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Antimicrobial drug resistance at the human-animal interface in Vietnam

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CHAPTER 1
INTRODUCTION

Chapter 1: Introduction

The world is facing a major threat from the development of antimicrobial-resistant Gram-negative bacteria, including Enterobacteriaceae, that have become resistant to most available antibiotics [1]. In addition, development of novel and effective antimicrobials is lagging behind the increase in antimicrobial resistance [2].

It has been shown that antimicrobial use is one of the main drivers of antimicrobial resistance [3]. Therefore, it is crucial to understand the antimicrobial use and the epidemiology of antimicrobial resistance in both humans and animals to combat or delay resistant bacteria spreading in the community.

The aims of this chapter are (a) to describe the situation of antimicrobial usage and antimicrobial resistance in Vietnam, (b) to review current knowledge of transmission of antimicrobial resistant micro-organisms or resistance encoding genes between chickens and humans worldwide, and (c) to provide the outline of this thesis.

Antimicrobial Usage and Antimicrobial Resistance in Vietnam

Antimicrobial usage in Vietnam

According to the pharmaceutical law in Vietnam, antimicrobials are prescription-only drugs. Unfortunately, these regulations are just not enforced. As a result, antimicrobial drugs can be purchased without prescription from pharmacies. No official and detailed figures on antimicrobial usage are available in the country. Despite the continuous increase of the literacy rate in Vietnam, knowledge on antimicrobial usage is still poor. People have the tendency of buying antimicrobials from private pharmacies since it is faster and cheaper than visiting a clinic or hospital. Even if clinics and hospitals are visited, doctors do not always prescribe the correct type or dosage of antimicrobial drugs.

Hospitals in Vietnam commonly lack adequate infection control and diagnostic microbiology capacities. Therefore, broad-spectrum antimicrobials are commonly prescribed by many clinicians. Multiple studies have been performed to investigate the usage of antimicrobials in the

clinical setting in Vietnam. A study in 2008 indicated the widespread and often inappropriate use of antimicrobials in Vietnamese hospitals [4]. In the clinical setting, antimicrobials are frequently administered intravenously and as combination therapy, mostly with two antibiotics [5, 6]. While national antimicrobial therapy guidelines are not available, local guidelines are frequently used. Since infectious diseases are common in the country and infection control is not always efficient, even in a clinical setting, antimicrobials for prophylactic purposes may account for up to 10 % of the indications [5]. Interestingly, in intensive care units, the mean antimicrobial usage was 811 defined daily doses (DDD) in 1000 occupied bed days [7] which is similar to European data [8]. Cephalosporins, especially third-generation cephalosporins, are repeatedly reported as the most common antimicrobial class used in hospitals in Vietnam [4-7, 9].

The main suppliers of antimicrobials in the community in Vietnam are private pharmacies, where most antimicrobials are sold without a prescription. It is possible to rent a pharmacist license and own a pharmacy with no or very limited medical background [10]. As a result, knowledge about antimicrobials and antimicrobial resistance of those responsible for selling antimicrobials is inadequate [11]. These drug sellers, however, are consulted by patients and decide which antimicrobial drugs should be used for people in the community [12]. Therefore, antimicrobials are frequently dispensed inappropriately from these private pharmacies. An intervention study has shown that strengthening education and regulation of prescription effectively improved the knowledge and reported practices of drug sellers [13]. Obviously, continuous training of drug sellers on antimicrobial use and enforcement of regulations of antimicrobial distribution are equally important.

Although antimicrobial usage is common practice in animal farming, data on antimicrobial usage in animals in Vietnam are limited. The main purposes of using antimicrobials in animals are growth promotion, and prophylaxis and treatment of infectious diseases. A study has shown that antimicrobials were intensively used in chicken and pig farming in northern Vietnam [14]. Up to 10 different antimicrobial classes were used, of which colistin, chlortetracycline and oxytetracycline were the most common antimicrobials used in animal husbandry, both for prophylactic and therapeutic purposes [14]. However, quantitative data on antimicrobial usage are not available. Although an effort has been made to create a centralized system for registration and distribution of antimicrobials for animals in the country, it remains difficult to precisely

