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ARE WE USING ANTIBIOTICS RESPONSIBLY?

Assessing antibiotic use in rural Shandong province, China

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ARE WE USING ANTIBIOTICS RESPONSIBLY? Assessing antibiotic use in rural Shandong province, China

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No man is an island entire of itself,
every man is a piece of the continent,
a part of the main.
If a clod be washed away by the sea,
Europe is the less,
as well as if a promontory were,
as well as any manner of thy friends
or of thine own were.
Any man's death diminishes me,
because I am involved in mankind.
And therefore never send to know for whom the bell tolls,
it tolls for thee.

John Donne, English scholar and poet

PREFACE

The best time to plant a tree was twenty years ago. The second best time is today.
Anonymous.

On 31st December 2019, the World Health Organization was alerted to several cases of pneumonia in Wuhan city, Hubei province, China. The cause of these illnesses turned out to be a novel coronavirus, thought to have originated in illegally traded wildlife at a seafood market in Wuhan.

I write these words a month later, on the day that the *2019-nCoV outbreak* has been declared a Public Health Emergency of International Concern by the WHO. Our understanding of the outbreak is evolving daily, and there are still many unknowns: Where did the virus emerge from? Is there sustained person-to-person spread of the virus in the community? Is the virus contagious before symptoms show? How severe is the illness caused by the virus?

The list of actions already taken in China is fascinating, unprecedented, and potentially impossible to replicate elsewhere:

- The city of Wuhan, with a population that exceeds the entire of Sweden, has effectively been put into quarantine
- Two 1000-bed hospitals are being built within ten days in Hubei province
- A ban has been introduced on the sale of all wildlife at markets throughout China
- Several major cities have suspended public transport systems and taxis, and the city of Tianjin has asked taxi drivers to disinfect vehicles after every passenger
- The government in Shanghai has stopped businesses from returning to work after the Spring Holiday: this applies to all companies apart from utilities, medical firms, medical suppliers and supermarkets.

On our highly interconnected planet, one thing is clear: what happens in China matters for the world.

Lewis Mumford, an American historian and urban planner once wrote that *"Every culture lives within its dream"*. It seems to me that for a long time we have been living within a global dream that we can broadly use antibiotics however we like, in humans and animals, without needing to worry too much about any negative consequences that may follow. The journey described in these pages examines whether this is the case and concludes that to avoid the dream becoming a nightmare, we may need to wake up.

Antibiotic resistance has been referred to as an *invisible pandemic* and a *silent tsunami*. It is critical that we take actions globally to address antibiotic resistance. However, compared with the outbreak of a deadly virus, these individual actions are less urgent, less dramatic, and perhaps less open to scrutiny. Several novel resistance genes of global significance have been identified in China over the past decade. In response to this, and the worldwide situation, China has made many impressive commitments to address antibiotic resistance. But much more remains to be done, and it is my fervent hope that some clues as to what this could involve are contained within the pages you are about to read.

Stockholm, 30th January 2020

ABSTRACT

Background: Tackling the misuse and overuse of antibiotics is critical both for global sustainable development and for reducing social inequalities in the world. The World Health Organisation Global Action Plan on antimicrobial resistance calls on all Member States to develop multi-sectoral National Action Plans and to "monitor and promote optimization of antimicrobial use at national and local levels". There is a particular need to assess how antibiotics are being used in resource-limited settings, which tend to have the highest burdens of infections and of antibiotic resistance. In such settings antibiotics are commonly overused and misused in agriculture too, emphasizing the need for One Health approaches. In 2010, China was estimated to be the second largest consumer of antibiotics for human use by total volumes, and the largest consumer of antibiotics within food animal production. Information on antibiotic use in human healthcare in rural areas is lacking in China, as is knowledge of the volumes and patterns of antibiotic use in agriculture, particularly in backyard pig farms which remain highly prevalent.

Aim: To assess how antibiotics are being used for humans and on backyard pig farms in a rural region in China.

Methods: All studies were conducted in rural areas of Shandong province, located in eastern China. Two main methods were used: analyses of prescriptions from healthcare facilities, and surveys of doctors', rural residents' and backyard pig farmers' knowledge, attitudes and practices concerning antibiotic use and resistance. In **Paper I** we assessed the rates and types of antibiotics prescribed for patients with common cold diagnoses during one month at thirty healthcare facilities in three different counties. These healthcare facilities covered three different levels in the rural healthcare system: village clinics, township health centres and county hospitals. All 188 doctors working at the healthcare facilities were invited to participate in a questionnaire on knowledge and attitudes towards antibiotic use. In **Paper II** we prospectively monitored antibiotic prescribing over a 2.5 year period at eight village clinics located around a single town in a rural county. We conducted individual prescriber-level analyses in order to assess the extent of variations in prescribing practices, focussing on prescriptions containing diagnoses of likely viral acute upper respiratory tract infections (AURI). In **Paper III** we assessed the knowledge, attitudes and practices towards antibiotic use and resistance of 769 rural residents living in the twelve villages that are served by the village clinics in **Paper II**. In **Paper IV** we assessed the knowledge, attitudes and practices towards antibiotic use in pigs of the 271/769 rural residents who had backyard pig farms. We also observed the rates and types of antibiotics stored in households for use in humans and pigs in **Papers III and IV**.

Results: Over half of all prescriptions with a common cold diagnosis at healthcare facilities in **Paper I** contained at least one antibiotic, as did almost two-thirds of the prescriptions for likely viral AURIs at village clinics in **Paper II**. The majority of antibiotics prescribed were broad-spectrum. Antibiotics were more likely to be prescribed on common cold prescriptions from village clinics than on prescriptions from higher level healthcare facilities. There was widespread variation in the antibiotic prescribing practices of individual village doctors. Significant gaps existed between doctors' knowledge and attitudes, and their actual prescribing practices, despite a majority of doctors reporting that they had recently attended training on rational antibiotic use.

Rural residents and backyard pig farmers had low levels of knowledge about what antibiotics are and when they should be used. Rural residents more frequently thought that antibiotics are needed for infectious conditions than for non-infectious conditions, but they did not differentiate significantly between infections caused by bacteria, where antibiotics may be needed, and those caused by viruses, where they are not. Rural residents commonly reported acquiring antibiotics without prescriptions, as well as using leftover antibiotics. Similarly, backyard pig farmers reported frequently using antibiotics in healthy pigs when they are not needed, and purchasing antibiotics without consulting veterinarians. Backyard pig farmers had differences in their knowledge, attitudes and practices towards antibiotic use in humans compared with other rural residents, and these appeared to be inter-related with their knowledge, attitudes and practices towards antibiotic use in pigs. Household storage of antibiotics for human use was common, and similar to levels identified in previous studies in Asia; storage of antibiotics on backyard pig farms was also frequent, and many of the stored antibiotics are considered to be critically important for human medicine.

Conclusions: The work in this thesis strongly suggests that antibiotics are not being used responsibly enough for humans and on backyard pig farms in the study region: doctors, rural residents and backyard pig farmers in rural Shandong province are frequently overusing and misusing antibiotics. There is a need to investigate which additional drivers are causing doctors to prescribe antibiotics unnecessarily, despite knowing that they are not needed. Rural residents' and backyard pig farmers' knowledge and attitudes may be contributing to overuse and misuse of antibiotics, for example through having expectations to receive antibiotics from healthcare professionals in situations for which they are not clinically needed. In resource-limited settings, high quality, cross-sectoral assessments of antibiotic use at a small number of study sites can provide valuable insights into how responsibly antibiotics are being used.

