เลี้ยงสัตว์)</u> (number of worker) ....
8. เป็นฟาร์มมาตรฐานหรือไม่ (Government standard farm)
   - ☐1 . ใช่ (yes) ☐ 2. ไม่ใช่ (no) ☐ 3 .ไม่ทราบ (unknown)
9. เป็นสมาชิกสหกรณ์หรือไม่ (Cooperative member)
   - ☐1 . ใช่ (yes) If answer Y, please provide a name of association..................................
     - ☐ 1.1 สหกรณ์ผู้เลี้ยงสุกรโพธาราม
     - ☐ 1.2 สหกรณ์ผู้เลี้ยงสุกรบ้านโป่ง
     - ☐ 1.3 อื่นๆ..
   - ☐ 2. ไม่ใช่ (no) ☐ 3 .ไม่ทราบ (unknown)
10. เป็นฟาร์มลูกเล้าหรือไม่ (Integrated contracting farming system)
    - ☐ 1. ไม่ใช่ (no) ข้ามไปข้อ 12 Please go to 12.
    - ☐ 2. ใช่ (yes) ถามต่อ ระบุรูปแบบ
      - ☐ 2.1 <u>ไม่ได้</u>รับปัจจัยการผลิต แต่ขายผลผลิตให้บริษัทต้นทางโดยกำหนด<u>ราคาล่วงหน้า</u> ข้ามไปข้อ 12

        <u>No</u> input but sell products <u>at a predetermined price</u> (Please go to 12.)
      - ☐ 2.2 <u>ไม่ได้</u>รับปัจจัยการผลิต แต่ขายผลผลิตให้บริษัทต้นทางที่<u>ราคาตลาด</u> ข้ามไปข้อ 12

        No input but sell products <u>at market price</u> (Please go to 12.)
      - ☐ 2.3 <u>รับ</u>ปัจจัยการผลิต และขายผลผลิตให้บริษัทต้นทางโดยกำหนด<u>ราคาล่วงหน้า</u>

        Some input and purchase products <u>at predetermined price</u>
      - ☐ 2.4 <u>รับ</u>ปัจจัยการผลิต และขายผลผลิตให้บริษัทต้นทางที่<u>ราคาตลาด</u>

        Some input and purchase products <u>at market price</u>
    - ☐ 3 .ไม่ทราบ (unknown)

11. ชนิดของปัจจัยการผลิตที่ซื้อ (Type of input)

		Type of input	Piglets	Feeds	Medicines
☐	1.	สุกรเท่านั้น (Only pigs)	*		
☐	2.	อาหารสัตว์เท่านั้น (Only animal feed)		*	
☐	3.	เวชภัณฑ์เท่านั้น (Only medicine)			*
☐	4.	สุกรและอาหารสัตว์ (Pigs and feed)	*	*	
☐	5.	สุกรและเวชภัณฑ์ (Pigs and medicine)	*		*
☐	6.	อาหารสัตว์และเวชภัณฑ์ (Feed and medicine)		*	*
☐	7.	ทั้งสุกร อาหารสัตว์และเวชภัณฑ์ (Pig, feed and medicine)	*	*	*

1.3 การผลิตสุกร (productivity)

12. ในฟาร์ม มีสุกรแม่พันธุ์หรือไม่ (Breeding sow)

☐ ไม่มี ข้ามไปข้อ 13 No (Please go to 13.)

☐ มี (ถามต่อ) Yes

จำนวนตัว (Number of breeding sow) .... ตัว

จำนวนแม่พันธุ์ขึ้นคลอด (Number of breeding sow giving birth per week) .... ตัว/ สัปดาห์

จำนวนลูกสุกรแรกเกิดทั้งหมด (Number of total born) .... ตัว/ แม่สุกร

จำนวนลูกสุกรแรกมีชีวิต (Number of born alive) .... ตัว/ แม่สุกร

จำนวนลูกสุกรหย่านม (Number of weaning piglets) .... ตัว/ แม่สุกร

13. จำนวนสุกรอนุบาล (ปัจจุบัน) (Number of weaner) .... ตัว

อัตราการสูญเสีย สุกรอนุบาล (percentage of nursing pigs loss) ร้อยละ ....

14. จำนวนสุกรขุน (ปัจจุบัน) (Number of fattener) .... ตัว

อัตราการสูญเสีย สุกรขุน (percentage of fattening pigs loss) ร้อยละ ....

15. จำนวนสุกรขุนที่ขายต่อเดือน (Number of fattener sold per month) .... ตัว

16. การขายผลผลิต (Destination of pig products including piglets and fatteners)

☐ 1. ผู้รับซื้อ/นายหน้า (Broker, Trader)

☐ 2. เขียงหมู (Fresh pork market)

☐ 3. ผู้บริโภคโดยตรง (Consumer)

☐ 4. ฟาร์มอื่น (Other farms)

☐ 5. กินเองในครัวเรือน (Household own consumption)

☐ 6. อื่นๆ (ETC) ระบุ (i.e.) ....

17. รายได้จากการขายสุกรรายเดือน (Average income from selling pigs per month)

☐ 1. ต่ำกว่า 10,000 บาท (< BHT 10,000)

☐ 2. 10,000-50,000 บาท (BHT 10,000-50,000)

☐ 3. 50,001-100,000 บาท (BHT 50,001-100,000)

☐ 4. 100,001-500,000 บาท (BHT 100,001-500,000)

☐ 5. มากกว่า 500,000 บาท (>BHT 500,000)

☐ 6. อื่นๆ (ETC) ระบุ (i.e.) ....

18. แนวโน้มรายได้จากการขายสุกรในช่วง 3 ปีที่ผ่านมา (trend of income from selling pigs in the last three year)

☐ 1. เพิ่มขึ้นมาก (Significantly increased)

☐ 2. เพิ่มขึ้นเล็กน้อย (Slightly increased)

☐ 3. เท่าเดิม (Equal)

☐ 4. ลดลงเล็กน้อย (Slightly ddecreased)

☐ 5. ลดลงมาก (Significantly decreased)

ส่วนที่ 2 การจัดการอาหารและสุขภาพ
(Section B – Feed and health management)

2.1 โปรแกรมอาหาร

	สูตรอาหาร/ ชื่อรุ่น/ ID number	ระยะเวลาที่ให้, สัปดาห์ (period, week)	ซื้อจาก (source) 1) โรงงานผลิตอาหารสัตว์ (Feed mill) 2) ผสมเองในฟาร์ม (In-house mixing) 3) สหกรณ์ (Cooperative) 4) บริษัทขายอาหารสัตว์ (Feed company) 5) อื่นๆ	ชื่อ (name)	ใส่ยาปฏิชีวนะ (ใส่/ไม่ใส่/ไม่ทราบ/ไม่ให้คำตอบ) (Antibiotic: use/do not use/ do not know/ do not tell)
19. สุกรแม่พันธุ์ (breeding sow) เฉพาะระยะอุ้มท้องและคลอด Only pregnant phase (ประมาณ 3-4 เดือน) (~3-4 months)	1				
	2				
	3				
	4				
	5				
20. สุกรดูดนม (breeding piglet) (ประมาณ 1 เดือน) (1 month)	1				
	2				
	3				
	4				
	5				
21. สุกรอนุบาล (nursery pig) (ประมาณ 1-2 เดือน) (1-2 months)	1				
	2				
	3				
	4				
	5				
22. สุกรขุน (fattener) (ประมาณ 3 เดือน) (3 month)	1				
	2				
	3				
	4				
	5				

23. แหล่งที่มาของการสั่งใช้/แนะนำให้กิน *อาหารสัตว์ (ผสมยา)* (ตอบได้มากกว่า 1 คำตอบ)

(Prescription/advise to administration of medicated feed) (Multiple answers possible)

☐ ไม่ได้รับคำแนะนำในการใช้*อาหารสัตว์* (Do not get advice about administration of medicated feed)

☐ ได้รับคำแนะนำในการใช้*อาหารสัตว์* (Get advice about administration of medicated feed)

☐1. สัตวแพทย์ประจำฟาร์ม (Farm veterinarian) จำนวน .... ครั้ง/เดือน (Time/month)

☐2. โรงงานผลิต/ บริษัทอาหารสัตว์ (Feed mill or feed company) จำนวน .... ครั้ง/เดือน (Time/month)

☐3. บริษัท contract (Contract company) จำนวน .... ครั้ง/เดือน (Time/month)

☐4. สัตวแพทย์จากกรมปศุสัตว์ (DLD veterinarian) จำนวน .... ครั้ง/เดือน (Time/month)

☐5. สั่งซื้อเอง (Self-medication for their own animals) จำนวน .... ครั้ง/เดือน (Time/month)

☐6. อื่นๆ (Others) ระบุ (i.e.) .... จำนวน .... ครั้ง/เดือน (Time/month)

24. รายจ่ายจากการซื้ออาหารสัตว์รายเดือน

(Average spending on purchasing feed per month)

☐ 1. ต่ำกว่า 1,000 บาท (< BHT 1,000)

☐ 2. 1,000-5,000 บาท (BHT 1,000-5,000)

☐ 3. 5,001-10,000 บาท (BHT 5,001-10,000)

☐ 4. 10,001-50,000 บาท (BHT 10,001-50,000)

☐ 5. มากกว่า 50,000 บาท (>BHT 50,000)

☐ 6. อื่นๆ (ETC) ระบุ (i.e.) ....

2.2 โรคและการจัดการ

25. ในปีที่ผ่านมา โรคที่พบบ่อยและการใช้วัคซีน (Common disease and vaccination in the last year) ตอบเฉพาะสุกรกลุ่มที่มีการเลี้ยงในฟาร์ม Please answer only animal groups that you have.

A. สุกรแม่พันธุ์ (Breeding sow) (เฉพาะระยะอุ้มท้องและคลอด)

โรค (Disease category) อาการ (clinical signs)	ไม่เคย (Never)	บางครั้ง (Occasionally)	เป็นประจำ (Regularly)
1. โรคระบบทางเดินหายใจ (Respiratory system) (ไอ จาม หอบ หายใจลำบาก) (cough, sneezing, panting, breathing difficulty)			
2. โรคระบบทางเดินอาหาร (Gastro-intestinal system) (ขี้ไหล ถ่ายเหลว) (diarrhoea)			
3. โรคระบบประสาท (Nervous system) (เดินวน ชัก หัวเอียง) (walking in circles, seizure)			
4. โรคระบบสืบพันธุ์ (Reproductive system) (มดลูกอักเสบ) (Metritis)			
5. ขาเจ็บ (lameness)			

6. โปรแกรมยาฉีด/กินเพื่อป้องกันโรค (Antibiotic program (both injectable and oral antibiotics) for prevention)

ชนิดของยา (antibiotic)	ปริมาณ (ซีซี/ตัว) (cc/ตัว)	จำนวนครั้ง (time)	จำนวนวัน (day)	ให้เพื่อ (system) 1.โรคระบบทางเดินหายใจ (Respiratory system) 2.โรคระบบทางเดินอาหาร (Gastro-intestinal system) 3. โรคระบบประสาท (Nervous system) 4. โรคระบบสืบพันธุ์ (Reproductive system) 5. ขาเจ็บ (lameness)	หมายเหตุ (remark)

7. โปรแกรมวัคซีน (ตอบได้มากกว่า 1 คำตอบ) (Vaccination program) (Multiple answers possible)

☐ ไม่ได้ทำ (No vaccination) ☐ ปากและเท้าเปื่อย (FMD) ☐ ปากและเท้าเปื่อย (FMD)

☐ อหิวาต์สุกร (Swine fever) ☐ PRRS ☐ ไมโคพลาสมา (Mycoplasma)

☐ .... ☐ .... ☐ ....

B. สุกรดูดนม (Breeding piglet)

โรค (Disease category) อาการ (clinical signs)	ไม่เคย (Never)	บางครั้ง (Occasionally)	เป็นประจำ (Regularly)
1. โรคระบบทางเดินหายใจ (Respiratory system) (ไอ จาม หอบ หายใจลำบาก) (cough, sneezing, panting, breathing difficulty)			
2. โรคระบบทางเดินอาหาร (Gastro-intestinal system) (ขี้ไหล ถ่ายเหลว) (diarrhoea)			
3. โรคระบบประสาท (Nervous system) (เดินวน ชัก หัวเอียง) (walking in circles, seizure)			
4. โรคระบบสืบพันธุ์ (Reproductive system) (มดลูกอักเสบ) (Metritis)			
5. ขาเจ็บ (lameness)			

6. โปรแกรมยาฉีด/กินเพื่อป้องกันโรค

ชนิดของยา (antibiotic)	ปริมาณ (ซีซี/ตัว) (cc/ตัว)	จำนวนครั้ง (time)	จำนวนวัน (day)	ให้เพื่อ (system) 1.โรคระบบทางเดินหายใจ (Respiratory system) 2.โรคระบบทางเดินอาหาร (Gastro-intestinal system) 3. โรคระบบประสาท (Nervous system) 4. โรคระบบสืบพันธุ์ (Reproductive system) 5. ขาเจ็บ (lameness)	หมายเหตุ (remark)

7. โปรแกรมวัคซีน (ตอบได้มากกว่า 1 คำตอบ) (Vaccination program) (Multiple answers possible)

☐ ไม่ได้ทำ (No vaccination) ☐ ปากและเท้าเปื่อย (FMD) ☐ ปากและเท้าเปื่อย (FMD)

☐ อหิวาต์สุกร (Swine fever) ☐ PRRS ☐ ไมโคพลาสมา (Mycoplasma)

☐ .... ☐ .... ☐ ....