quantify antimicrobial usage in animals since commercial feeds commonly contain antimicrobial drugs [10]. Not only the quantity but also the quality of antimicrobial drugs for animals is a concern in Vietnam. A study on antimicrobials in Vietnam found that in a considerably small percentage of antimicrobials the concentrations of active ingredients were correctly declared [15]. Strikingly, some mixed antimicrobial products did not even contain any of the labeled ingredients [15]. Clearly, review of the approval procedures and monitoring of the quality of antimicrobials in animal husbandry are urgently needed. In addition, it is notable that a considerable amount of antimicrobials in agriculture is discharged and hence accumulating in the environment [16], where they may accelerate antimicrobial resistance selection in bacteria [17]. In addition, farmers do not always respect the withdrawal period of antimicrobials when used for their food animals [14]. As a consequence, concentrations of antimicrobial residues in food sources may be high [18].

Antimicrobial resistance in Vietnam

Since no active national surveillance programs and systematic data collection on antimicrobial resistance are conducted in the country, data on antimicrobial resistance are fragmented.

In recent years, bacterial antimicrobial resistance levels in Vietnam are on the rise. We observed a substantial increase of antimicrobial resistance in various bacterial pathogens in the clinical setting. Notably, amongst Gram-negative bacteria causing intra-abdominal and urinary tract infections, particularly in *E. coli* and *K. pneumoniae*, high rates of extended-spectrum β-lactamase (ESBL) producers up to 50% were reported between 2009 - 2011 [19, 20]. Among diarrheal pathogens, resistance to at least two antimicrobials of different classes was detected in 78.6% of *Shigella* strains and 89.5% of *E. coli* strains [21]. The rate of multidrug resistance (resistance to at least three antimicrobial agents of different classes) in *Streptococcus pneumoniae* in 2008 - 2009 was 75.5% [22]. In addition, a study in 2004 – 2005 has found that all *Neisseria gonorrhoeae* isolates were resistant to ciprofloxacin [23] whilst multidrug resistance (resistance to erythromycin, tetracycline and chloramphenicol) in *Streptococcus suis* has increased from 2.5% to 12.5% during the period of 1998 - 2008 [24]. Meanwhile, multidrug resistance (resistance to chloramphenicol, ampicillin, and trimethoprim- sulfamethoxazole) in *Salmonella enterica* Typhi has increased from 63.2% in 1993 to 80.4% in 2007 – 2008 [25].

In a community-based study in 2007, more than 65% of fecal commensal *E. coli* was shown to be resistant to tetracycline, co-trimoxazole and ampicillin. Multidrug resistance (resistance to 3 antimicrobials) among those isolates was 60% [26]. In another study performed in 2013 - 2014, the carriage rate of ESBL-producing *E. coli* in healthy individuals in Vietnam was reported to be around 50% [27].

Antimicrobial resistance in food-borne pathogens and in commensal bacteria of food animals is a major threat to public health worldwide and certainly in Vietnam. Multidrug resistant was observed in 41.1% *Salmonella* isolated from raw meats and seafood in 2012 - 2015 [28]. The rate of multidrug resistance in *E. coli* isolates from pork was 75% in 2004 [29]. In another study in 2007, 86.5% of *Enterococcus faecium* isolated from chickens was resistant to enrofloxacin [30].

Transmission of Antimicrobial Resistance between Chickens and Humans

Many studies have examined the link between antimicrobial resistance indifferent bacterial species isolated from chickens and humans, including commensal and pathogenic bacteria. There are multiple routes of transmission of antimicrobial resistant bacteria or genomic antimicrobial resistance determinants from chickens to humans and vice versa. Transmission from chickens to humans can occur via direct contact with chickens or food of chicken origin as well as through indirect routes such as by contaminated foods or through environmental contamination [31].