Keywords: Community; Consumption; Outpatient; Rational use; Prescriptions; Knowledge, attitudes and practices; Antibiotic resistance; Antibiotic stewardship; Global health.

LIST OF SCIENTIFIC PAPERS

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These papers are referred to in the text by their Roman numerals [I-IV].

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CONTENTS

LIST OF ABBREVIATIONS

APR	Antibiotic prescribing rate
AURI	Acute upper respiratory tract infection
CH	County hospital
ESBL	Extended-spectrum beta-lacatamase
FAO	Food and Agriculture Organization of the United Nations
GDP	Gross domestic product
Intl$	International dollar (adjusted for purchasing power parity)
MPR	Multiple antibiotics prescribing rate
NHC	National Health Commission of the People's Republic of China
OIE	World Organization for Animal Health
OR	Odds ratio
PAPR	Parenteral antibiotic prescribing rate
RMB	Renminbi (official currency of China)
THC	Township health centre
USD PPP	United States Dollars in purchasing power parity
VC	Village clinic
WHO	World Health Organization

The world is full of paradox: we discover the existence of antibiotics, a remarkable class of drugs that adds several years to the average human's lifespan and radically alters our expectations of normal life. Then, over the course of 70 years we fail to make the value of these drugs accessible to all. At the same time, we knowingly overuse these drugs in both humans and animals, accelerating the rate at which their value is eroded, while failing to invest in ways to maintain and to renew this value.

This raises a crucial question that we must ask ourselves: are we using antibiotics responsibly?

Dyar OJ *et al.*, Future Microbiology, 2016

1 INTRODUCTION

There is an old saying: as a medicine, it is somewhat toxic. How can medicines cure diseases if there are no poisonous components? There will surely be side effects.
Focus group respondent, rural Shandong province

1.1 THE IMPORTANCE OF USING ANTIBIOTICS RESPONSIBLY

1.1.1 It matters how we use antibiotics

Antibiotics can be life-saving medicines. Since their introduction into clinical practice, they have transformed how we treat bacterial infections, and our ability to rely on their effectiveness underpins many aspects of modern medicine [1]. Antibiotics are also essential for animal welfare and for food production [2].

Antibiotics may be the epitome of a wonder drug [3], but it still matters how we choose to use them [4,5]. As with other medicines, they can be overused (i.e. used when they are not needed), misused (i.e. an inappropriate antibiotic choice or dose is selected) and underused (i.e. not used when they are needed). The overuse and misuse of antibiotics has direct consequences for individual patients, including elevated risks of adverse events such as organ-specific toxicities and hypersensitivity reactions [6,7], impacts on the normal microbiome [8,9], and economic costs such as out-of-pocket expenditures [10,11]. The consequences of underusing antibiotics depend on the specific infection that goes untreated.

Critically, antibiotic use also accelerates the naturally occurring processes of development and spread of resistant bacteria [12,13]. In individual patients antibiotic use can lead to the development of resistance during treatment [14], as well as an increased probability of colonisation with resistant bacteria after treatment [15–17]. Overusing and misusing antibiotics further increases the likelihood of these processes happening [5]. For example, healthy livestock are sometimes fed low doses of antibiotics over extended periods of time as growth promoters, separate from using antibiotics to treat and prevent infections; these livestock tend to have higher subsequent isolation rates of resistant bacteria [18].

Rising prevalence rates of resistant bacteria in turn have important consequences. For individuals, infections caused by resistant bacteria are associated with longer illness durations and higher mortality rates, as well as elevated costs from needing second- or third-line treatments and longer-hospital stays [19,20]. For societies, rising antibiotic resistance rates lead to increased treatment costs and longer recovery times during which individuals are unable to work [21,22]. Modelling suggests that resistant bacteria already account for at least 33,000 additional human deaths in Europe each year [23]. If trends continue, global gross domestic product (GDP) is predicted to be 2-3.5% lower by 2050 than it would otherwise be [24], similar to estimates for the impact of climate change over the same time period [25,26].

The growing scientific and political understanding of the threats posed by antibiotic resistance has led to several high-level actions and commitments. These include the World Health Organization's (WHO) Global Action Plan on antimicrobial resistance, which was adopted in 2015 [4]. Broadly, the challenges of antibiotic resistance can be tackled by developing antibiotics with new mechanisms of action (innovation), by improving access to existing effective antibiotics (access) and by preserving the effectiveness of existing antibiotics (conservation), which includes reducing the need to use antibiotics through improvements in public health, vaccination coverage, and infection prevention and control [27,28]. Currently, innovation efforts are being impeded by a range of economic, regulatory and societal challenges [29]. A recent analysis found that most of the sixty products in clinical development bring little benefit over existing treatments, and only two are active against the critical multidrug resistant gram-negative bacteria [30]. This further highlights the urgent need to invest in conservation efforts, which includes minimising the misuse and overuse of antibiotics. A recent United Nations Children's Fund (UNICEF) report termed antimicrobial resistance as one of the biggest generational threats to childhood health and survival, and prioritised three responses which are all related to conservation: reducing infection rates, promoting access to and optimal use of antibiotics, and increasing awareness and understanding of antimicrobial resistance [31].

In summary, the misuse and overuse of antibiotics has important negative consequences for patients, the healthcare system and society, including unnecessarily exacerbating the burden of antibiotic resistance.

1.1.2 Antibiotic resistance and social inequalities are interlinked

The burden of antibiotic resistance is not spread equally [32]. It is increasingly clear that social inequalities can drive antibiotic resistance, and that antibiotic resistance can in turn exacerbate social inequalities [33,34]. This occurs on a global scale, as well as within individual countries. Diderichsen *et al.* developed a framework for illustrating the central mechanisms related to social inequalities in health (Figure 1) [35]. This framework can highlight the paths through which social inequalities can occur for *infections with resistant bacteria* and also for *antibiotic overuse and misuse*, as described below.

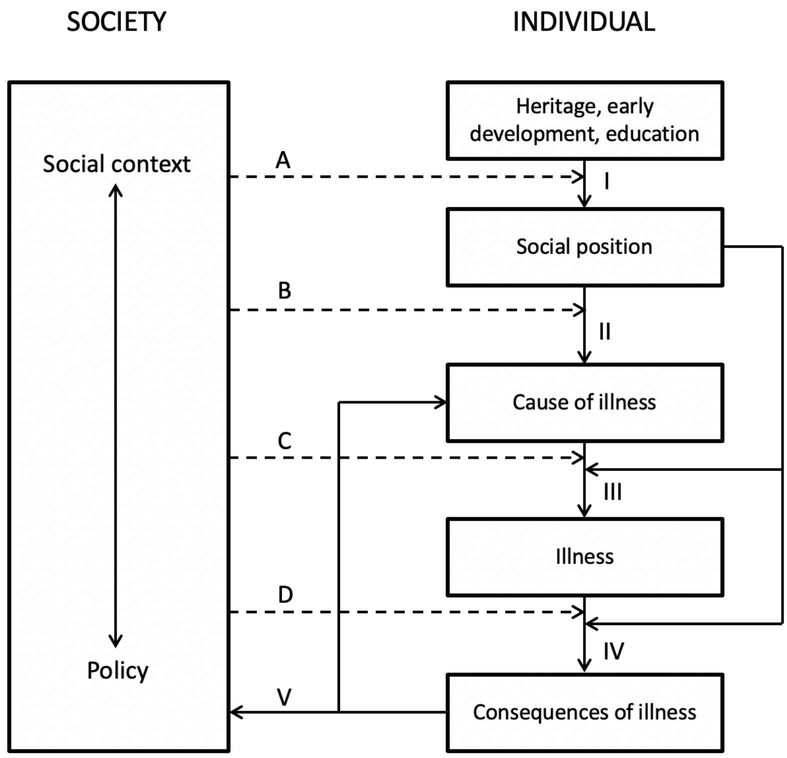


Figure 1. Central mechanisms (I-V) and policy entry points (A-D) related to social inequalities in health (adapted from [35])