C. สุกรอนุบาล (Nursery pigs)

โรค (Disease category) อาการ (clinical signs)	ไม่เคย (Never)	บางครั้ง (Occasionally)	เป็นประจำ (Regularly)
1. โรคระบบทางเดินหายใจ (Respiratory system) (ไอ จาม หอบ หายใจลำบาก) (cough, sneezing, panting, breathing difficulty)			
2. โรคระบบทางเดินอาหาร (Gastro-intestinal system) (ขี้ไหล ถ่ายเหลว) (diarrhoea)			
3. โรคระบบประสาท (Nervous system) (เดินวน ชัก หัวเอียง) (walking in circles, seizure)			
4. โรคระบบสืบพันธุ์ (Reproductive system) (มดลูกอักเสบ) (Metritis)			
5. ขาเจ็บ (lameness)			

6. โปรแกรมยาฉีด/กินเพื่อป้องกันโรค

ชนิดของยา (antibiotic)	ปริมาณ (ซีซี/ตัว) (cc/ตัว)	จำนวนครั้ง (time)	จำนวนวัน (day)	ให้เพื่อ (system) 1.โรคระบบทางเดินหายใจ (Respiratory system) 2.โรคระบบทางเดินอาหาร (Gastro-intestinal system) 3. โรคระบบประสาท (Nervous system) 4. โรคระบบสืบพันธุ์ (Reproductive system) 5. ขาเจ็บ (lameness)	หมายเหตุ (remark)

7. โปรแกรมวัคซีน (ตอบได้มากกว่า 1 คำตอบ) (Vaccination program) (Multiple answers possible)

☐ ไม่ได้ทำ (No vaccination) ☐ ปากและเท้าเปื่อย (FMD) ☐ ปากและเท้าเปื่อย (FMD)

☐ อหิวาต์สุกร (Swine fever) ☐ PRRS ☐ ไมโคพลาสมา (Mycoplasma)

☐ .... ☐ .... ☐ ....

D. สุกรขุน (Fattener)

โรค (Disease category) อาการ (clinical signs)	ไม่เคย (Never)	บางครั้ง (Occasionally)	เป็นประจำ (Regularly)
1. โรคระบบทางเดินหายใจ (Respiratory system) (ไอ จาม หอบ หายใจลำบาก) (cough, sneezing, panting, breathing difficulty)			
2. โรคระบบทางเดินอาหาร (Gastro-intestinal system) (ขี้ไหล ถ่ายเหลว) (diarrhoea)			
3. โรคระบบประสาท (Nervous system) (เดินวน ชัก หัวเอียง) (walking in circles, seizure)			
4. โรคระบบสืบพันธุ์ (Reproductive system) (มดลูกอักเสบ) (Metritis)			
5. ขาเจ็บ (lameness)			

6. โปรแกรมยาฉีด/กินเพื่อป้องกันโรค

ชนิดของยา (antibiotic)	ปริมาณ (ซีซี/ตัว) (cc/ตัว)	จำนวนครั้ง (time)	จำนวนวัน (day)	ให้เพื่อ (system) 1.โรคระบบทางเดินหายใจ (Respiratory system) 2.โรคระบบทางเดินอาหาร (Gastro-intestinal system) 3. โรคระบบประสาท (Nervous system) 4. โรคระบบสืบพันธุ์ (Reproductive system) 5. ขาเจ็บ (lameness)	หมายเหตุ (remark)

7. โปรแกรมวัคซีน (ตอบได้มากกว่า 1 คำตอบ) (Vaccination program) (Multiple answers possible)

☐ ไม่ได้ทำ (No vaccination) ☐ ปากและเท้าเปื่อย (FMD) ☐ ปากและเท้าเปื่อย (FMD)

☐ อหิวาต์สุกร (Swine fever) ☐ PRRS ☐ ไมโคพลาสมา (Mycoplasma)

☐ .... ☐ .... ☐ ....

2.3การใช้ยาปฏิชีวนะ (Use of antibiotics)

26. คำปรึกษาในการจัดการสุขภาพสุกร (ตอบได้มากกว่า 1 คำตอบ) (Source of advice on farming pigs, feeding, health management, using medicine (Multiple answers possible))

- ☐ 1. สัตวแพทย์ประจำฟาร์ม (Farm veterinarian)
- ☐ 2. สัตวแพทย์จากกรมปศุสัตว์ (DLD veterinarian)
- ☐ 3. บริษัทเวชภัณฑ์สัตว์
- ☐ 4. บริษัท contract (Contract company)
- ☐ 5. อื่นๆ (other) ระบุ (i.e.) ....

27. จำนวนครั้งของการตรวจ/เยี่ยมโดยปศุสัตว์จังหวัด ในเดือนที่ผ่านมา จำนวน .... ครั้ง
(Number of visit/inspection by DLD last month) (visit) (Time)

28. แหล่งที่มาของการ<u>สั่งใช้</u>/<u>แนะนำให้ใช้</u> *ยาปฏิชีวนะ* (ตอบได้มากกว่า 1 คำตอบ)
(<u>Prescription/advise to administration</u> of antibiotic) (Multiple answers possible)

- ☐ ไม่ได้รับคำแนะนำในการ<u>ใช้</u>*ยาปฏิชีวนะ* (Do not get advice about administration of antibiotics)
- ☐ ได้รับคำแนะนำในการ<u>ใช้</u>*ยาปฏิชีวนะ* (Get advice about administration of antibiotics)
  - ☐1. สัตวแพทย์ประจำฟาร์ม (Farm veterinarian) จำนวน .... ครั้ง/เดือน (Time/month)
  - ☐2. สัตวแพทย์จากบริษัทยา (Veterinarian from drug company) จำนวน .... ครั้ง/เดือน (Time/month)
  - ☐3. สัตวแพทย์/สัตวบาลจากบริษัท contract (Veterinarian at contract company) จำนวน .... ครั้ง/เดือน (Time/month)
  - ☐4. สัตวแพทย์จากกรมปศุสัตว์ (DLD veterinarian) จำนวน .... ครั้ง/เดือน (Time/month)
  - ☐5. สั่งซื้อยาเอง (Self-medication (for their own animals)) จำนวน .... ครั้ง/เดือน (Time/month)
  - ☐6 .อื่นๆ (Other sources) ระบุ (i.e.)................................ จำนวน .... ครั้ง/เดือน

(Time/month)

29. แหล่งที่มาของการซื้อ*ยาปฏิชีวนะ* (ตอบได้มากกว่า 1 คำตอบ)

Source of antibiotic purchasing (Multiple answers possible)

☐1. บริษัทยา (Drug company) จำนวน .... ครั้ง/เดือน (Time/month)

☐2. ร้านขายยา (คน((Drug store, human) จำนวน .... ครั้ง/เดือน (Time/month

☐3 .ร้านขายสัตว์ (สัตว์) (Drug store, animal) จำนวน .... ครั้ง/เดือน (Time/month)

☐4 .อินเตอร์เนท ออนไลน์ (Internet, online) จำนวน .... ครั้ง/เดือน (Time/month)

☐5. อื่นๆ ระบุ... จำนวน .... ครั้ง/เดือน (Time/month)

30. รายจ่ายจากการซื้อยาปฏิชีวนะรายเดือน

(Average spending on purchasing antibiotics per month)

☐ 1. ต่ำกว่า 1,000 บาท (< BHT 1,000)

☐ 2. 1,000-5,000 บาท (BHT 1,000-5,000)

☐ 3. 5,001-10,000 บาท (BHT 5,001-10,000)

☐ 4. 10,001-50,000 บาท (BHT 10,001-50,000)

☐ 5. มากกว่า 50,000 บาท (>BHT 50,000)

☐ 6. อื่นๆ (ETC) ระบุ (i.e.) ....

ส่วนที่ 3 ความรู้และความตระหนักในการใช้ยาปฏิชีวนะและเชื้อดื้อยา

(Section C – Knowledge and awareness of antibiotic use and AMR

31. จากข้อความต่อไปนี้ ท่านคิดว่าข้อความต่อไปนี้ จริงหรือไม่ (For each of the following statements Please tell me whether you think it is true or false? Please only indicate 'Don't know' if you really don't know.)

1) ท่านรู้จักยาปฏิชีวนะ/ยาฆ่าเชื้อ หรือไม่ ☐ 1. รู้ (Know) ☐ 2. ไม่รู้ (Do not know)
(Do you know "antibiotic"?)

หมายเหตุ: ผู้สัมภาษณ์ให้ข้อมูล
ยาปฏิชีวนะ หมายถึง ยาที่ยับยั้ง/ฆ่า/ต้านเชื้อโรค ที่มักเป็นสาเหตุของการเกิดโรคและอาการเจ็บป่วยในคนและสัตว์ อาจเรียกว่า "ยาฆ่าเชื้อ"
ยาปฏิชีวนะ ไม่ใช่ วิตามิน หรือ วัคซีน

Note: Interviewer will provide information about antibiotic to respondent.
Antibiotics: antibiotic is considered substance that exhibits antimicrobial activity (kill or inhibit the growth of micro-organisms) at concentrations attainable in vivo.

2) ยาปฏิชีวนะ/ยาฆ่าเชื้อ ฆ่าเชื้อไวรัสได้* ☐ 1. จริง ☐ 2. ไม่จริง ☐ 3. ไม่ทราบ
(Antibiotics kill the viruses) True False Do not know

3) ยาปฏิชีวนะ/ยาฆ่าเชื้อ รักษาไข้หวัดได้* ☐ 1. จริง ☐ 2. ไม่จริง ☐ 3. ไม่ทราบ
(Antibiotics are effective against cold and flu

4) ยาปฏิชีวนะ/ยาฆ่าเชื้อ กับยาแก้อักเสบเป็นยาชนิดเดียวกัน*
☐ 1. จริง ☐ 2. ไม่จริง ☐ 3. ไม่ทราบ
(Antibiotic is anti-inflammation drug.)

5) การได้รับยาปฏิชีวนะ/ยาฆ่าเชื้อ บ่อยครั้ง มีผลข้างเคียง เช่น ท้องเสีย*
(Taking antibiotics too often has side-effects such as diarrhoea)
☐ 1. จริง ☐ 2. ไม่จริง ☐ 3. ไม่ทราบ

6) การใช้ยาปฏิชีวนะ/ยาฆ่าเชื้อ โดยไม่จำเป็น ทำให้รักษาไม่ได้ผล หรือเชื้อดื้อยา*

☐ 1. จริง ☐ 2. ไม่จริง ☐ 3. ไม่ทราบ

(Unnecessary or unreasonable use of antibiotics have negative impacts such as ineffective treatment, AMR)

7) คุณรู้หรือไม่ว่า การใช้ยาปฏิชีวนะ/ยาฆ่าเชื้อ ในสัตว์มีโอกาสให้เกิดเชื้อดื้อยาในสัตว์ได้*

(Do you know whether antibiotic use in food producing animals can induce AMR in those animals?)

☐ 1. รู้ (Know) ☐ 2. ไม่รู้ (Do not know)

8) คุณรู้หรือไม่ว่ามีการแพร่กระจายของเชื้อดื้อยาในฟาร์มสุกรของประเทศไทย**

☐ 1. รู้ ☐ 2. ไม่รู้

(Resistance to antibiotics is widespread in Thai pig farming)

9) คุณรู้หรือไม่ว่ารัฐบาลประกาศห้ามใช้ยาปฏิชีวนะ/ยาฆ่าเชื้อ เพื่อเร่งการเจริญเติบโตในสัตว์ที่นำมาเป็นอาหารในประเทศไทย* ☐ 1. รู้ ☐ 2. ไม่รู้

(Do you know whether Thailand ban using antibiotic as a growth promoter in food producing animals?)

10) คุณคิดว่ายาปฏิชีวนะ/ยาฆ่าเชื้อจำเป็นต่อการเลี้ยงสุกรของท่านหรือไม่

(Do you think the use of antibiotics is necessary for the pig farming?

☐ 1. จำเป็น (yes) ☐ 2. ไม่จำเป็น (no) ☐ 3. ไม่แน่ใจ (not sure)

* คำถามเดียวกับข้อคำถามในการสำรวจอนามัยและสวัสดิการ (Same questions with the National Health Welfare Survey conducted in Thai people)

** คำถามเดียวกับข้อคำถามในการสำรวจของภูมิภาคยุโรป (Revised from the 2017 EU Insights – Perceptions on the human health impact of antimicrobial resistance (AMR) and antibiotics use in animals across the EU. European Food Safety Authority)

ส่วนที่ 4 ปัจจัยที่ส่งผลกับการใช้ยาปฏิชีวนะ

(Section D – Factors which influence the use of antibiotics)

32. กรุณาแสดงความคิดเห็นว่าปัจจัยต่อไปนี้ส่งผลต่อการใช้ยาปฏิชีวนะในฟาร์มของท่านหรือไม่
Please rate your level of agreement or disagreement with the following reasons contribute to the use antibiotics in your pig farm.