In 1976, one of the first studies demonstrating potential transmission of antimicrobial resistant bacteria between chicken and humans in the United States was published [32]. The authors showed that 2 weeks after the introduction of tetracycline–medicated feed, intestinal bacteria of the chickens were almost all tetracycline resistant. Interestingly, the farmers on those farms also showed an increase of fecal carriage of tetracycline resistant bacteria within 6 months. One year later, in 1977, a study in the UK showed that antimicrobial resistant *E. coli* from chickens were established and persisted for about 10 days as part of the flora in exposed humans [33]. A similar trend of increasing quinolone-resistant *Campylobacter* was observed in poultry products and humans in the Netherlands during the period between 1982 and 1989 [34]. During this time, the prevalence of quinolone-resistant *Campylobacter* has grown from 0% to 14% in poultry products

and from 0% to 11% in humans. This observation coincided with the increasing usage of fluoroquinolones, especially enrofloxacin, in poultry farming in the Netherlands.

Chicken products were also demonstrated as a source of fluoroquinolone-resistant *E. coli* that colonized and caused bacteremia in humans in Spain, since resistant isolates from humans were phylogenetically indistinguishable from chicken isolates [35]. These findings were supported by a study from Iceland showing quinolones in chicken feed driving resistance development of *E. coli* in chickens, which could subsequently be a source of ciprofloxacin resistant *E. coli* in humans [36].

Similar observations were shown for gentamicin-resistant bacteria. A study in the USA reported evidence for transmission of gentamicin resistant Enterococci from chickens to humans via the food supply [37]. In another study, the risk of colonization with gentamicin resistant *E. coli* was significantly higher in chicken farmers than in non-exposed individuals in the USA [38].

In a study performed in the Netherlands, *E. coli* with an identical pulsed-field gel electrophoresis pattern was isolated from a chicken and a chicken farmer [39]. In a population based study from the US, the authors concluded that human antimicrobial resistant *E. coli* likely originated from poultry since phylogenetic distribution and drug-resistance of isolates from poultry were similar to isolates from humans [40]. Another study in Europe has also shown that antimicrobial resistant *E. coli* isolated from chickens were genetically similar to resistant isolates in humans [41].

Another study in Denmark also concluded that chickens and chicken meat probably were the source of extraintestinal pathogenic *E. coli* (ExPEC) in community-based individuals and patients with urinary tract infections (UTI) since cluster analysis showed strong similarities of antimicrobial resistance profiles as well as virulence genes between UTI patients, community-based individuals and chicken isolates [42]. The relationship of *Klebsiella pneumoniae* isolates originating from chickens and those from humans in a clinical setting was investigated in the USA. The authors observed a close relatedness of *K. pneumoniae* isolates from chicken meat and clinical isolates. These findings suggested that retail meat could be a vehicle for spreading antimicrobial resistant *K. pneumoniae* from chickens to humans [43].

In a study from China, apramycin-resistant *E. coli* were isolated from poultry farm workers, although apramycin is licensed for use in animals only and has never been used in humans. This observation indicated the likely transfer of apramycin-resistance genes between *E. coli* isolates from chickens and humans [44].

Most studies on the transmission of antimicrobial resistance bacteria or mobile genetic elements between chickens and humans have focused on extended-spectrum cephalosporins, because these are important and critical antimicrobials to treat infections in both animals and humans. The increasing prevalence of extend-spectrum cephalosporin-resistant microorganisms is a great concern worldwide [45].

A study in Canada in 2010 showed an association between the use of ceftiofur in chickens and the occurrence of extended spectrum cephalosporin-resistant bacteria in chickens and humans. Temporal changes in ceftiofur-resistant *Salmonella* and *E. coli* in chickens and humans was observed and related to voluntary withdrawal or reintroduction of ceftiofur use in chickens [46]. Another study in Spain has detected two ESBL *E. coli* of two different clonal groups (A and D) from poultry farms that were having similar backgrounds of virulence genes and PFGE profiles to human clinical isolates suggesting potential zoonotic transmission of these *E. coli* isolates [47].

Studies from the Netherlands also supported the possibility of transmission of antimicrobial resistance between chickens and humans [48-50] since genetic analyses of Enterobacteriaceae, mostly *E. coli,* from chicken meat and humans revealed similarities between ESBL genes, plasmids and bacterial strains. These studies suggested the transmission of bacterial strains and antimicrobial resistance determinants including ESBL genes or plasmids from chickens to humans via the food chain.