Differential exposures (arrow II): the social position of a person within a society affects the risk factors that they are exposed to through their work, economic circumstances, physical environment and health behaviours [35]. Several of these factors are relevant to both *infections with resistant bacteria* and *inappropriate or unnecessary antibiotic use*. For example, household crowding has been associated with an elevated risk of community-associated methicillin-resistant *Staphylococcus aureus* (MRSA) infections in the US, and with higher antibiotic use rates in New Zealand [36,37]. Similarly, studies have shown associations between working with livestock and human carriage of resistant bacteria [38,39].

Differential vulnerabilities (arrow III): due to interaction effects, the strength of the effect of an individual risk factor is affected by the presence of other risk factors for the same illness [35,40]. Particularly in poor resource settings, several risk factors for *infections in general* can cluster among individuals in lower socioeconomic groups, for example poor nutrition, and poor access to clean water and sanitation facilities [33,34,41]. Risk factors for *infections in general* will also tend to act as risk factors for *infections with resistant bacteria* and for *inappropriate or unnecessary antibiotic use*: as infection rates rise, so too does the risk in absolute terms for suffering from an infection caused by resistant bacteria (since a proportion of all infections will be caused by resistant bacteria), as does the risk for antibiotic overuse or misuse (since a proportion of all antibiotic use will prove to be unnecessary or inappropriate).

Differential disease consequences (arrow IV): social position can impact access to treatment and rehabilitation, and thus affects survival, functional ability, quality of life and employment [35]. As antibiotic resistance rates rise, access to antibiotics that work is an important challenge in poor resource settings. It has been estimated that nearly 450,000 childhood pneumonia deaths each year are due to an inability to access effective therapy that already exists [42]. Second- and third-line antibiotics tend to be more expensive, so even when effective antibiotic therapy is available, individuals may struggle to afford them [34].

Tackling antibiotic resistance, including the drivers of overuse and misuse, is critical both for global sustainable development and for reducing social inequalities in the world [41,43].

1.1.3 Defining responsible antibiotic use

Over the past few years there have been several efforts to define what responsible antibiotic use is, both in human medicine and veterinary medicine [44–48]. These efforts include a large expert consensus procedure which ultimately reached agreement on 22 separate elements [49]. I summarised some of these discussions together with co-authors in a perspective piece [50], and further highlighted two dimensions in the Oxford English Dictionary definition of "responsible" [51] that we felt were particularly relevant.

First, *a responsible practice* is one that is carried out in a morally principled way. This is where the majority of discussions on antibiotic use have centred, particularly when defining "optimal use", "rational use" and "appropriate use" in the context of antimicrobial stewardship efforts [47]. Second, *to be responsible* is to be capable of fulfilling an obligation or duty. We suggested that we have a global obligation to ensure sustainable access to antibiotics for all those who need them, but that this dimension has been under-emphasised in discussions so far [50]. This perspective encourages viewing antibiotics as resources that are potentially non-renewable, and there is indeed much that can be learnt from examining how societies manage other non-renewable resources. *Being responsible* involves looking beyond individual antibiotic uses to the broader environments in which they occur: for example, what regulations and educational efforts are we putting in place as a society to promote using antibiotics in sustainable ways? Using antibiotics responsibly is thus about individual antibiotic practices and also how we can shape contexts to be conducive to responsible antibiotic use. Table 1 shows examples of where we may fail in this responsibility.

Table 1. Responsibility in the context of using antibiotics

Individual practices that are not responsible	Not being responsible – the broader context
Using antibiotics for conditions where there is no evidence of efficacy (e.g. common colds)	Failing to educate the public about antibiotics in contexts where they have easy access to antibiotics (e.g. over-the-counter)
Prescribing broad-spectrum antibiotics when narrow-spectrum antibiotics are as effective	Allowing widespread variations in the quality of antibiotic use between prescribers

1.1.4 Why do we not always use antibiotics responsibly?

Ideally, antibiotics would only be used when they provide a clinical benefit, and when this benefit is considered to not outweigh the need to conserve antibiotic effectiveness for future patients – i.e. antibiotics would not be overused. Furthermore, when an antibiotic is used, an optimal choice, dose and route would be selected – i.e. antibiotics would not be misused. These principles can be applied to antibiotic use in both humans and animals [46,47,52–54]. There are, however, a wide range of broader determinants that shape how responsibly antibiotics are used today, in addition to clinical need [1,55,56].

At the individual-level, limitations in prescriber and patient knowledge and attitudes are common and can lead to inappropriate and unnecessary antibiotic use [57–59]; even when appropriate knowledge is held, entrenched behaviours and habits can take precedence and result in suboptimal practices [60]. Several additional factors may nudge prescribers, patients and societies into overusing or misusing antibiotics in humans and animals. For example, reimbursement systems may leave hospitals and veterinarians reliant on antibiotic sales to generate income to cover their operating costs [61,62]; pharmacies and drugstores may dispense antibiotics to patients as a way to make additional profits, whilst also selling other over-the-counter symptom-relieving medications to patients [63]; a lack of restrictions on pharmaceutical industry advertising may promote unnecessary antibiotic use [21,64]; and more broadly, a culture may encourage healthcare-seeking and use of antibiotics for non-life-threatening illnesses so that its population can experience symptoms for shorter periods of time, return to productive work more quickly, or simply feel reassured [65].

These individual-level and system-level determinants of antibiotic use can vary widely between settings [21]. A context-specific understanding of the determinants of antibiotic use is thus needed to support interpretations of data on how antibiotics are being used, as well as to adapt interventions to improve antibiotic use.

1.2 ANTIBIOTIC USE NEEDS TO BE ASSESSED

Since antibiotics may not always be used responsibly, there is a need to assess how antibiotics are actually being used in practice. There is evidence from a wide range of countries that not all antibiotic use today is optimal; indeed, studies commonly suggest that up to a half of all antibiotic prescriptions in human medicine are either unnecessary or inappropriate, both in inpatient and outpatient settings [66–69], and that patient adherence with prescribed antibiotics is also suboptimal [58]. It is harder to estimate the proportion of antibiotic overuse and misuse in animals, but there are suggestions that it is of at least the same order of magnitude as in humans [70].