ปัจจัยที่ส่งผลต่อการใช้ยาปฏิชีวนะ (Reasons to use the antibiotics)	เห็นด้วยอย่างยิ่ง Strongly agree	เห็นด้วย Agree	อาจจะเห็นด้วย หรือไม่เห็นด้วย Somewhat agree or disagre	ไม่เห็นด้วย Disagree	ไม่เห็นด้วยอย่างยิ่ง Strongly disagree
ก) การเข้าถึงยาปฏิชีวนะและกฎหมายที่เกี่ยวข้อง (Access to antibiotics and regulation)					
1. การบริการของบริษัทเวชภัณฑ์ โฆษณา และการส่งเสริมการขายเวชภัณฑ์ (Services from pharmaceutical company, advertising, promotion of product)	☐	☐	☐	☐	☐
2. กฎหมายที่เกี่ยวข้อง เช่น การตรวจประเมินฟาร์ม การตรวจยาตกค้าง (Legal restriction such as farm inspection, ABO residue testing)	☐	☐	☐	☐	☐
3. นโยบายของรัฐในการลดการเกิดเชื้อดื้อยา (Practice policy on a reduction of AMR)	☐	☐	☐	☐	☐
ข) ประสบการณ์ เพื่อน และสัตวแพทย์ (Experience, peer and veterinarians)					
4. ประสบการณ์ของท่านที่ผ่านมาการใช้ยาปฏิชีวนะสามารถการลดการป่วยและการตายของสุกร (Past experiences that antibiotic reduced morbidity and mortality rate)	☐	☐	☐	☐	☐
5. คำแนะนำจากสัตวแพทย์ (advice by veterinarian)	☐	☐	☐	☐	☐
6. ข้อมูล คำแนะนำจากเพื่อนเกษตรกร หรือสหกรณ์ผู้เลี้ยงสุกร (Information, advice and experiences from peer farmers, pig cooperatives)	☐	☐	☐	☐	☐
ค) การจัดการฟาร์ม (Farm management)					
7. การจัดการสุขลักษณะฟาร์ม ความสะอาดและสุขอนามัย ที่ไม่เหมาะสม (Poor farm management i.e. no biosecurity)	☐	☐	☐	☐	☐
8. อาหารสัตว์ที่ไม่มีคุณภาพ (Suboptimal feed quality leading to digestive disorders)	☐	☐	☐	☐	☐
9. การเกิดโรคระบาดในฟาร์มและพื้นที่จังหวัด (Disease outbreaks in farm and province)	☐	☐	☐	☐	☐
10. โปรแกรมวัคซีนที่มีประสิทธิภาพ (Good vaccination program)	☐	☐	☐	☐	☐
ง) ผลผลิต (Farm productivity)					
11. กำไรที่ได้จากการเลี้ยงสุกร เพิ่มผลผลิต (Economic advantage, Increase productivity)	☐	☐	☐	☐	☐
12. แนวคิดและความต้องการ อาหารที่ปลอดภัยในสังคมไทย เช่น ผู้บริโภคต้องการเนื้อสุกรที่ไม่มียาปฏิชีวนะตกค้าง (Food safety concern in the society. For example, consumer demand for pork product without antibiotic residue)	☐	☐	☐	☐	☐

ส่วนที่ 5 อื่นๆ (Section E – Others)

ข้อเสนอแนะเพิ่มเติม (หากมี) (Do you have any advice and suggestion, open ended responses?)

Table A1 Characteristics of the 84 pig farmers and farms surveyed in the study

	Pig farmers (n=84) (%)
Respondent	
Gender	
• Male	34 (40.5)
• Female	50 (59.5)
Age (year, mean±SD)	48.9 (±14.2)
Farmer's educational level	
• Primary school	37 (44.0)
• Secondary school	25 (29.8)
• Bachelor's degree or higher	22 (26.2)
Position	
• Owner	61 (72.6)
• Manager	5 (6.0)
• Owner's dependent	18 (21.4)
Years of working at the pig farm (year, mean±SD)	15.1 (±11.2)
Farm	
Size of farm[a]	
• Smallholder farm	26 (31.0)
• Commercial farm	58 (69.0)
Type of farm	
• Farrowing to finisher farm	54 (64.3)
• Fattening	30 (35.7)
GMP certified farm [b]	31 (36.9)
Member of cooperative farm	17 (20.2)
Contract farm	8 (9.5)
Income per month [c]	
• Less than BHT 10,000 (<US$317)	28 (33.3)
• BHT 10,000-50,000 (US$317-1,590)	19 (22.6)
• BHT 50,001-100,000 (US$1,590-3,170)	6 (7.1)
• BHT 100,001-500,000 (US$3,170-15,900)	8 (9.5)
• More than 500,000 (>US$15,900)	9 (10.7)
• No response	14 (16.7)
Trend of income in the past 3 years	
• Significantly increased	2 (2.4)
• Slightly increased	7 (8.3)
• Equal	7 (8.3)
• Slightly decreased	15 (17.9)
• Significantly decreased	53 (63.1)
Average spending on purchasing feed per month [c]	

• Less than BHT 1,000 (<US$32)	9 (10.7)
• BHT 1,000-5,000 (US$32-159)	14 (16.7)
• BHT 5,001-10,000 (US$159-317)	7 (8.3)
• BHT 10,001-50,000 (US$317-1,590)	13 (15.5)
• More than 50,000 (>US$1,590)	18 (21.4)
• No response	23 (27.4)
Average spending on purchasing medicine per month [c]	
• Less than BHT 1,000 (<US$32)	31 (36.9)
• BHT 1,000-5,000 (US$32-159)	9 (10.7)
• BHT 5,001-10,000 (US$159-317)	1 (1.2)
• BHT 10,001-50,000 (US$317-1,590)	8 (9.5)
• More than 50,000 (>US$1,590)	7 (8.3)
• No response	28 (33.3)
Destination of pig products	
• Broker only	27 (32.1)
• Pork retailer only	18 (21.4)
• Both broker and pork retailer	12 (14.3)
• Consumer directly	7 (8.3)
• Other farms	8 (9.5)
• Household own consumption	2 (2.4)

a: According to the catagorisation by the Department of Livestock Development, there are greater than or equal to 50 pigs per farm in commercial farms and smallholder farms with less than 50 pigs per farm.
b: DLD certified Good Agriculture Practice (GAP) for farms with a good standard of animal husbandry
c: THB 1= US$ 31.5

Table A2 Source of advice on animal health management, antibiotics and medicated feed from 84 farms

	Health (N=84, %)	Antibiotic (N=84, %)	Feed (N=84, %)
Received advice			
• Received advice	68 (81.0)	48 (77.4)	36 (42.9)
• Did not receive advice	16 (19.0)	36 (42.9)	48 (57.1)
Source of advice			
• Veterinarian at farm	12 (17.6)	11 (22.9)	7 (19.4)
• DLD veterinarian	4 (5.9)	2 (4.2)	1 (2.8)
• Pharmaceutical, feed company, feed mill	8 (11.8)	5 (10.4)	6 (16.7)
• Contracting company	4 (5.9)	3 (6.3)	4 (11.1)
• Others	31 (45.6)	22 (45.8)	16 (44.4)
• More than one source	9 (13.2)	5 (10.4)	2 (5.6)

Supplementary 2

Table S1 Number of farms that farmers agreed to participated and did not participate in the studied area in the farmer survey

	Number of farms (%)	Number (%) of farms participated in the study			Number (%) of farms *did not* participate in the study		
			By size of farm			By size of farm	
		Total	Smallholder farm	Commercial farm	Total	Smallholder farm	Commercial farm
District A							
- Sub-distrct A1	30	25 (83.3)	9 (36)	16 (64)	5 (16.7)	2 (40)	3 (60)
- Sub-distrct A2	16	6 (37.5)	3 (50)	3 (50)	10 (62.5)	9 (90)	1 (10)
District B							
- Sub-distrct B1	16	16 (100)	4 (25)	12 (75)	0	0	0
- Sub-distrct B2	14	12 (85.7)	0	12 (100)	2 (14.3)	1 (50)	1 (50)
District C							
- Sub-distrct C1	12	11 (91.7)	7 (63.6)	4 (36.4)	1 (8.3)	0	1 (100)
- Sub-distrct C2	14	14 (100)	11 (78.6)	3 (21.4)	0	0	0
	102	84	34	50	18	12	6

Lekagul A, *et al*. *BMJ Global Health* 2020; 5:e001918. doi: 10.1136/bmjgh-2019-001918

Appendix 4 Supplement study paper 2

A 4.1 Interview guide for antibiotic use and factors influencing the use of antibiotic in pig production with pig farmers

A4.2 Interview guide for antibiotic use and factors influencing the use of antibiotic in pig production with experts

Participant's code:

LONDON SCHOOL of HYGIENE &TROPICAL MEDICINE

Interview guide: Antibiotic use and factor influencing the use of antibiotics in pig production

THIS GUIDE IS PREPARED TO PROVIDE BACKGROUND IDEA ABOUT THE FACTOR INFLUENCING THE USE OF ANTIBIOTIC IN PIGS. I WILL NOT READ THROUGH THE QUESTIONS.

Topic: Towards an understanding of antibiotic use in swine production systems in Thailand

Student: Angkana Sommanustweechai

Supervisor: Dr Shunmay Yeung, Professor Anne Mills, Professor Jonathan Ruston

Objective of the study

1) To describe the pattern of antibiotic use and estimate the total amount of antibiotics used in pig production globally and in Thailand
2) To investigate the regulatory system and analyse its effectiveness in controlling the use of antibiotics in pig production in Thailand
3) To explore factors contributing to the use of antibiotics in pigs in Thailand
4) To identify potentially effective policy to enhance the rational use of antibiotics in pig production in Thailand

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Interviewer……

Name of respondent………

Working address………

Tel ……………………………………………………………………………Mobile phone ………………………………………………………

- **Qualitative interview introduction**

Antibiotic use and factor influencing the use of antibiotics in pig production: semi-structured interview

Length: 45-60 minutes

Objective of the interview: To see things the way you (respondent) see them. It does not aim to assess or evaluate your work. More like a conversation with a focus on your (respondent) experience, your (respondent) opinions and what you think or feel about the topics covered.

- **Verbal consent**

Discussion of **confidentiality** measures, include mention that subjects will be asked for oral rather than signed consent.

- **Background Information**

Invite interviewee to briefly tell interviewer about him/herself: general information about background... mostly about experiences and perspectives on issues surrounding the use of antibiotics in pig production in Thailand.

1: Animal health and farm management

Sub-area: General views and practices related to health management

1. Can you tell me about health management practices in your farm?
2. What is the main health problem(s) in your farm?
3. Do pigs at different production stages have different health issues?
4. If your pigs get sick, how do you treat them? Do you use any medicines? If so, what kind of medicines? Do you use them for the prevention of treatment of diseases?
5. <In case the farmer does not use antibiotics> Why did you decide to not use antibiotics?
6. Are your pigs vaccinated? If so, what kinds of vaccination program do you use?
7. Do you think that vaccination helps reducing antibiotic use?

Sub-area: Farm management and antibiotic use

1. Do you believe that antibiotics are necessary for animal farming? If so, why?
2. Do you think any of these issues may be associated with increased antibiotic use in the farm?
   - Poor farm management
   - Suboptimal feed quality
3. In this period, is there any disease outbreaks in your farm or other parts of the province?
   - If so, does this affect farm management including the use of antibiotics? How?
4. If you work for a larger company, does this company set the standards of health management including antibiotic use? If so, how?
   -

Area 2: Pig production and market demand

Sub-area: Pig production and antibiotic use

- In your experience, what is the effect of antibiotics on the morbidity and mortality of pigs?
- Do you think antibiotics are necessary to sustain economic profit?
- What about their cost? Are antibiotics expensive?

Sub-area: food safety, market demand (consumer preference)

- What do you think about antibiotics and food safety? Is there a way to monitor the antibiotic residue in your meat?
- What do you think about consumer's demand for organic food or antibiotic-free pig products? Do you think this may affect antibiotics use in the farms? If so, how?

Area 3: Relationships with other farmers, veterinarian, pharmaceutical company

Sub-area: Relations with other farmers

1. Have you ever talked or shared information about antibiotics with other farmers you know? If so, can you explain?
2. Do you belong to a cooperative association? If so, has this ever involved the discussion or sharing of information about antibiotic use? If so, can you explain?

Sub-area: roles of veterinarians in diagnosing disease and prescribing antibiotics

1. Who does animal health checks and prescribes antibiotics in your farm?
   - Do you receive regular visits from farm veterinarians? If so, can you explain?
   - Have you ever received visits in your farm from DLD officers? If so, can you explain?
   - Do you rely on the service of veterinarian consultants? If so, are they from academia? Which university are they from? Do they influence your decision on the use of antibiotics?

Sub-area: Sources of antibiotics

1. Where do you buy the medicines (including antibiotics) and medicated feed?
2. Can you tell me more about how you purchase them?
   - What about sale representatives? Do they try to influence the way you use antibiotics in the farm? If so, how?