Despite this growing evidence of zoonotic transmission of antimicrobial resistant bacteria or resistance determinants between chickens and humans, there also were studies that did not support such transmission. With the increased access to whole genome sequencing, more accurate and detailed analysis and comparison of bacterial isolates from animals and humans have become possible and the results of such analyses have changed earlier views.

In a study from the USA, *E. coli* ST 131 pulsotype isolates from diverse sources and locales collected during the period of 1967 -2009 did not show similarities between isolates from humans, food-producing animals and foods [51]. Several other studies worldwide have documented divergence in sequence types and resistance genes of *E. coli* isolates originating from chickens and humans [52-55]. Even in the Netherlands, a country with strong evidence for transmission of ESBL-producing bacteria or ESBL genes, whole genome sequence analyses suggested that ESBL genes are disseminated in chickens and humans through transmission of different plasmids [56]. In addition, another study from the Netherlands revealed that the risk of carriage of ESBL-producing Enterobacteriaceae among individuals in high and low broiler densities was the same [57], suggesting that chickens are not a major contributor to colonization with ESBL-producing Enterobacteriaceae in humans. Similarly, a study from northern Vietnam in 2015 also showed limited transmission of an ESBL gene (CTX-M-9 type) between human and chicken *E. coli* isolates [58].

Although there have been an increasing number of studies on transmission of antimicrobial resistance worldwide, there are still many knowledge gaps about antimicrobial use in chickens, as well as the prevalence and transmission of AMR between chickens and humans in Vietnam. This is especially true for backyard farms settings, which represent the majority of chicken farming in Vietnam and South East Asia but which have rarely been studied.

Thesis Outline

The aims of this thesis are (1) to assess the prevalence of antimicrobial drug resistance among non-typhoidal *Salmonella* and *E. coli* strains isolated from backyard farm chickens and humans in Vietnam; (2) to relate these findings to antimicrobial usage; and (3) to estimate the risk of human colonization with antimicrobial resistant bacteria and transmission of genomic resistance determinants as a result of chicken farming in southern Vietnam.

Chapter 1 provides a review of the current situation of antimicrobial usage and antimicrobial resistance in humans and chicken in Vietnam. In addition, current knowledge of the transmission of antimicrobial resistant bacteria and genomic resistance determinants is reviewed.

In Vietnam, although antimicrobials are used commonly in chicken production, quantitative data are not available. Therefore, studies reported in **chapter 2** investigated and quantified antimicrobial usage in chicken farming in the Mekong Delta of Vietnam.

In **Chapters 3** to **7** the prevalence of colonization with antimicrobial resistant *E. coli* and *Salmonella* as well as transmission of antimicrobial resistance genes between these bacteria isolated from chickens and humans in southern Vietnam were studied. **Chapter 3** describes studies investigating the prevalence of colonization with non-typhoidal *Salmonella* (NTS) in chickens and humans in the southern of Vietnam as well as the risk of human NTS colonization through direct chicken exposure. The prevalence of antimicrobial resistance among commensal *E. coli* isolates on non-intensive chicken farms, common in southern Vietnam, and the association between antimicrobial resistance and farming practices as well as antimicrobial usage are described in **Chapter 4**. **Chapter 5** assesses the potential presence of highly pathogenic Enterohaemorrhagic *E. coli* (EHEC) O104:H4 strains in samples collected from Vietnamese chicken farms, farmers and matched asymptomatic humans not exposed to chickens. **Chapter 6** was conducted to study the potential contribution of transmission from poultry to colonization with ESBL-producing *E. coli* in humans. This was done by determining the prevalence and relatedness of resistance-encoding genes in ESBL-positive *E. coli* isolated from humans and chickens and to relate these to antimicrobial drug usage. In **Chapter 7,** we investigated the consequences of colistin usage in non-intensive poultry farms for the prevalence of colonization with bacteria carrying the *mcr-1* - a plasmid-mediated colistin resistance gene. In addition, the risk of onward transmission to humans was studied by molecular epidemiological analyses of isolates from chickens, their farmers and unexposed populations in a defined geographical area of southern Vietnam**.** The main findings of this thesis and future perspectives are discussed in **Chapter 8.**

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