The WHO Global Action Plan on antimicrobial resistance calls on all Member States to develop multi-sectoral National Action Plans and to "monitor and promote optimization of antimicrobial use at national and local levels" [4]. Assessing how antibiotics are being used is needed for several reasons, including:

- To understand when, how and why antibiotics are overused, misused and underused
- To provide feedback to individual prescribers, dispensers and consumers of antibiotics, in order to improve practices
- To assess the impact of interventions that aim to improve antibiotic prescribing, dispensing and use
- To better understand the relationship between intensity of antibiotic use and the emergence and spread of antibiotic resistance within countries and individuals

1.2.1 One Health approaches are needed

One Health is the collaborative effort of multiple disciplines – working locally, nationally, and globally – to attain optimal health for people, animals and the environment [71]. The WHO, the World Organization for Animal Health (OIE) and the Food and Agriculture Organization of the United Nations (FAO) all acknowledge the importance of One Health approaches in coordinating global activities to address health risks, as demonstrated by the tripartite concept note in 2010 [72]. Antibiotic resistance has been described as the quintessential One Health issue [73] with bacteria such as *Escherichia coli* capable of spreading between humans, animals and the environment, along with antibiotic resistance genes and antibiotic residues. This One Health perspective is particularly relevant in many resource-limited rural community settings in which humans and animals live closely, often with small-scale "backyard farms" on the same site as a house (Figure 2) [39].

Figure 2. Potential spread of *E. coli* on backyard farms (adapted from [74])

The WHO Global Action Plan on antimicrobial resistance, in which OIE and FAO have distinct roles, recognizes that antibiotic use needs to be assessed in both human and animal sectors, moving towards a One Health perspective [4,75,76]. To facilitate this, the OIE has developed a voluntary data collection system on the use of antimicrobial agents in animals, to which any country can contribute [77]. These approaches are necessary to understand the total antibiotic use occuring within a region, and consequently the overall ecological pressure placed on bacteria [78,79]. Furthermore, determinants for misuse and overuse may cross sectors within settings; for example, ease of access to antibiotics without prescriptions in pharmacies for both human and animal use. Similarly, it is possible that interventions can be developed that can simultaneously improve antibiotic use in humans and animals [80,81].

Data are also needed from environmental sources to complete the One Health perspective [82]. These include information on how pharmaceutical companies dispose of potentially active by-products from the antibiotic manufacturing process [83], and on the antibiotic residue contents of hospital wastewater effluents [84]. These assessments lie outside of the scope of the present thesis which focusses on antibiotic use in humans and animals, and so are not considered in further detail.

1.2.2 Methods and data sources for assessing antibiotic use

Figure 3 shows a simplified map of the main pathways that antibiotics take through a healthcare system, from manufacturing through to consumption. Similar pathways exist for antibiotic use in animals, although a greater diversity of actors may be involved.

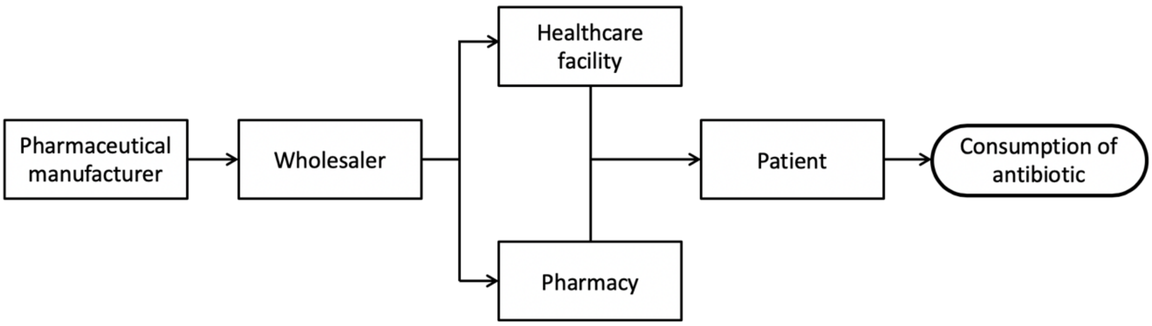


Figure 3. Simplified flows of antibiotics through a healthcare system

Typically, a manufacturer sells antibiotics to a wholesaler, which will then sell the antibiotics to healthcare facilities (e.g. hospitals, outpatient clinics) and to pharmacies. In some settings a central procurement agency may act as an intermediary between multiple wholesalers and multiple healthcare facilities and pharmacies [85]. At healthcare facilities antibiotics are then prescribed by doctors and other qualified personnel to patients, and they can either be dispensed in the facility (normal for inpatients) or at a separate outpatient pharmacy. In some settings antibiotics can also be acquired by consumers directly from pharmacies without a prescription (referred to as over-the-counter use) [86]. The final stage is the consumption of an antibiotic by the consumer. Patients may have leftover antibiotics, for example if they choose not to complete the full course prescribed; they may choose to store these for a later illness and use them independently of healthcare providers (an example of self-treatment).

Assessments of antibiotic use can be made at different points on these pathways. The common strengths and limitations of different methods and data sources for assessing antibiotic use are presented in Table 1, compiled from studies conducted in high-, middle-and low-income settings. In general, data from higher levels in the healthcare system (e.g. wholesaler sales to healthcare facilities and pharmacies) provide information on *quantity* that allows comparisons to be made between facilities, regions and countries in terms of intensity of antibiotic use [87,88]. These data are important for policy makers [89,90], and can permit observation of the potential influences that changes in policy have at a whole system level; however, in isolation these data may not provide much insight into the *quality*, or appropriateness, of individual antibiotic uses. Their distance from the end consumer also means they may provide less accurate estimates of actual consumption by patients [89]. Assessing the quality of antibiotic use is facilitated by capturing clinically relevant information [91–93], which is available at lower levels in the healthcare system (e.g. from healthcare facilities, pharmacies, consumers) [94,95]. This data on the appropriateness of antibiotic use is important for identifying targets to improve antibiotic use [96], and can be used as a source of feedback to healthcare facilities and prescribers [97,98]. However, data at the lower levels are often resource-intensive to collect and they can lack generalisability beyond the specific setting in which they are collected [89].

In general, there have been far fewer efforts to assess antibiotic use in animals, compared with in humans [79,99]. Many of the methods used for assessing antibiotic use in humans can be applied to assessing how antibiotics are being used in animals, and the strengths and limitations will be broadly similar.

1.2.3 Assessing antibiotic use within a region

Adapting assessment methods to the context in which they are used strengthens their power to provide accurate, reliable and actionable information on how antibiotics are being used. No single assessment method is capable, however, of comprehensively describing how antibiotics are being used across the whole healthcare system in a region. The different assessment methods provide information that complement one another, and a holistic understanding of how antibiotics are being used can only be reached by combining the data from multiple assessment methods. Furthermore, each assessment method provides information on different parts of the healthcare system as a whole [1], which can be essential for providing the context necessary to interpret results: for example, procurement data can shed light on financial incentives for facilities to overuse antibiotics, and prescription data can indicate how frequently alternatives to antibiotic therapy are being used.

1.2.4 Challenges in resource-limited settings

There is a particular need to assess how antibiotics are being used in resource-limited settings [100,101]. Globally, these settings have the highest burdens of infections and of antibiotic resistance [33,34,102]. Antibiotics have often been used to plug gaps in public health, and there is frequently evidence of concurrent antibiotic overuse, misuse and underuse [103,104]. In such settings antibiotics are commonly overused and misused in agriculture too, emphasizing the need for One Health approaches to understand and tackle problems [39,76].