Area 4: Regulation and policy on antibiotic use

Sub-area: Regulations

1. Do you have an official standard farm certification?
2. Do you receive any inspections from the DLD? If yes, how frequently? What do they monitor?
3. Is there any other organisation inspecting your farm? If yes, who and how?
4. Have you heard about any regulations restricting the use of active pharmaceutical ingredient in animal feed and antibiotic use for growth promotion?
   a. If so, what do you think?
   b. Can regulations be applied easily in your farm?
5. The Thai-FDA and DLD are currently working on a new regulation to optimise the use of antibiotics in livestock to reduce AMR
   a. Do you know this? If so, what do you think?

Sub-area: Policy on antibiotic use

1. Are you aware of the National Strategic Plan on AMR, and the national target to reduce 30% of antibiotic use in animals? If so, what do you think?

<u>Comments</u>: INTERVIEWER, use this space to summarize how the SSI went, including the mood or feelings of the participant during the interview.

Regulations on antibiotic use in pig production in Thailand

LONDON SCHOOL of HYGIENE &TROPICAL MEDICINE

Interview guide: Regulations on antibiotic use in pig production in Thailand

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Topic: Towards an understanding of antibiotic use in swine production systems in Thailand

Student: Angkana Sommanustweechai

Supervisor: Dr Shunmay Yeung, Professor Anne Mills, Professor Jonathan Ruston

Objective of the study

1) To describe the pattern of antibiotic use and estimate the total amount of antibiotics used in pig production globally and in Thailand
2) To investigate the regulatory system and analyse its effectiveness in controlling the use of antibiotics in pig production in Thailand
3) To explore factors contributing to the use of antibiotics in pigs in Thailand
4) To identify potentially effective policy to enhance the rational use of antibiotics in pig production in Thailand

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Interviewer……

Name of respondent………

Working address………

Tel ……………………………………………………………………………Mobile phone ……………………………………………………

Theme: Regulatory system and its enforcement mechanism

(Item 1-4, do not ask farmers.)

1. What is the aim of the regulations (under your responsibility: Drug Act, Animal Feed Quality Control Act, Pharmaceutical Profession Act, Veterinary Profession Act) in controlling the use of antibiotics?
2. What kinds of regulatory system according to the regulations in controlling the use of antibiotics?
    a. Legal requirement for **registration of professionals/ prescription control/ control antibiotic use at farm**
    b. Organization and structure to control **registration of professionals/ prescription control/ control antibiotic use at farm**
        i. National and local levels of the country
        ii. Decentralized activities
    c. International standard: related to the WHO/ OIE guidance
    d. Quality management system: quality management, relevant to the WHO/OIE guidance
    e. Internal planning and procedures: monitoring programs
    f. Records and outputs: lists and database of professionals, operators
    a. Availability of information: publication of database, data publicly available
3. What is the **registration of professional** procedure?
    a. Process for pharmacist registration
    b. Process for veterinarian registration
    c. Specific process in relation to antibiotic control
    d. Inspection
    e. Sanction for non-compliance regulations
4. What is the **prescription control** procedure?
    a. Process for prescription control
    b. Specific process in relation to antibiotic control
    c. Inspection
    d. Sanction for non-compliance regulations
5. What is the **control antibiotic use at farm** procedure?
    a. Process for control antibiotic use at farm
    b. Specific process in relation to antibiotic control
    c. Inspection
    d. Sanction for non-compliance regulations
6. In the light of your experience of **the regulatory capacity in prescription control/ control antibiotic use at farm**:
    a. Which aspects are working well? (strength)
    b. Which aspects are in most need of improvement? (weakness)
7. Please describe any concerns, worries or emotional stress you have about **the regulatory system and enforcement mechanism of antibiotic distribution and use**. *(Probes: Were you concerned or worried about the working process, complain or sue by operators, affecting your work in any other way?)*
8. If you were to compare about **the regulatory system and enforcement mechanism of antibiotic distribution and use** in Thailand with other countries:

a. How are they similar?
b. How are they different?

Theme: Factors contributing the effectiveness of regulation

1. Your opinion on the **design** of regulation on antibiotic use:
   - How appropriate is the intervention given its aim (to ensure the safety, efficacy and quality of drugs)?
   - How appropriate is the intervention given to rational use of antibiotics?
   - How clearly specified is the implementation process (e.g. regulatory body?)
   - What is the accountability of the regulator? Are there clear complaints mechanisms?
   - How passive or active is the monitoring and implementation?
2. Do you know whether (**information**)?
   - The Drug Act classifies most antibiotics as "dangerous drugs" which can be accessed without prescription in retail pharmacies but are dispensed by professional pharmacists in pharmacies
   - The Animal Feed Quality Control Act prohibits the direct use of API in animal feed
   - Thailand ban using antibiotic as a growth promoter in food producing animals
3. Your opinion on the **capacity** of regulation on antibiotic use:
   - What resources are available to undertake inspection/monitoring (Probes: human resource (quantity and competency of personnel), financial support, policy support, recording system, etc.)?
   - How much did you like capacity of the regulatory system in terms of registration of professionals/ prescription control/ control antibiotic use at farm?
   - Please describe any concerns, worries or emotional stress you have about the capacity of the regulatory system. (Probes: Were you concerned or worried about the working process, complain or sue by operators, affecting your work in any other way?)
   - Please describe any actual problems that you experienced while working about the capacity of the regulatory system. (Probes: Did you experience working problem anywhere else? Please provide detailed info on where the problem was experienced?)
4. Your opinion on the **power/authority** of regulation on antibiotic use:
   - What is the relative authority of the regulator/regulatee?
   - What is the credibility of the judicial system (e.g. is there effective sanctioning)
   - What is the strength of consumer groups, media, professional associations?
   - What are the sources of power/conflict (e.g. resource availability)?
5. Your opinion on the **context** of regulation on antibiotic use:
   - Political context about the regulation
   - Social and cultural context about the regulation
   - Economic context about the regulation

Recommendations

1. Would you like to change anything about **the regulatory system and its enforcement mechanism** in controlling the use of antibiotics in pig production? If so, how?
2. Would you like to change anything about **design, information, capacity, authority and context of the regulatory system** in controlling the use of antibiotics in pig production? If so, how?
3. Do you have any other recommendations about **the regulatory system and its enforcement mechanism**?
4. Do you have any other recommendations about **design, information, capacity, authority and context of the regulatory system** in controlling the use of antibiotics in pig production?

Other

Comments: INTERVIEWER, use this space to summarize how the SSI went, including the mood or feelings of the participant during the interview.

Appendix 5 Information sheet and consent form

A 5.1 Ethical approval document by Institute for the Development of Health Research Protections

A 5.2 Ethical approval document by London School of Hygiene and Tropical Medicine

A 5.3 Participant information leaflet and consent for research participation for pig farmers

A 5.3 Participant information leaflet and consent for research participation for experts

A 5.4 Participant information leaflet and consent for research participation for pig farmer and experts in Thai

Ethics Committee

Institute for the Development of Human Research Protections (IHRP)

Building 8 Floor 7 Room 702 Department of Medical Science Ministry Public Health Nonthaburi Thailand 11000

Certificate of Approval

Title of Project: Towards an understanding of antibiotic use in swine production systems in Thailand. (Version 2/ Date: January 24, 2018)

Principal Investigator: Angkana Sommanustweechai

Responsible Organization: International Health Policy Program (IHPP), Ministry of Public ,Health.

The Ethics Committee of Institute for the Development of Human Research Protections (IHRP) had reviewed the research proposal. Concerning on scientific, ICH-GCP and ethical issues, the committee has approved for the implementation of the research study mentioned above.

V ....¥.................................	[redacted] ....
(Dr.Vichai Chokevivat)	(Dr.Pramote Stienrut)
Chairman	Committee and Secretary

Date of First Meeting: January 23, 2018

Date of Approval: January 26, 2018

London School of Hygiene & Tropical Medicine
Keppel Street, London WC1E 7HT
United Kingdom
Switchboard: +44 (0)20 7636 8636

www.lshtm.ac.uk

Observational / Interventions Research Ethics Committee

Dr Angkana Sommanustweechai
LSHTM

1 June 2018

Dear Dr Angkana Sommanustweechai

Study Title: Towards an understanding of antibiotic use in swine production systems in Thailand

LSHTM Ethics Ref: 14860

Thank you for responding to the Observational Committee's request for further information on the above research and submitting revised documentation.

The further information has been considered on behalf of the Committee by the Chair.

Confirmation of ethical opinion

On behalf of the Committee, I am pleased to confirm a favourable ethical opinion for the above research on the basis described in the application form, protocol and supporting documentation as revised, subject to the conditions specified below.

Conditions of the favourable opinion

Approval is dependent on local ethical approval having been received, where relevant.

Approved documents

The final list of documents reviewed and approved by the Committee is as follows:

Document Type	File Name	Date	Version
Investigator CV	CV-angkana20180112	28/01/2018	1
Protocol / Proposal	SSI with experts_20180220_CT	02/02/2018	1
Protocol / Proposal	Data sheet for AMU volume collection_20180222	22/02/2018	1
Protocol / Proposal	Use of antimicrobial in livestock_EC submission_20180502	02/05/2018	2
Protocol / Proposal	SSI with farmers_20180502	02/05/2018	2
Protocol / Proposal	Questionaire_ 20180502	02/05/2018	2
Information Sheet	Consent form_farmer_20180515	15/05/2018	2
Covering Letter	Cover letter to LSHTM EC_20180517	17/05/2018	1
Information Sheet	Consent form_expert_20180517	17/05/2018	2
Local Approval	EC Eng	21/05/2018	1

After ethical review

The Chief Investigator (CI) or delegate is responsible for informing the ethics committee of any subsequent changes to the application. These must be submitted to the Committee for review using an Amendment form. Amendments must not be initiated before receipt of written favourable opinion from the committee.

The CI or delegate is also required to notify the ethics committee of any protocol violations and/or Suspected Unexpected Serious Adverse Reactions (SUSARs) which occur during the project by submitting a Serious Adverse Event form.

An annual report should be submitted to the committee using an Annual Report form on the anniversary of the approval of the study during the lifetime of the study.

At the end of the study, the CI or delegate must notify the committee using an End of Study form.

All aforementioned forms are available on the ethics online applications website and can only be submitted to the committee via the website at: http://leo.lshtm.ac.uk

Additional information is available at: www.lshtm.ac.uk/ethics

Yours sincerely,

[redacted]

Professor John DH Porter
Chair

ethics@lshtm.ac.uk
http://www.lshtm.ac.uk/ethics/

PARTICIPANT INFORMATION LEAFLET AND CONSENT FOR RESEARCH PARTICIPATION

Study Title: Swine production systems and health management in Thailand

Principal Investigator: Angkana Sommanustweechai

I am a graduate student at the London School of Hygiene and Tropical Medicine. I am planning to conduct a research study, which I invite you to take part in. This form has important information about the reason for doing this study, what we will ask you to do if you decide to be in this study, and the way we would like to use information about you if you choose to be in the study.

Respondent: pig farmer

<u>Why are you doing this study?</u>
You are being asked to participate in a research study about swine production systems, health management and the use of medicines in pig farms in Thailand. Now there is no information about Thai swine production. This study will generate information for better understanding about Thai swine production and its context such as regulation, the use of antibiotics and pig market.

<u>What will I do if I choose to be in this study?</u>
You will be asked to provide information, your opinions, views, experiences about farm management. The interview will cover details of productivity of your farm, animal health and illness, market demand, your relationship with DLD and other farmers, and regulation.

You will be asked to provide data through questionnaire and semi-structured interview. After the interview, I would like to ask for permission to stay on your farm for 3-5 days to learn more about the farm management, husbandry and biosecurity.

In order to understand about medicines used in your farm, data on the antibiotic use in your farm will be explored. Potential sources include antibiotic prescription record, treatment records or antibiotic invoices at farms, where they are available. The duration of antibiotic use data will cover the last batch of production in breeder in farrowing period (about 1 month), weaner or breeding piglet (about 2 months) and fattener (about 3 months).

For the interview, I would like to record this interview so as to make sure that I remember accurately all the information you provide. I will keep these audio file in my laptop and LSHTM database and they will only be used by the research team.
[If respondent may participate without being taped, state so. If audio/video recording are not optional, then clearly state that it is required for participation.]

Study time:
The questionnaire will take approximately 30 minutes.
The semi-structured interview will take approximately 1-1.30 hours
The observation period and antimicrobial use data collection will take 1-3 days each.

Study location: All study procedures will take place at Bangkok and Ratchaburi province.

<u>What are the possible risks or discomforts?</u>

This research does not involve taking any samples from you or from the farm. We expect that any risks or discomforts to you will be minimal. It is unlikely, but possible that some of the topics that we discuss or questions we ask may make you feel uncomfortable, in which case you are free to not answer or to skip to the next question.

What are the possible benefits for me or others?
You are not likely to have any direct benefit from being in this research study. This study is designed to gain more about insight and understanding pig production and health management. The knowledge received may be of value to humanity.