In most countries, the vast majority of human antibiotic use occurs for outpatients in community settings, but these are often the hardest settings in which to obtain data. Beyond the inherent methodological limitations mentioned in Table 1, there are additional challenges when assessing antibiotic use in resource-limited settings [100]. First, systems for capturing data may be less mature and less comprehensive (e.g. paper-based prescriptions and dispensing records; surveillance limited to public sector facilities); second, fewer resources may be available (e.g. trained personnel; technology; funding); third, a wider range of sources for antibiotics may exist (e.g. over-the-counter sales; cross-border sales; donations; self-medication); fourth, different patterns of disease prevalence and antibiotic susceptibility may exist both between and within countries.

Table 2. Strengths and limitations of data sources used for assessing antibiotic use in humans

Data sources	Strengths	Common limitations and missing data
Wholesaler data and aggregated sales data	• May capture over-the-counter sales [105,106] • Allows for standardised data collection across a range of facilities [107] • Can compare trends in sales of antibiotics with sales of other medicines (and potentially assess changes in response to policies) [108]	• Potentially a large number of independent wholesalers • May be difficult to define population denominator • May be limited to public or private sector only [90] • Cannot account for spoiled or expired stock that is not consumed [109] • Lacks patient-specific data and clinical usage data
Procurement records	• May be possible to disaggregate data (e.g. to healthcare facility type and location) [85,110] • Potentially only one data source needed if centralised procurement is used [110] • Can be used to assess the impact of new policies [111] • Can compare trends in procurement of antibiotics with other medicines [111]	• May only provide data for the public sector [85,111] • Rare medicines may not be covered by main procurement mechanisms [110] • May miss over-the-counter sales [110] • Cannot account for spoiled or expired stock that is not consumed [109] • Lacks patient-specific data and clinical usage data
Insurance and reimbursement records	• May be the only information system available that links clinical diagnosis with antibiotic prescriptions [94] • May be simple to collect data if only a small number of insurance providers exist [87,112] • Can help in benchmarking and in assessing variation between healthcare facilities [112] • Insurance data may provide denominators for numbers of people covered [113]	• Some antibiotics may be excluded due to not being reimbursed (e.g. due to antibiotic type, or patient demographic) [105,106] • May only include limited clinical data [112] • Insurance schemes may differ in patient membership (e.g. socio-demographics, co-morbidities) [113] • Misses over-the-counter sales [105,106]

Data sources	Strengths	Common limitations and missing data
Prescribing records (inpatient and outpatient)	• Defined patient population (particularly for inpatient data) [32] • Prescribed antibiotics are likely to be consumed (particularly for inpatient data) [32,114] • May capture prescription and patient characteristics, so can be possible to assess influencing factors (diagnosis, socio-demographics) [32,69,115,116] • Allows analysis of other medicines prescribed concurrently with antibiotics [117] • Potential to capture behaviour at individual prescriber level or facility level, and provide feedback [32,116] • May allow easy access to population subgroups (e.g. pediatric populations) [118]	• Not all outpatient prescriptions will be dispensed or consumed • Misses over-the-counter sales [115,119] • May not be possible to validate diagnoses for data from only prescriptions rather than medical records [69,116] • Outpatient encounters may not always lead to a prescription, making comparisons between settings difficult • Datasets for outpatient care may not be comprehensive (e.g. missing long-term care facilities, emergency department visits) [69]
Pharmacy dispensing records (outpatient)	• Can capture over-the-counter sales [63,86,120] • May capture financial incentives for sales [86] • May allow easy access to population subgroups (e.g. pediatric populations) [118] • May allow individual patient exposure to antibiotics to be calculated [121]	• May be resource intensive due to large number of facilities [63] • Private companies may be unwilling to share data [63] • Small drugstores may have incomplete records [63] • Data may only be available at pack level (i.e. not on prescribed duration of courses) [115,118]
End consumers	• May accurately reflect end consumption of antibiotics for individual patients [63,122] • Provides information on storage of leftovers, self-medication or sharing with others [95,123,124] • May capture over-the-counter acquisition [63,124,125] • Can help identify patterns of healthcare seeking behaviours [63,125,126]	• Can be highly resource intensive [61,127] • May include selection biases and recall biases [124,127] • Clinical information may be lacking (i.e. clinical signs, microbiological investigations) [122]

1.3 ANTIBIOTIC USE IN HUMANS AND ANIMALS IN CHINA

1.3.1 The People's Republic of China: an introduction

China is an upper-middle income country covering approximately 9.6 million square kilometres, with landscapes ranging from deserts in the arid north to subtropical forests in the wetter south and including the third longest river in the world. China has been a one-party socialist state since the end of the Chinese Civil War in 1949 and is divided into 22 provinces, five autonomous regions, and four municipalities (collectively referred to as "mainland China"), as well as the special administrative regions of Hong Kong and Macau.

China is the most populous country in the world and had a population of 1.38 billion in 2018 [128]. The majority of the population (57%) now lives in urban areas, a rapid increase from 25% thirty years ago, and there are over 100 cities in China with more than a million inhabitants. Life expectancy at birth is 73.6 years for males and 79.4 for females, although there are regional variations [128]. China is one of the world's fastest growing economies, and it has been the largest economy in the world since 2014 by purchasing power parity [129]. Economic inequality has increased considerably since the 1990s, reaching a Gini coefficient of approximately 0.50 in 2013 [128,130]; a Gini coefficient of 0 signifies that everyone has the same income, and 1 implies that a single person or household has all the income. For comparison, Sweden had a Gini coefficient of 0.29 in 2015 [128]. The extreme level of income inequality is thought to be driven by structural factors including long-standing government development policies that have favoured urban residents over rural residents, and residents from coastal, more developed regions, over residents from less developed, inland regions [130]. The average annual per capita income of urban households in China in 2018 was almost 40,000 RMB (11,000 Intl$), compared with just under 15,000 RMB (4,200 Intl$) for rural households [128,131]. Historically, there have also been important differences in access to education between rural and urban residents. Several government policies have been introduced in recent years to address growing inequalities, spanning the labour market, healthcare and education [132].

1.3.2 Antibiotic use and resistance in China

In 2010, China was estimated to be the second largest consumer of antibiotics for human use by total volumes, and the largest consumer of antibiotics within food animal production [70,107]. As in many countries, around half of all antibiotics used in China are thought to be consumed by livestock [133,134], both as growth promoters and to prevent and treat disease. The volume of antibiotics used in agriculture is predicted to increase by two-thirds by 2030 due to human population growth and the rising demand for meat [70].

There are national surveillance systems for monitoring antibiotic use (*Mohcas*) and antibiotic resistance (*Mohnarin*), but both systems mainly include data from large urban hospitals, and so are not fully representative of China as a whole [62]. Studies that have assessed per capita antibiotic consumption levels in humans have generally reported these to be similar to European levels, and lower than levels in high-income Asian countries [107,110]. Smaller scale studies, however, suggest that there is frequent over-prescribing of antibiotics, combined with high levels of self-treatment [95,119,125]. One study reported that over 60% of parents living in a rural region had given their children antibiotics in the previous year without consulting a doctor; in the same study, children were reported to also have been prescribed a median of two courses of antibiotics by doctors in the preceding six months [95].