How will you protect the information you collect about me, and how will that information be shared?
Study data will be handled as confidentially as possible. All information will be kept in secret with the primary investigator for their confidentiality. The paper documents will be kept in the locked cabinet at the International Health Policy Program to which only the primary investigator will have access. All audio files and transcripts will be password protected and kept in the primary investigator's computer which will also be password protected. The files will be encrypted and backed up on LSHTM's secure FILR system and on a password protected portable storage.

Summary results of this study may be used in publications and presentations. Individual names and other personally identifiable information will not be used. Participants' names and other information that could be used to identify individuals or individual farms will be removed or changed to keep confidentiality.

Sometimes it is helpful to use direct quotations (i.e. to use the same words that you use in the interview, in academic publication or other academic outlets. If we do this, we will make sure that it is completely anonymous so that there is no way that individuals can be identified from other information in the interview. However, if you would prefer that we do not use direct quotations in this way then we will not. We will give you the choice when we ask for your consent.

What are my rights as a research participant?
Participation in this study is voluntary. If at any time and for any reason, you would prefer not to participate in this study, please feel free not to. If at any time you would like to stop participating, please tell me. We can take a break, stop and continue at a later date, or stop altogether. You may withdraw from this study at any time, and you will not be penalized in any way for deciding to stop participation.

If you decide to withdraw from this study, the researchers will ask you if the information already collected from you can be used.

Who can I contact if I have questions or concerns about this research study?
You have the right to ask questions about this research study and to have those questions answered by me before, during or after the research. If you have any further questions about the study, at any time feel free to contact a researcher at

Angkana Sommanustweechai
International Health Policy Program,
Tivanond Road,
Amphur Muang
Nonthaburi, 11110
Mobile: 081-451-7850.
Email: angkanasc@gmail.com

Consent Section

Ask respondent to provide "I agree" or "I do not agree" options at the end of the consent form.

I agree to join in

- Questionnaire
- In-depth interview (if yes, you agree if your quote is made available through academic publication or other academic outlets with anonymity.
  - Agree
  - Do not agree
- Observation
- Antimicrobial use data collection

I do not agree to join in the interview

Participant:

I have read the foregoing information, or it has been read to me. I have had the opportunity to ask questions about it and any questions that I have asked been answered to my satisfaction. I consent voluntarily to participate as a participant in this research.

___________________________	__________	________	_________________________
Signature of Participant	Date	Time	Printed Name

Researcher/person taking the consent:

I have accurately read out the information sheet to the potential participant, and to the best of my ability made sure that the participant understands. I confirm that the participant was given an opportunity to ask questions about the study, and all the questions asked by the participant have been answered correctly and to the best of my ability. I confirm that the individual has not been coerced into giving consent, and the consent has been given freely and voluntarily.

___________________________	__________	________	_________________________
Signature of researcher/ person took this research	Date	Time	Printed Name

PARTICIPANT INFORMATION LEAFLET AND CONSENT FOR RESEARCH PARTICIPATION

Study Title: Swine production systems and health management in Thailand

Principal Investigator: Angkana Sommanustweechai

I am a graduate student at the London School of Hygiene and Tropical Medicine. I am planning to conduct a research study, which I invite you to take part in. This form has important information about the reason for doing this study, what we will ask you to do if you decide to be in this study, and the way we would like to use information about you if you choose to be in the study.

Respondent: experts about regulations in relation to the use of antibiotics in pig production in Thailand.

Why are you doing this study?
You are being asked to participate in a research study about swine production systems and health management in Thailand. The aim of the study is to understand how farmers manage the pig production, how and why the antibiotics are used in pig production in Thailand.

What will I do if I choose to be in this study?
You will be asked to provide your opinions, views, experiences about the regulations in relation to antibiotic use.

Study time: Study participation will take approximately 1-1.30 hours

Study location: All study procedures will take place at Bangkok and Rachburi province.

I would like to record this interview so as to make sure that I remember accurately all the information you provide. I will keep these audio file in my laptop and LSHTM database and they will only be used by the research team.

[If respondent may participate without being taped, state so. If audio/video recording are not optional, then clearly state that it is required for participation.]

What are the possible discomforts?
This research does not involve taking any samples from you or from the farm. We expect that any risks or discomforts to you will be minimal. It is unlikely, but possible that some of the topics that we discuss or questions we ask may make you feel uncomfortable, in which case you are free to not answer or to skip to the next question.

What are the possible benefits for me or others?
You are not likely to have any direct benefit from being in this research study. This study is designed to gain more about insight and understanding pig production and health management. The knowledge received may be of value to humanity.

How will you protect the information you collect about me, and how will that information be shared?
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access. All audio files and transcripts will be password protected and kept in the primary investigator's computer which will also be password protected. The files will be encrypted and backed up on LSHTM's secure FILR system and on a password protected portable storage.

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Sometimes it is helpful to use direct quotations (i.e. to use the same words that you use in the interview, in academic publication or other academic outlets. If we do this, we will make sure that it is completely anonymous so that there is no way that individuals can be identified from other information in the interview. However, if you would prefer that we do not use direct quotations in this way then we will not. We will give you the choice when we ask for your consent.

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Participation in this study is voluntary. If at any time and for any reason, you would prefer not to participate in this study, please feel free not to. If at any time you would like to stop participating, please tell me. We can take a break, stop and continue at a later date, or stop altogether. You may withdraw from this study at any time, and you will not be penalized in any way for deciding to stop participation.

If you decide to withdraw from this study, the researchers will ask you if the information already collected from you can be used.

Who can I contact if I have questions or concerns about this research study?

You have the right to ask questions about this research study and to have those questions answered by me before, during or after the research. If you have any further questions about the study, at any time feel free to contact a researcher at

Angkana Sommanustweechai
International Health Policy Program,
Tivanond Road,
Amphur Muang
Nonthaburi, 11110
Mobile: 081-451-7850.
Email: angkanasc@gmail.com

Consent Section

Ask respondent to provide "I agree" or "I do not agree" options at the end of the consent form.

Participant:

I have read the foregoing information, or it has been read to me. I have had the opportunity to ask questions about it and any questions that I have asked been answered to my satisfaction. I consent voluntarily to participate as a participant in this research.

☐ I agree to join in the interview

☐ I disagree to be quoted directly.

☐ I agree to be quoted directly if my name is not published.

___________________________	__________	________	_________________________
Signature of Participant	Date	Time	Printed Name

Researcher/person taking the consent:

I have accurately read out the information sheet to the potential participant, and to the best of my ability made sure that the participant understands. I confirm that the participant was given an opportunity to ask questions about the study, and all the questions asked by the participant have been answered correctly and to the best of my ability. I confirm that the individual has not been coerced into giving consent, and the consent has been given freely and voluntarily.

___________________________	__________	________	_________________________
Signature of researcher/ person took this research	Date	Time	Printed Name

รายการที่ 1

รายการที่ 1เอกสารชี้แจงวัตถุประสงค์โครงการและการยินยอมให้ข้อมูล

โครงการวิจัย การใช้ยาปฏิชีวนะในการเลี้ยงสุกรของประเทศไทย

นักวิจัย สพ.ญ. อังคณา สมนัสทวีชัย

ข้าพเจ้าเป็นนักศึกษาระดับปริญญาเอกจาก London School of Hygiene and Tropical Medicine ประเทศสหราชอาณาจักร โดยวางแผนในการเก็บข้อมูลในการศึกษาวิจัยเรื่องการใช้ยาปฏิชีวนะในการเลี้ยงสุกรของประเทศไทย โดยขอเชิญท่านเป็นผู้ให้ข้อมูลประกอบการศึกษาดังกล่าว เอกสารฉบับนี้มีข้อมูลที่เกี่ยวข้องกับการศึกษา การนำข้อมูลไปใช้ และสอบถามความยินยอมในการให้ข้อมูลของท่าน

ผู้ให้ข้อมูล เกษตรกรผู้เลี้ยงสุกร

เหตุผลในการศึกษาวิจัย

ท่านกำลังได้รับรายละเอียดเพื่อสอบถามความสมัครใจในการเข้าร่วมการศึกษาวิจัยเกี่ยวกับการเลี้ยงสุกร โดยครอบคลุมการจัดการทางสุขภาพและการใช้ยา ซึ่งในปัจจุบันยังไม่มีการศึกษาเกี่ยวกับการเลี้ยงสุกรในประเทศไทย การศึกษาวิจัยนี้จะทำให้เกิดความรู้ และความเข้าใจเกี่ยวกับการเลี้ยงสุกรในบริบทประเทศไทย เช่น กฎหมาย การใช้ยาปฏิชีวนะ และตลาดสุกร

สิ่งที่ท่านต้องทำในการให้ข้อมูล

ผู้สัมภาษณ์จะสอบถามข้อมูล ความคิดเห็น มุมมอง และประสบการณ์ในการจัดการฟาร์มของท่าน การสัมภาษณ์จะครอบคลุมรายละเอียดเกี่ยวกับผลผลิตสุกรในฟาร์มของท่าน สุขภาพและความเจ็บป่วยของสุกร ความต้องการของตลาด ความสัมพันธ์ของท่านและกรมปศุสัตว์ และกฎหมายที่เกี่ยวข้อง

ผู้สัมภาษณ์จะสอบถามข้อมูลในรูปแบบแบบสอบถาม และการสัมภาษณ์กึ่งโครงสร้าง หลังจากการสัมภาษณ์ นักวิจัยอาจจะขออนุญาตที่จะเข้าศึกษาดูงานในฟาร์มของท่านเป็นเวลา 3-5 วัน เพื่อเรียนรู้เกี่ยวกับการจัดการฟาร์ม สุขาภิบาล และความปลอดภัยในการป้องกันโรค

เพื่อที่จะเข้าใจถึงการใช้ยาในฟาร์มของท่าน นักวิจัยจะขอสำรวจข้อมูลเกี่ยวกับการใช้ยาปฏิชีวนะ จากแหล่งข้อมูล ดังต่อไปนี้ ได้แก่ บันทึกการใช้ยาปฏิชีวนะในฟาร์มของท่าน บันทึกการสั่งจ่ายยาโดยสัตวแพทย์ หรือใบเสร็จการซื้อยาปฏิชีวนะ ระยะเวลาในการสำรวจข้อมูลการใช้ยาปฏิชีวนะจะครอบคลุมหนึ่งรุ่นย้อนหลังของการเลี้ยงสุกรในแต่ละช่วงอายุ ได้แก่ ประมาณ 1 เดือนในสุกรแม่พันธุ์ ประมาณ 2 เดือนในสุกรดูดนมและสุกรอนุบาล และประมาณ 3 เดือนในสุกรขุน

ผู้ทำการสัมภาษณ์ขออนุญาตบันทึกเนื้อหาการสัมภาษณ์ ในเครื่องบันทึกเทป โดยจะเก็บข้อมูลเสียงให้คอมพิวเตอร์ที่มีการป้องกันการเข้าถึงจากบุคคลอื่นที่ไม่ใช่คณะผู้วิจัย (กรณี ผู้ให้ข้อมูลไม่ยินดีที่จะให้บันทึกเสียง สามารถแจ้งผู้เก็บข้อมูล)

ระยะเวลาในการให้ข้อมูล

- แบบสอบถาม ประมาณ 30 นาที
- สัมภาษณ์เชิงลึก ประมาณ 1-1.30 ชั่วโมง
- การสังเกต ประมาณ 1-3 วัน

สถานที่ในการให้ข้อมูล กทม. และจังหวัดราชบุรี

ความเสี่ยงที่อาจเกิดขึ้นในการให้ข้อมูล

งานวิจัยนี้ไม่ได้มีขั้นตอนการเก็บตัวอย่างจากท่าน หรือฟาร์มของท่าน นักวิจัยคาดว่างานวิจัยนี้จะก่อให้เกิดความเสี่ยงน้อยต่อผู้ให้ข้อมูล หากมีประเด็นในการอภิปราย หรือคำถามที่อาจก่อให้เกิดความไม่สบายใจต่อผู้ให้ข้อมูล ท่านสามารถไม่ตอบคำถามนั้นได้

ประโยชน์ที่อาจเกิดขึ้นในการให้ข้อมูล

ท่านอาจจะไม่ได้รับประโยชน์โดยตรงจากการให้ข้อมูลในการศึกษาวิจัยนี้ อย่างไรก็ตาม การศึกษานี้เป็นการสร้างองค์ความรู้ในการเลี้ยงและการจัดการสุขภาพสุกร ความรู้ที่เกิดขึ้นจากการศึกษาวิจัยนี้ จะสร้างประโยชน์ต่อสังคมส่วนรวม ให้มีความรู้ความเข้าใจ เพื่อนำไปสู่การพัฒนาการเลี้ยงสุกรในองค์รวม

การปกป้องและเผยแพร่ข้อมูล

ข้อมูลที่ได้จากการสัมภาษณ์จะถูกเก็บไว้เป็นความลับ และไม่มีการเผยแพร่เป็นรายบุคคล ไม่มีการระบุชื่อของท่านในการอ้างถึงเนื้อความในการสัมภาษณ์ ข้อมูลเอกสารจะเก็บไว้ในตู้ที่สำนักงานพัฒนานโยบายสุขภาพระหว่างประเทศที่มีการจำกัดการเข้าถึง ซึ่งมีเพียงนักวิจัยหลักที่มีกุญแจเท่านั้น ข้อมูลเสียงและข้อมูลสนทนาทั้งหมดจะถูกเก็บไว้ในคอมพิวเตอร์ของนักวิจัยหลักที่มีการจำกัดการเข้าถึงด้วยรหัสผ่าน ไฟล์ทั้งหมดจะมีการสำรองข้อมูลที่ระบบฐานข้อมูลของ London School of Hygiene & Tropical Medicine และอุปกรณ์ในการสำรองข้อมูลที่จำกัดการเข้าถึงด้วยรหัสผ่าน

ข้อมูลที่ได้จากการศึกษานี้อาจมีการเผยแพร่ในการตีพิมพ์และการเสนอผลงานทางวิชาการ อย่างไรก็ตาม จะไม่มีการอ้างอิงถึงชื่อหรือข้อมูลที่อ้างอิงถึงตัวบุคคลของผู้ให้ข้อมูล ชื่อและข้อมูลอื่นๆของผู้ให้ข้อมูลรวมทั้งฟาร์มจะถูกลอบออกเพื่อเก็บรักษาข้อมูลเป็นความลับ

หากต้องมีการอ้างอิงคำพูดของผู้ให้ข้อมูล ในการตีพิมพ์ข้อมูลทางวิชาการ ผู้วิจัยยืนยันว่า จะไม่มีการระบุตัวตนของผู้ให้ข้อมูล หรือข้อมูลที่สามารถสืบค้นย้อนหลังได้ อย่างไรก็ตาม หากท่านไม่สะดวกที่จะให้อ้างอิงคำพูด ท่านสามารถแจ้งสิทธิ์ได้ในเอกสารส่วนท้าย

สิทธิ์ในการให้ข้อมูล

การให้ข้อมูลนี้เป็นแบบสมัครใจ หากท่านไม่ต้องการให้ข้อมูล ท่านสามารถเสนอความจำนงได้ตลอดเวลา ทั้งก่อน ระหว่าง และหลังการให้ข้อมูล ท่านสามารถหยุดพักระหว่างการให้ข้อมูล หรือยกเลิกการให้ข้อมูล โดยไม่มีเงื่อนไขใดๆ ทั้งสิ้น หากท่านต้องการยุติการให้ข้อมูล นักวิจัยจะสอบถามความยินยอมในการนำข้อมูลไปใช้

บุคคลที่ติดต่อได้ หากมีคำถามเกี่ยวกับการให้ข้อมูล

ท่านมีสิทธิ์ในการถามคำถามเกี่ยวกับการให้ข้อมูล ทั้งก่อน ระหว่าง และหลังการให้ข้อมูล โดยหากมีคำถามเพิ่มเติม สามารถติดต่อผู้วิจัยได้ที่

สพ.ญ. อังคณา สมนัสทวีชัย

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สำนักงานพัฒนานโยบายสุขภาพระหว่างประเทศ กระทรวงสาธารณสุข

ความยินยอมในการให้ข้อมูล

สอบถามผู้ให้ข้อมูลว่า “ยินดี” หรือ “ไม่ยินดี” ในการให้ข้อมูล ตามส่วนท้ายของเอกสาร

ข้าพเจ้ายินดีในการให้ข้อมูล

- ☐ แบบสอบถาม
- ☐ สัมภาษณ์เชิงลึก (หากยินดี ท่านสามารถให้มีการระบุคำพูดในเอกสารวิชาการต่อไปหรือไม่ ทั้งนี้ ข้อมูลดังกล่าวจะไม่มีการอ้างอิงถึงผู้ให้ข้อมูล)
  - ☐ ยินดี
  - ☐ ไม่ยินดี
- ☐ การสังเกต
- ☐ ข้อมูลการใช้ยาปฏิชีวนะ

☐ ข้าพเจ้าไม่ยินดีในการให้ข้อมูล

ผู้ให้ข้อมูล

ข้าพเจ้าได้อ่านข้อมูลในเอกสารฉบับนี้ (หรือมีผู้อ่านให้ข้าพเจ้าฟัง) และได้มีโอกาสในการถามคำถามรวมถึงได้รับคำตอบที่ข้าพเจ้าพอใจ ข้าพเจ้ายินยอมเข้าร่วมโครงการวิจัยนี้

ลงชื่อผู้ให้ข้อมูล	วันที่	เวลา	ผู้ให้ข้อมูล(ตัวบรรจง)

ผู้สัมภาษณ์

ข้าพเจ้าได้อ่านข้อมูลในเอกสารฉบับนี้อย่างครบถ้วน และเต็มความสามารถแก่ผู้ให้ข้อมูล ข้าพเจ้ายืนยันว่าผู้ให้ข้อมูลมีโอกาสในการสอบถาม และข้าพเจ้าได้ตอบคำถามแก่ผู้ให้ข้อมูลจนพอใจ ข้าพเจ้ายืนยันว่าผู้ให้ข้อมูลได้ใช้สิทธิ์ในการให้ข้อมูลโดยสมัครใจ

ลงชื่อผู้สัมภาษณ์	วันที่	เวลา	ผู้ให้ข้อมูล(ตัวบรรจง)

Appendix 6 Associated publications and conferences presentations

A 6.1 Lists of associated publications

1. **Lekagul A,** Tangcharoensathien V, Mills A, Rushton J and Yeung S. How antibiotics are used in pig farming: a mixed- methods study of pig farmers, feed mills and veterinarians in Thailand. BMJ Global Health 2020;0:e001918. doi:10.1136/ bmjgh-2019-001918
2. **Lekagul, A**, Yeung S, and Tangcharoensathien V. Patterns of antibiotic use in global pig production: A systematic review. Veterinary and Animal Science 2019;7:100058
3. **Lekagul, A**, Yeung S, and Tangcharoensathien V. The use of antimicrobials in global pig production: a systematic review of methods for quantification. Preventive Veterinary Medicine 2018;160:85-98.
4. **Sommanustweechai A,** Chanvatik S, Sermsinsiri V, Sivilaikul S, Patcharanarumol W, Yeung S, and Tangcharoensathien V. Antibiotic distribution channels in Thailand: results of key-informant interviews, reviews of drug regulations and database searches. Bulletin of the World Health Organization 2018;96:101-9.

Not included in the PhD thesis

1. Schar D, **Sommanustweechai A,** Laxminarayan R, and Tangcharoensathien V. Surveillance of antimicrobial consumption in animal production sectors of low- and middleincome countries: Optimizing use and addressing antimicrobial resistance. PLOS Medicine 2018;15:e1002521.
2. Tangcharoensathien V, Chanvatik S, and **Sommanustweechai A.** Complex determinants of inappropriate use of antibiotics. Bulletin of the World Health Organization 2018;96:141-4.

Note: My maiden name is Angkana Sommanustweechai

A 6.2 Lists of presentations

2017

- Poster presentation: "How are antibiotics used and controlled in pig farms in Thailand?" (Draft of proposal), 2017 London School of Hygiene and Tropical Medicine RD Poster Day, UK (*Received the award of the ITD best poster presentation*)

2018

- Oral presentation: Antibiotic distribution in Thailand: factors contributing to excessive and inappropriate use, Prince Mahidol Award Conference 2018, Thailand

2019

- Oral presentation: Towards understanding the use of antibiotics in pig production in Thailand, Bristol AMR meeting, UK
- Poster presentation: "How antibiotics are used in Thai pig production" (Preliminary results) 2019 London School of Hygiene and Tropical Medicine RD Poster Day, UK
- Poster presentation: The use of "Critically Important Antimicrobials" in Thai pig production: survey of 84 pig farms and 31 feed mills, American Society Tropical Medicine and Hygiene Annual Meeting, USA

2020

- Poster presentation: "How and why are antibiotics used in Thai pig production" 2020 London School of Hygiene and Tropical Medicine RD Poster Day, UK

A 6.3 LSHTM poster 2017: How are antibiotics used and controlled in pig farms in Thailand

How antibiotics are used in pig production in Thailand

Angkana Lekagul[1,2], Shunmay Yeung[1], Anne Mills[1], Viroj Tangcharoensathien[2]

LONDON SCHOOL of HYGIENE &TROPICAL MEDICINE

[1] London School of Hygiene & Tropical Medicine, UK [2] International Health Policy Program, Ministry of Public Health, Thailand

Introduction

- In agriculture, antibiotics are used to treat infections but are also used to increase livestock production through the control and prevention of disease maintaining food availability.
- However, the increase of antimicrobial resistance has given rise to concerns with regards the overuse of antibiotic in animals (1,2,3).
- Humans and animals often share the same pathogens and the same classes of antibiotics. Many common antibiotics used in animals are categorised as critically important antimicrobials for human medicine according to the WHO priority list (4).
- While data from High-income countries are available, there are few published studies investigating the use of antibiotics in pigs in Low and Middle-income countries (5).

Objectives

To describe the pattern of antibiotic use and estimate the total amount of antibiotics used in pig production in Thailand.

Methods

- **Questionnaire survey of pig farmers (84 farmers)**: to investigate antibiotic consumption profiles at farm-level (July-September 2018)
- **Survey of feed mills (23 feed mills)**: to gather data on volume of medicated feed at country level. Data were collected by International Health Policy Program, MoPH. The volume of antibiotics mixed in feed in 2017 was measured by kg of active ingredient (volume of antibiotics x strength) by ATCvet Code.
- **Statistical analysis**:
  - Descriptive analysis
  - Univariate analysis: to assess the association between the dependent variable (the use of antibiotics in pig farms) and each independent variable

Findings

Oral and parenteral antibiotics

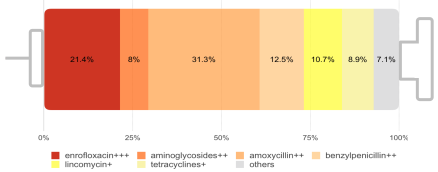


Fig. 1 Type of oral and parenteral antibiotics for prevention from farm survey (N=84)

Medicated feed

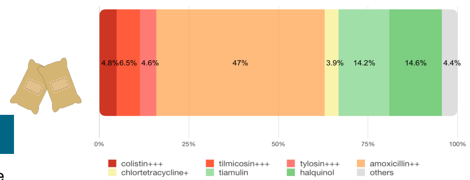
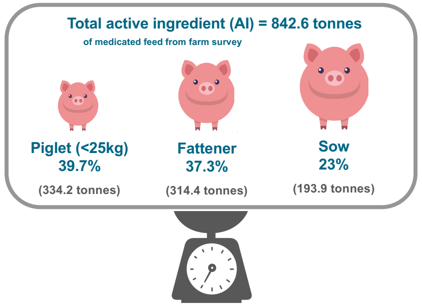


Fig. 2 Type of antibiotics in medicated feed from feed mill survey (N=23)

+++ Highest Priority Critically important antimicrobials for human medicine, WHO's list
++ High Priority Critically important antimicrobials for human medicine, WHO's list
+ Highly Important Antimicrobials, WHO's list



Farmers characteristics that appear to be risk factors for use of antibiotics for prevention in the past 12 months (N=84) [a]

Education		
Primary school	Secondary school	Bachelor's degree
46% (17/37)	68% (17/25)	59% (13/22)

Experience *	
≤10 years	>10 years
43.2% (16/37)	66% (31/47)

*OR = 2.54: 95%CI= 1.1-6.2, P-value=0.04

Knowledge [b]	
Score <60%	Score ≥60%
48.3% (14/29)	61.5% (32/52)

Household income/ month					
≤BHT 10,000	BHT 10,000-50,000	BHT 50,001-100,000	BHT 100,001-500,000	>BHT 500,000	Others
42.9% (12/28)	47.4% (9/19)	50% (3/6)	87.5% (7/8)	88.9% (8/9)	57.1% (8/14)

Size of farm [c]	
Smallholder	Commercial
42.3% (11/26)	62.1% (36/58)

Type of farm	
FtoF	Fattener
66.7% (36/54)	36.7% (11/30)

GAP certified farm [d]	
YES	NO
67.7% (21/31)	49.1% (26/53)

Member of cooperative farm *	
YES	NO
82.4% (14/17)	49.3% (33/67)

*OR = 4.81: 95%CI= 1.2-19.4, P-value=0.01

Contracted farm	
YES	NO
62.5% (5/8)	55.3% (42/76)

Advice on animal health *	
Receiving advice	Not receiving advice
61.8% (42/68)	31.3% (5/16)

*OR = 3.55: 95%CI= 1.1-11.4, P-value=0.03

Advice on feed administration	
Receiving advice	Not receiving advice
58.3% (21/36)	54.2% (26/48)

*Statistically significant

a: Number of farms where information is available; b: Knowledge: five true/false questions in relation to the use of antibiotics and AMR, followed the 2017 National Health Welfare survey; c: According to the catagorisation by the government, there are ≥50 pigs per farm and smallholder farms as those with <50 pigs per farm; d: Government certified GAP for farms with good standard of animal husbandry

Conclusion

- A majority of oral and parenteral antibiotics used at farm level, and antibiotics added to medicated feed belong to the category of Critically Important Antimicrobials for human medicine (WHO's list).
- Farmer with >10 years experience, cooperative farms and farms having received animal health advice were significantly associated with higher use of antibiotics.
- Information about medicated feed could not be captured at farm due to 1) no recording system at farm, 2) recall bias, 3) no antibiotic data in feed products, and 4) farmers were not willing to provide information.
- The small sample size of farmers limited the ability to identify the potential risk factors of the use of antibiotics.