In general, data on antibiotic use in rural areas is lacking. A systematic review published in 2013 only included two studies from rural healthcare facilities [135]. There is also currently little data on the volumes and patterns of antibiotic use in agriculture, in particular in household backyard farms which are highly prevalent in rural China [136]. Many drivers promote the overuse of antibiotics in humans and animals, including financial incentives for facilities and individual prescribers; a lack of microbiology facilities in rural healthcare facilities; pharmaceutical industry advertising to consumers; low levels of public knowledge about antibiotic use and resistance; and low numbers of trained veterinarians for backyard farms [136–138].

Clinical studies at individual hospitals and national surveillance data collected by the Ministry of Health have identified high rates of resistance in a variety of bacterial pathogens, in particular *Enterobacteriaceae* and *Acinetobacter* spp. [139,140]. Highly resistant bacteria have been identified in a range of agricultural settings too, as have individual antibiotic resistance genes such as *mcr-1* which confers resistance to colistin, a last-resort antibiotic in human medicine [141,142]. Several factors have contributed to the spread of resistant bacteria in China, including high population densities; economic migration; frequent human and animal interactions (particularly in rural areas); and inadequate wastewater treatment facilities [61,139].

1.3.3 The healthcare system in rural China

1.3.3.1 Structure and resources

The main health authority at the state level is the National Health Commission of the People's Republic of China (NHC) [143]. The central government remains the leading force in law-making and decision-making, despite several waves of reform attempting to streamline administration and promote decentralization.

China has had a three-tier healthcare delivery system in urban and rural areas since the 1960s [143]. In rural areas this consists of village clinics, township health centres, and county hospitals. In 2018 there were approximately one million medical institutions in China, with 8.7 hospital beds per 1,000 people in urban areas and 4.6 in rural areas, and with 4.0 licensed doctors per 1,000 people in urban areas and 1.8 in rural areas [131]. In comparison, in Sweden there were 2.4 hospital beds and 4.3 licensed doctors per 1,000 people in 2016 [144].

Health resources tend to be concentrated in hospitals in both urban and rural areas. Primary care facilities (village clinics and township health centres) provide primary medical services and basic public health services to rural residents. Hospitals are responsible for most specialist outpatient and inpatient services, but will additionally offer primary medical services [143]. The majority of hospitals are private (64% in 2018), whereas most village clinics are public (67% in 2018) [131].

1.3.3.2 Financing, including reimbursements of medicines

In 2018, China's total health expenditure accounted for 6.6% of its GDP, with 28% covered by the government's budget, 44% by social insurance and 29% by individual out-of-pocket payments [131]. Almost all rural residents are covered by one of two social insurance schemes: the urban employee-based health insurance scheme (mandatory for workers in urban areas, and financed by premiums from employers and employees) and the new rural cooperative medical scheme (financed by individual premiums and the government). All medicines on the national essential medicines list [145] are included in the pharmaceutical reimbursement catalogues for the basic medical insurance schemes, and these are reimbursed at higher rates than other medicines. Further local adaptation of the essential medicines list is permitted. A policy of zero mark-up on sales of essential medicines has been in place since 2012 at village clinics, and earlier at other public primary care facilities [143,146]. This means that village doctors are unable to profit from sales of essential medicines; instead, village doctors are compensated with supplemental subsidies [85,143].

1.3.3.3 Medical education and types of doctor

China has, over time, established a comprehensive medical education system. This consists of undergraduate education, postgraduate education and continuing professional development. It is organized by the Ministry of Education, but local health authorities manage the training of medical specialists within each jurisdiction [143]. In rural areas, county hospitals and township health centres are staffed by a mixture of licensed physicians who typically have a five-year bachelor's degree or above, and who majored in medicine at college or university. In addition, there are many assistant licensed physicians who are graduates of colleges, universities or junior college, and who typically hold a three-year medical vocational degree. Village clinics are staffed by village doctors who hold a "village doctor" certificate and who have had varying durations of basic training. Many village doctors were first trained as part of the "barefoot doctor" programme in the 1960s and 1970s which led to the remarkable achievement of every village in China having at least one village doctor and one village clinic [143]. However, their training was short, commonly less than six months long. Continued professional development exists today for doctors at all health facilities, but varies in its availability and quality [143]. Village doctors do not have exactly the same prescribing rights as doctors working at township health centres and county hospitals, but all doctors are permitted to prescribe a wide range of narrow- and broad-spectrum antibiotics [147].

1.3.3.4 Outpatient pathways

Patients are able to freely choose which medical facilities they seek help at. Importantly, there is no fully developed gatekeeping and referral system, so hospitals must also offer primary healthcare services [143]. Higher level facilities are perceived in general to be of higher quality, but patients are required to pay higher out-of-pocket costs for attending these. For outpatient care, approximately half of all rural residents will first seek help at a village clinic, a quarter at township health centres, and the remainder at county or higher-level hospitals [143]. For residents living in villages, the village clinic will usually be their first choice if they believe their illness is not severe.

1.3.3.5 Policies and regulations on antibiotic use in human medicine

National policies and guidelines have been issued over the past decade to address irrational antibiotic use in human healthcare, and these have led to some improvements [62,114]. These efforts include guidelines for antimicrobial use which were published in 2004, the creation of an antimicrobial use and monitoring network in 2005, and guidelines for prescription audits which were published in 2010 [114]. Over-the-counter sales of antibiotics have been illegal since 2004 [61]. The NHC launched a three-year national campaign in 2011 to further improve the use of antibiotics. This campaign focussed on secondary and tertiary hospitals, and involved implementing antibiotic stewardship programmes, classifying antibiotics into three categories depending on the rights needed to prescribe them (non-restricted; restricted; specialist only), and introducing penalties for facilities that failed to reach specific targets (e.g. the proportions of outpatient prescriptions and inpatient medical records with prescriptions of antibiotics should be <20% and <60%, respectively). The Chinese National Action Plan on Antimicrobial Resistance was published in 2016. This included targets for the developing new drugs, restrictions on over-the-counter access to antibiotics, improvements in surveillance, and improvements in antibiotic use in both human and animal sectors [148]. Overall, the implementation and effectiveness of policies on improving antibiotic use has been limited in rural settings due to a relative lack of supervision and supporting infrastructure, and fewer training opportunities [62,66,138].

1.3.4 Agriculture in rural China: focusing on pigs

With the exception of milk, China is the largest producer of all major agricultural products, accounting for 28% of global meat production in 2013 [134]. In 2016, pork accounted for 62% of all meat produced in China, followed by poultry meat (22%), beef (8%) and sheep meat (5%) [134].

Pig production occurs at a mixture of large-scale commercial farms, medium-scale specialised farms, and small-scale backyard pig farms [149]. Backyard farms are still highly prevalent in rural areas, despite recent waves of consolidation within the pork industry. Farms with fewer than 50 pigs (a typical size for backyard farms) accounted for 95% of all pig farms and 35% of all slaughtered pigs in China in 2011 [150,151]. Backyard pig farms are usually managed by a single household, as in many low- and middle-income countries [39].

1.3.4.1 Veterinary services in rural China

A veterinary and para-veterinary workforce supports farmers in rural areas. This includes government veterinarians who are responsible for disease prevention and control, and private veterinarians, who are sought by farmers when their animals are ill. Para-veterinarians are permitted to diagnose diseases, but only licensed veterinarians can prescribe antibiotics. Antibiotics should be prescribed from an essential medicines list that contains broad- and narrow-spectrum agents [152]. As with human pharmacies, animal pharmacies must be licensed and are expected to be inspected annually [153]. Farmers pay for medicines and the services of veterinarians, and they are required to maintain records of all drugs that they administer to their animals [153].