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3. McCrackin MA, et al. Crit Rev Food Sci Nutr. 2016 Oct 2;56(13):2115-32. doi: 10.1080/10408398.2015.1119798.
4. World Health Organization. Critically important antimicrobials for human medicine – 5th revision2016. Available from: http://apps.who.int/iris/bitstream/10665/255027/1/9789241512220-eng.pdf
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A 6.4 ASHTM poster 2019: The use of Critically Important Antimicrobials in Thai pig production: survey of 84 pig farms and 31 feed mills

The use of "Critically Important Antimicrobials" in Thai pig production: survey of 84 pig farms and 31 feed mills

Angkana Lekagul [a, b], Viroj Tangcharoensathien [b], Anne Mills [a], Jonathan Rushton [c], Shunmay Yeung [a]

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Introduction

- Antimicrobial resistance is recognised as a growing threat to global health security and is driven by the use of antimicrobials in both humans and animals (1,2,3).
- Of particular concern is the use in animals of Critically Important Antimicrobials (CIA) (4), in particular the Highest Priority CIA such as colistin, which are reserved as a last resort for the most severe and resistant human infections.
- In agriculture, antibiotics are used to treat infections, to control and prevent disease, and to promote livestock's growth.
- There are few published studies investigating the use of antibiotics in pigs in low- and middle-income countries (5).

Objective

To describe the pattern and estimate the volume of CIA use in pig production in Thailand.

Methods

- Cross-sectional questionnaire based survey of 84 pig farmers to determine the patterns of antibiotic use at farm-level (March-December 2018)
- Secondary analysis of data from a national survey of feed mills (31 feed mills), having an estimated 80% of total market share to estimate the total amount of antibiotics mixed in pig feed in 2017
- Statistical analysis:
  - Descriptive analysis
  - Univariate analysis: to assess the association between the use of CIA and independent variables of pig farmer characteristics.

Results

Survey of pig farmers

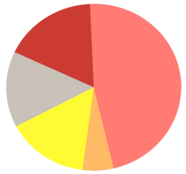
31% (26/84) of farmers reported the use of antibiotics in the CIA lists

46% (37/80) of antibiotics reported belong to CIA list

Highest priority CIA*		High priority CIA*		Highly Important antimicrobials		Important antimicrobials	
Ceftiofur (a 3rd generation cephalosporin)	7.7%	Amoxicillin	73.1%	Chloramphenicol	3.8%	Tiamulin	11.5%
Enrofloxacin (a quinolone)	42.3%	Gentamicin	3.8%	Lincomycin (a lincosamide)	19.2%		
		Kanamycin	11.5%	Penicillins, combinations	23.1%		
		Streptomycin	3.8%	Tetracycline	23.1%		

Fig. 1 Percentage of farms reporting the use of any CIA (one farm can report more than one type of antibiotic.)

Survey of feed mills



Highest priority CIA **17.3%** (145 tonnes)

Highest priority CIA	
Colistin (a phosphonic acid derivatives)	4.8%
Fosfomycim	0.1%
Kitasamycin (a macrolide)	1.1%
Tilmicosin (a macrolide)	6.5%
Tylosin (a macrolide)	4.6%
Tylvalosin (a macrolide)	0.2%

High priority CIA **47%** (395.9 tonnes)

High priority CIA	
Amoxicillin	47%
Apramycin (an aminoglycoside)	0.1%

Highly Critically Important antimicrobials **5.7%** (483.2 tonnes)

Highly Critically Important antimicrobials	
Chlortetracycline	3.9%
Doxycycline	0.3%
Lincomycin	0.9%
Oxytetracycline	0.6%
Sulfadimidine	0.1%

Important antimicrobials **15.3%** (128.5 tonnes)

Important antimicrobials	
Bacitracin	1.1%
Tiamulin (a pleuromutilin)	14.2%

Antimicrobials currently not used in humans **14.7%** (123.7 tonnes)

Antimicrobials currently not used in humans	
Avilamycin (an orthosomycin)	0.1%
Bambermycin (a phosphoglycolipid)	0.1%
Halquinol (a chlorhydroxyquinoline compound)	14.6%

Fig. 2 Estimated amount of CIA added to medicated feed in tonnes, 2017

Characteristics	Categories (No. of farms with data available)	Use of CIA (%)	OR (95%CI)	P-value
Farmer's highest level of education	Primary school (37)	8 (21.6)	1	
	Secondary school and higher (47)	24 (51.1)	3.78 (1.43-9.97)	0.01*
Farmer's experience	≤10 years (37)	8 (21.6)	1	
	>10 years (47)	24 (51.1)	3.78 (1.43-9.97)	0.01*
Farmer's knowledge [a]	Score <60% (29)	12 (41.4)	1	
	Score ≥60% (52)	19 (36.5)	0.82 (0.32-2.07)	0.67
Size of farm	Smallholder farm (26)	3 (11.5)	1	
	Commercial farm (58)	26 (50.0)	7.67 (2.07-28.37)	0.01*
Type of farm	Farrowing to finisher farm (54)	25 (46.3)	1	
	Fattening (30)	7 (23.3)	0.35 (0.13-0.96)	0.04
Good Agriculture Practice certified farm	No (53)	14 (26.4)	1	
	Yes (31)	18 (58.1)	3.86 (1.51-9.87)	0.01*
Member of cooperative	No (67)	20 (29.9)	1	
	Yes (17)	12 (70.6)	5.64 (1.75-18.12)	0.01*
Contracted farm	No (76)	30 (39.5)	1	
	Yes (8)	2 (25.0)	0.51 (0.10-2.70)	0.43
Household income/ month	Less than BHT 50,000 (47)	11 (23.4)	1	
	More than BHT 50,000 (23)	15 (65.2)	6.1 (2.06- 18.23)	0.02*
Advice on animal health	Not receiving advice (16)	2 (12.5)	1	
	Receiving advice (68)	42 (44.1)	5.53 (1.16-26.22)	0.03

Table 1 Factors associated with the use of CIA for disease prevention in the past 12 months from the survey of pig farmers

Note: *Statistically significant at p <0.05, a: Knowledge: five true/false statements in relation to the use of antibiotics and AMR, taken from the AMR module in the 2017 National Health Welfare survey

Conclusion and recommendations

- Consumption of CIA in pig production in Thailand is high, both as oral and injectable medications and medicated feed
- The use of CIA was significantly and positively associated with farmers' educational level, experience in raising pigs, farm income, farm size, receiving advice on animal health, good agricultural practice farms certification, and being members of a farm cooperative membership
- No correlation was found between the use of CIA and farmers' knowledge about antibiotics and AMR
- Progressive restriction of the use of CIA is recommended guided by the research findings through legislation and alternative animal health management.

Fig. 3 a) smallholder farm, b) commercial farm (sow barn), c) commercial farm (fattener barn) in the study and d) antibiotics storage in one of the study farms

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5. Cuong, N. V. Antibiotics. 2018. https://doi.org/10.3390/antibiotics7030075

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A 6.5 LSHTM poster 2019: How are antibiotics used in Thai pig production

How are antibiotics used and controlled in pig farms in Thailand?

Angkana Sommnustweechai[1,2], Shunmay Yeung[1], Anne Mills[1]

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[2] International Health Policy Program, Ministry of Public Health, Thailand

Introduction

Antimicrobial Resistance (AMR)

- Antimicrobial resistance (AMR) has recently been recognized as a major threat to global health, causing serious implications for health and the economy (1).
- Antimicrobial resistance is a natural phenomenon, but the use of antibiotics in humans and animals is considered to be a major driving force in the emergence of AMR.

Fig. 1 Concerns over illegal antibiotics and 'colistin' widely used, and MCR-1 resistant gene found in pig farms
Source: Kom Chad Leuk Newspaper, 23 Jan 2017

Fig. 2 Pig farm in Thailand

Fig. 3 Pigs been injected with antibiotics

Antibiotic use in livestock

- Antibiotic use is frequently a feature of **intensive farming**.
- The purpose of the use of antibiotics in livestock includes: **treatment, control and prevention of infection; growth promotion**(2); and increased productivity.
- Of 26 EU countries, the overall consumption of antimicrobials was **higher in animals than in human** (3).
- Many classes of antibiotics that are used for humans are also being used in food animals.
- There is increasing debate about the **trade-off** between the benefits of the use of antibiotics, particularly in terms of non-therapeutic use of antibiotics vs. the AMR threat to humans.
- **Global concern**: MCR-1 gene (resistant bacteria to colistin- a last resort antibiotic for treating MDR infections in humans) found in patients in Scotland and US (4), and in pig farms in China (5) and Thailand (6).

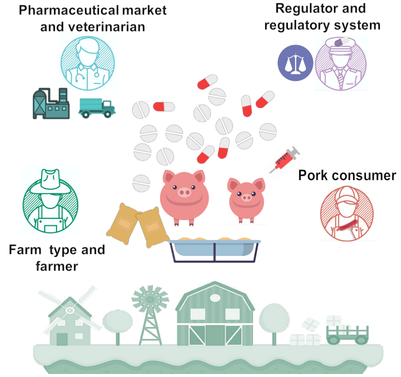

Fig. 4 Possible factors contributing the use of antibiotics in pigs

Factors contributing the use of antibiotics in pigs

It is known that there is a wide range of factors that influences antibiotic use by farmers:

- **Farm type and farmer**: Type of farm, farmers' knowledge and personal attitudes (7-9).
- **Pharmaceutical market and veterinarian** : Antibiotics are public goods; and also it could be said that there is market failure in terms of "supplier induced demand" for antibiotics in LMICs. Antibiotics prescribed based on the requests from farmers (10), and individual veterinarian's preference for antibiotics and their experiences, rather than scientific data or laboratory findings (11,12).
- **Food consumer**: Increasing consumer demand for products from livestock raised without antibiotics may affect the practices of retailers, e.g. fast-food companies (13).
- **Regulation:** Regulatory provisions related to medicine in LMICs focus on quality, less on market control (14,15). In terms of its effectiveness, it requires the commitment of government, adequate resources and cooperation.

Thailand

- Population: 68 million (2017
- GNI per capita (current US$): 5,720*
- Pig farmer: ~190,000 households (2016)
- Pig production: ~9.9 million animals/year (2016)

*Data from World Development Indicators (2015)

To date, there has been little evidence about the use of antibiotics in pig farms in Thailand. No research has been conducted specifically aiming to understand the factors influencing the use and control of antibiotics in pigs.

Objectives

1. To describe the pattern of antibiotic consumption in pig farms
2. To identify factors contributing to the use of antibiotics in pig farms
3. To explore the regulatory system and analyze its effectiveness in controlling the distribution and use of antibiotics in livestock
4. To identify relevant policy interventions to enhance rational use of antibiotics in livestock

Methods

- Questionnaire survey: to investigate antibiotic consumption profiles in pig farms
- In-depth interviews: to identify factors influencing the use of antibiotics by pig farmers
- Semi-structured interviews: to describe the role of pharmaceutical industries, veterinarians, consumers and regulators and attitudes to use of antibiotics in pig farming
- Document review: to review the regulations regarding to antibiotic control
- Questionnaire survey (adapted from WHO tool): to analyze the effectiveness of regulation

Impact

The excessive use of antibiotics in livestock is considered a major driver of the emergence of AMR. A better understanding of key factors contributing to the use of antibiotics in pigs will support the introduction of policies for optimal use of antibiotics and other alternatives which lead to the reduction in selective pressure on antibiotics and the emergence of AMR.

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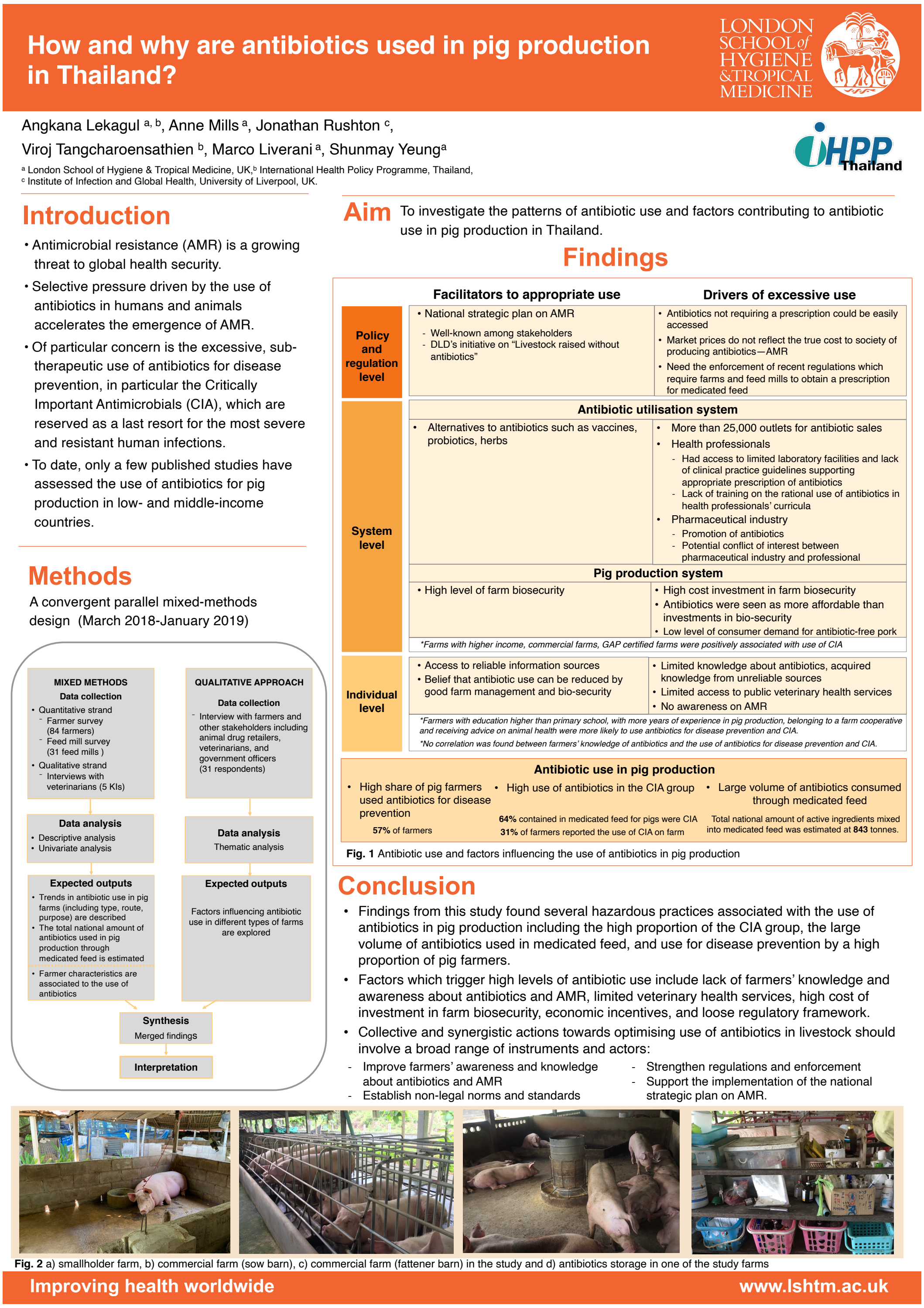
A 6.6 LSHTM poster 2020: How and why are antibiotics used in pig production in Thailand?



How and why are antibiotics used in pig production in Thailand?

LONDON SCHOOL of HYGIENE &TROPICAL MEDICINE

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IHPP Thailand

Introduction

- Antimicrobial resistance (AMR) is a growing threat to global health security.
- Selective pressure driven by the use of antibiotics in humans and animals accelerates the emergence of AMR.
- Of particular concern is the excessive, sub-therapeutic use of antibiotics for disease prevention, in particular the Critically Important Antimicrobials (CIA), which are reserved as a last resort for the most severe and resistant human infections.
- To date, only a few published studies have assessed the use of antibiotics for pig production in low- and middle-income countries.

Methods

A convergent parallel mixed-methods design (March 2018-January 2019)

MIXED METHODS

Data collection
- Quantitative strand
  - Farmer survey (84 farmers)
  - Feed mill survey (31 feed mills)
- Qualitative strand
  - Interviews with veterinarians (5 KIs)

Data analysis
- Descriptive analysis
- Univariate analysis

Expected outputs
- Trends in antibiotic use in pig farms (including type, route, purpose) are described
- The total national amount of antibiotics used in pig production through medicated feed is estimated
- Farmer characteristics are associated to the use of antibiotics

QUALITATIVE APPROACH

Data collection
- Interview with farmers and other stakeholders including animal drug retailers, veterinarians, and government officers (31 respondents)

Data analysis
Thematic analysis

Expected outputs
Factors influencing antibiotic use in different types of farms are explored

Synthesis
Merged findings

Interpretation

Aim

To investigate the patterns of antibiotic use and factors contributing to antibiotic use in pig production in Thailand.

Findings

	Facilitators to appropriate use	Drivers of excessive use
Policy and regulation level	• National strategic plan on AMR - Well-known among stakeholders - DLD's initiative on "Livestock raised without antibiotics"	• Antibiotics not requiring a prescription could be easily accessed • Market prices do not reflect the true cost to society of producing antibiotics—AMR • Need the enforcement of recent regulations which require farms and feed mills to obtain a prescription for medicated feed
System level	**Antibiotic utilisation system**	
	• Alternatives to antibiotics such as vaccines, probiotics, herbs	• More than 25,000 outlets for antibiotic sales • Health professionals - Had access to limited laboratory facilities and lack of clinical practice guidelines supporting appropriate prescription of antibiotics - Lack of training on the rational use of antibiotics in health professionals' curricula • Pharmaceutical industry - Promotion of antibiotics - Potential conflict of interest between pharmaceutical industry and professional
	Pig production system	
	• High level of farm biosecurity	• High cost investment in farm biosecurity • Antibiotics were seen as more affordable than investments in bio-security • Low level of consumer demand for antibiotic-free pork
	**Farms with higher income, commercial farms, GAP certified farms were positively associated with use of CIA*	
Individual level	• Access to reliable information sources • Belief that antibiotic use can be reduced by good farm management and bio-security	• Limited knowledge about antibiotics, acquired knowledge from unreliable sources • Limited access to public veterinary health services • No awareness on AMR
	**Farmers with education higher than primary school, with more years of experience in pig production, belonging to a farm cooperative and receiving advice on animal health were more likely to use antibiotics for disease prevention and CIA.* **No correlation was found between farmers' knowledge of antibiotics and the use of antibiotics for disease prevention and CIA.*	

Antibiotic use in pig production

- High share of pig farmers used antibiotics for disease prevention
  57% of farmers
- High use of antibiotics in the CIA group
  64% contained in medicated feed for pigs were CIA
  31% of farmers reported the use of CIA on farm
- Large volume of antibiotics consumed through medicated feed
  Total national amount of active ingredients mixed into medicated feed was estimated at **843** tonnes.

Fig. 1 Antibiotic use and factors influencing the use of antibiotics in pig production

Conclusion

- Findings from this study found several hazardous practices associated with the use of antibiotics in pig production including the high proportion of the CIA group, the large volume of antibiotics used in medicated feed, and use for disease prevention by a high proportion of pig farmers.
- Factors which trigger high levels of antibiotic use include lack of farmers' knowledge and awareness about antibiotics and AMR, limited veterinary health services, high cost of investment in farm biosecurity, economic incentives, and loose regulatory framework.
- Collective and synergistic actions towards optimising use of antibiotics in livestock should involve a broad range of instruments and actors:
  - Improve farmers' awareness and knowledge about antibiotics and AMR
  - Establish non-legal norms and standards
  - Strengthen regulations and enforcement
  - Support the implementation of the national strategic plan on AMR.

Fig. 2 a) smallholder farm, b) commercial farm (sow barn), c) commercial farm (fattener barn) in the study and d) antibiotics storage in one of the study farms

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Appendix 7 Additional results from the farmer survey

A 7.1 Pig farmers' knowledge about antibiotics and AMR

Table A7.1 Pig farmers' knowledge about antibiotics and AMR (n=81)

Question	Respondent who answered "know"
Do you know "antibiotic"?	48 (59.3)
Do you know whether antibiotic use in food producing animals can induce AMR in those animals"?	46 (56.8)
Resistance to antibiotics is widespread in Thai pig farming	40 (49.4)
Do you know whether Thailand ban using antibiotic as a growth promoter in food producing animals?	48 (59.3)
	Respondent who gave correct answer
Antibiotics kill the viruses (F)	23 (28.4)
Antibiotics are effective against cold and flu (F)	17 (21)
Antibiotic is anti-inflammation drug (F)	34 (42)
Taking antibiotics too often has side-effects such as diarrhea (T)	17 (21)
Unnecessary or unreasonable use of antibiotics have negative impacts such as ineffective treatment, AMR (T)	52 (64.2)

Appendix 8 Medically Important Antimicrobials

CRITICALLY IMPORTANT ANTIMICROBIALS HIGHEST PRIORITY	
HIGHEST PRIORITY	HIGH PRIORITY
• Cephalosporins (3rd and higher generation) • Glycopeptides • Macrolides and ketolides • Polymyxins • Quinolones	• Aminoglycosides • Ansamycins • Carbapenems and other penems • Glycylcyclines • Lipopeptides • Monobactams • Oxazolidinones • Penicillins (antipseudomonal, aminopenicillins, aminopenicillins with ß-lactamase inhibitors) • Phosphonic acid derivatives • Drugs used solely to treat tuberculosis/ mycobacterial diseases
HIGHLY IMPORTANT ANTIMICROBIALS	
• Amphenicols • Cephalosporins (1st and 2nd generation) and cephamycins • Lincosamides • Penicillins (amidinopenicillins, anti-staphylococcal, narrow spectrum) • Pseudomonic acids • Riminofenazines • Steroid antibacterials • Streptogramins • Sulfonamides, dihydrofolate reductase inhibitors and combinations • Sulfones • Tetracyclines	
IMPORTANT ANTIMICROBIALS	
• Aminocyclitols • Cyclic polypeptides • Nitrofuran derivatives • Nitroimidazoles • Pleuromutilins	

Sources: World Health Organization (66)

Appendix 9 Thailand's National Strategic Plan on Antimicrobial Resistance 2017-2021

Vision: Reduction of mortality, morbidity and economic impacts from AMR

Mission: Establish policies and national multi-sectoral mechanisms which support an effective and sustained AMR management system

Goals: By the year 2021

1. 50% reduction in AMR morbidity
2. 20% reduction in antimicrobial consumption in humans
3. 30% reduction in antimicrobial consumption in animals
4. 20% increase of public knowledge on AMR and awareness of appropriate use of antimicrobials
5. Capacity of the national AMR management system is improved to level 4

	Strategy 1 AMR surveillance system using One Health approach	**Strategy 2** Regulation of antimicrobial distribution	**Strategy 3** Infection prevention and control and antimicrobial stewardship in humans	**Strategy 4** AMR prevention and control and antimicrobial stewardship in agriculture and animals	**Strategy 5** Public knowledge on AMR and awareness of appropriate use of antimicrobials
Strategic objective	The AMR surveillance system is capable of indicating problems as well as monitoring and reporting the AMR epidemiological situation in both humans and animals in order to provide timely alerts on AMR spread.	The systems of controlling and tracing distribution of human and veterinary antimicrobial medicines are integrated.	Healthcare facilities are equipped with efficient systems to prevent and control infection aiming at reducing infection rate and expenses caused by AMR pathogens, and to implement antimicrobial stewardship.	Integrated and harmonized systems of AMR management and reduction of antimicrobial use in agricultural and animal sectors are applied to both public and private sectors.	The public are knowledgeable of AMR and aware of appropriate antimicrobial use, including AMR environmental problems.
Strategic action	1.1 Develop the national integrated system of AMR surveillance and signaling 1.2 Strengthen capacity and networking of microbiology laboratories 1.3 Improve epidemiological capacity and networking on AMR	2.1 Strengthen the antimicrobial distribution control system for both humans and animals, 2.2 Enhance efficient law enforcement in conjunction with use of social measures to mitigate the problem of inappropriate distribution of antimicrobials	3.1 Address AMR problems in both public and private healthcare facilities in a systematic and integrated manner 3.2 Strengthen competency of infection control personnel 3.3 Implement, monitor and evaluate antimicrobial stewardship in healthcare facilities 3.4 Implement antimicrobial stewardship in private clinics 3.5 Implement antimicrobial stewardship in pharmacies	4.1 Reduce use of antimicrobials in livestock farming and fisheries 4.2 Reduce antimicrobial resistant bacteria in the food production chain 4.3 Establish surveillance of antimicrobial use in crop production 4.4 Implement antimicrobial stewardship in animal hospitals and clinics 4.5 Educate relevant stakeholders in food animals and agriculture regarding appropriate use of antimicrobials	5.1 Support roles of civil society and mass media agencies to increase public understanding of AMR and appropriate use of antimicrobials 5.2 Improve health literacy on AMR and awareness of appropriate use of antimicrobials for the public especially in children, adolescent and working age groups 5.3 Empower and reinforce participatory engagement of communities and lay people networks

Strategy 6 Governance mechanisms to move AMR policy and actions forward in a sustainable manner

Strategic objective AMR implementation mechanisms at national level are able to sustain AMR-related actions

Strategic action
6.1 Establish national level structure and mechanism to move the strategic plan and AMR operations forward
6.2 Administer, monitor and evaluate the implementation of the strategic plan
6.3 Support research and development to guide efficient AMR operations
6.4 Sustain Thailand's proactive and collaborative role in AMR at international level

Source: Ministry of Public Health and Ministry of Agriculture and Cooperatives, National Strategic Plan on Antimicrobial Resistance 2017-2021 Thailand. Nonthaburi; 2016