1.3.4.2 Policies and regulations on antibiotic use in agriculture

The earliest regulations on uses of antibiotics in agriculture focussed on counterfeit drugs and the potential risks of drug residues in meat products [134]. More recent regulations have addressed antibiotic resistance, such as the 2014 "Catalogue of veterinary prescription drugs" [152], in which 11 classes of antimicrobials that have high rates of resistance and are important in human healthcare were classified as prescription-only medicines. Some antibiotic agents have been completely banned for use in agriculture [154]. In 2015, a Five-Year National Action Plan of Comprehensive Management for Veterinary Medicines was launched [134]. This included targets such as improving the monitoring of antibiotic consumption, halving the numbers of antimicrobial prescriptions in agriculture, and educating veterinarians and farmers about responsible antibiotic use.

1.3.5 Collaborations between Sweden and China on antibiotic resistance

Sweden has long promoted antibiotic resistance on the international political agenda and has provided substantial funding for international research projects to address antibiotic resistance. These efforts recognise that antibiotic resistance is a problem that cannot be managed within a single country, and that some of the successes in tackling antibiotic resistance in Sweden may be relevant for other settings.

In 2006, a Memorandum of Understanding was formed between the Chinese and Swedish governments on several areas within the health sector. In 2010, the Chinese and Swedish health ministers signed a Plan of Action emphasising cooperation on antibiotic resistance. In 2012, the Ministry of Agriculture of China and the Ministry for Rural Affairs in Sweden signed a Memorandum of Understanding on agriculture cooperation, which again emphasised cooperation on antibiotic resistance [155]. Along with these actions, Chinese and Swedish researchers have worked together on several research projects to investigate antibiotic use and resistance in China [80,114,156].

The studies in this thesis all take place in the context of these collaborative efforts, supported by funding from the National Natural Science Foundation of China, the Swedish International Development Cooperation Agency, and the Swedish Research Council. Microbiological studies within the same research programmes have identified very high levels of resistant bacteria, in particular ESBL- and carbapenemase-producing *Enterobacteriaceae*, among healthy humans [156], healthy animals [157,158] and environmental sources [159,160] in rural Shandong province. The papers in this thesis complement these investigations by providing insights into the patterns of antibiotic use for humans and on backyard pig farms in the same study sites, as well as their determinants.

2 AIM

The overall aim was to assess how antibiotics are being used for humans and on backyard pig farms in a rural region in China. This included individual antibiotic use practices, as well as the broader knowledge, attitudes and practices that shape how antibiotics are used.

2.1 RESEARCH QUESTIONS

1. Are doctors prescribing antibiotics responsibly (**Papers I and II**), and are rural residents (**Paper III**) and backyard pig farmers (**Paper IV**) using antibiotics responsibly?

2. Is there significant variation in the antibiotic prescribing practices of doctors? (**Papers I and II**)

3. What are the knowledge and attitudes of doctors (**Paper I**), rural residents (**Paper III**) and backyard pig farmers (**Paper IV**) concerning antibiotic use and resistance?

4. Are there differences between backyard pig farmers and other rural residents in terms of knowledge, attitudes and practices concerning antibiotic use? (**Paper III**)

3 METHODS

3.1 STUDY SETTING: SHANDONG PROVINCE, CHINA

All studies were conducted in Shandong province, located in eastern China (Figure 4). In 2018, Shandong province had a population of 100 million living in over 100 counties, approximately half of which are rural [131]. It is known as 'the stockbreeding province without a prairie' and it is the second largest province in China by population and the third largest by GDP. Agriculture is the main economic activity in the rural areas of Shandong province, and the total production of meat in 2015 was 12.5 million tonnes, including poultry (4.6 million tonnes), pork (3.8 million tonnes) and beef (146,000 tonnes) [161]. The economic, education and health indicators of rural areas in Shandong province are generally similar to other rural areas in eastern China [131,162], and it is commonly used to represent this region in studies [66,150,163].

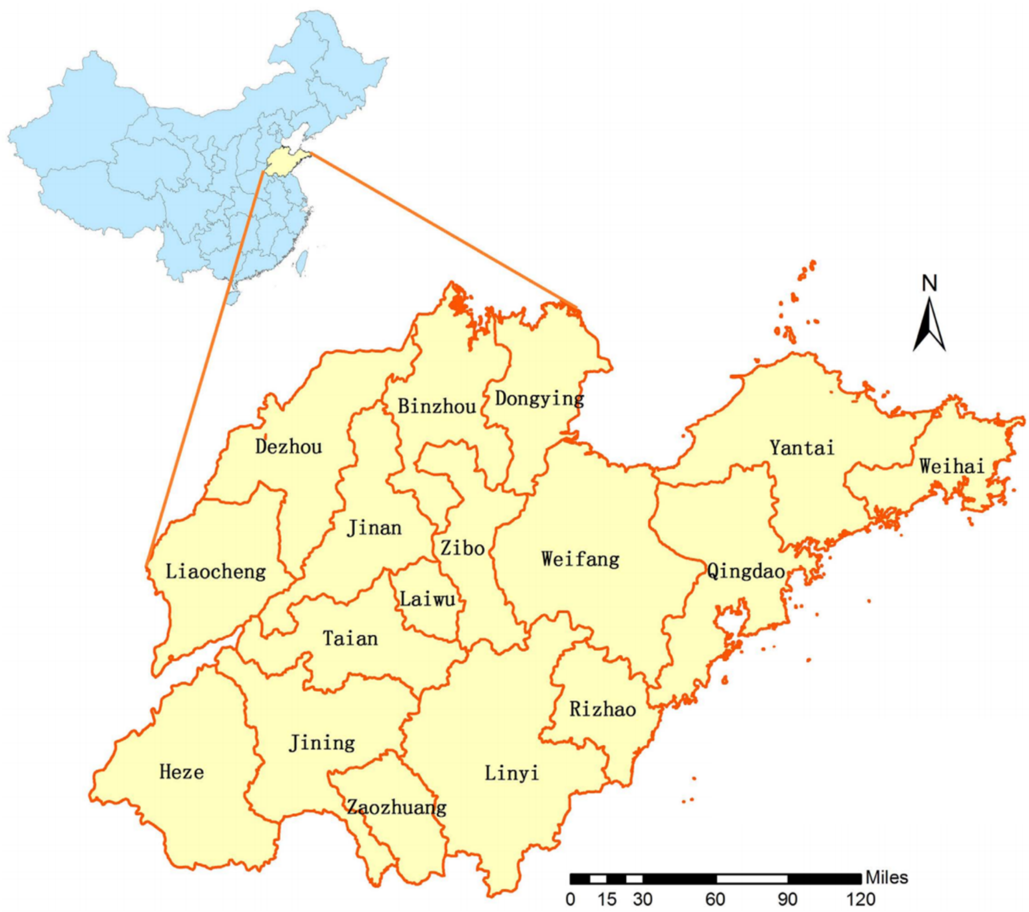


Figure 4. Shandong province (adapted from [164])

3.2 OVERVIEW OF STUDIES

Table 3 includes an overview of the studies included in the thesis.

Table 3. Overview of studies and their methods

Paper	Topic	Study design	Study population and data	Study period	Data analyses
I	• Antibiotic prescribing rates for common colds • Doctors' knowledge and attitudes towards antibiotic use	• Retrospective observational • Cross-sectional survey	• 8,400 outpatient prescriptions from 30 healthcare facilities • 188 doctors working at healthcare facilities	September – October 2012	• Frequencies • Chi-squared tests
II	Variations in antibiotic prescribing among village doctors	Prospective observational	• 14,471 outpatient prescriptions from eight village clinics	January 2015 – June 2017	• Frequencies • Kruskal-Wallis H-test • Mann-Whitney U-tests • Pearson correlation
III	Rural residents' knowledge, attitudes and practices concerning antibiotic use and resistance	Cross-sectional survey	• 769 adult rural residents • Medicines stored in households for humans	July 2015	• Frequencies • Chi-squared tests • Multivariable logistic regression
IV	Backyard pig farmers' knowledge, attitudes and practices concerning antibiotic use in pigs	Cross-sectional survey	• 271 adult rural residents with backyard pig farms • Medicines stored in backyard farms for pigs	July 2015	• Frequencies • Chi-squared tests • Univariate logistic regression

3.2.1 Study sites

Paper I was conducted at healthcare facilities in three counties that had around 2.5 million inhabitants in 2012. These counties were selected based on geographic location and feasibility of the study, and to be representative of rural Shandong province. In each county, one county hospital, three township health centres and six village clinics were included (Figure 5).

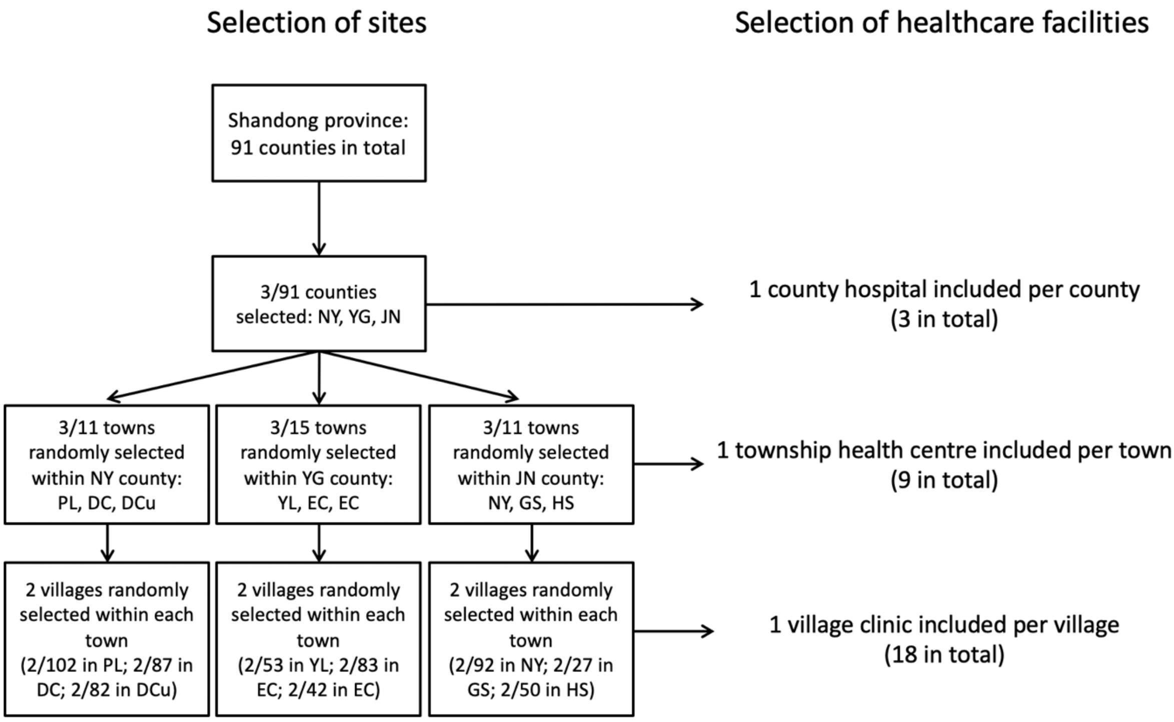


Figure 5. Selection of sites and healthcare facilities for Paper I (adapted from [116])

Papers II, III and IV were conducted in villages around a single town in one county, as part of the baseline data collection for a large interdisciplinary research programme called the Sino-Swedish integrated multi-sectoral partnership for antibiotic resistance containment (IMPACT) [161]. The study area was pragmatically selected based on the presence of local infrastructural support needed to coordinate all parts of the research programme (including baseline assessment; a pilot package of interventions delivered over a one-year period; and repeated data collection), and on the area being broadly representative of rural Shandong province. **Papers III and IV** took place in twelve villages located around the central town. These twelve villages were selected from seventeen possible villages using background data collected by the local Center for Disease Control and Prevention (CDC) so as to maximise: (i) the number of included backyard pig farms; and (ii) villages that had human healthcare clinics. The twelve villages contained between 100 and 350 households, of which 10-20% had backyard pig farms (similar to the national average [150]). **Paper II** took place in the eight village clinics that served these twelve villages, with some of the clinics being shared between villages.

3.2.2 Study design and data collection

Paper I included a cross-sectional survey of 188 doctors working at the thirty selected healthcare facilities in October 2012, and an analysis of outpatient prescriptions sampled from the same facilities over the preceding month. The questionnaire concerned knowledge and attitudes towards antibiotic prescribing, particularly in the context of patients with the common cold, and it was developed jointly between collaborators in Sweden and China. All doctors working at the selected village clinics and township health centres, and at the county hospitals in the departments of internal medicine, surgery, paediatrics and obstetrics & gynaecology, were invited to participate.

All available outpatient prescriptions were collected from the selected township health centres and village clinics for the month of September 2012. There was a much higher number of prescriptions at the county hospitals, so a systematic random sampling method was used to generate a maximum of 200 sample outpatient prescriptions from each department. Each prescription included the patient's name, sex, age, diagnosis, medicines prescribed and their costs. The name of the prescriber was not collected for individual prescriptions.

Data collection was carried out by ten master's programme students and researchers from the Center for Health Management and Policy at Shandong University.

Paper II was a prospective observational study in which 14,471 prescriptions were sampled over a 2.5 year period from the eight village clinics. The prescriptions of all village clinics in the study region are included in an e-prescription system that records the patient's name, sex, age, date of visit, diagnosis, medicines prescribed, total cost for the visit, and the name of the doctor. For each village clinic a target of 60 prescriptions per month (from an average total of around 300) were collected using a random sampling method in which every fifth consecutive prescription was selected, beginning with a randomly generated number between 1 and 10. The prescription details were exported individually from the e-prescription system in XPS format and entered into a Microsoft Excel database. In addition, in July 2015 the village doctors working at the clinics completed a short questionnaire concerning their socio-demographic information (gender, age, years of medical practice).

Papers III and IV were cross-sectional questionnaire surveys among adult rural residents living in the twelve villages included in the IMPACT research programme. The background data collected by the CDC was used to select individual households to invite to join the study, using a multistage sampling procedure: first, in each village up to 35 households with backyard pig farms (defined as containing at least one, but not more than 49 pigs) were randomly selected; if a village had fewer than 35 household backyard pig farms, all were selected. Second, the remaining number of households needed to produce a total of 65 households per village were selected from all households without backyard pig farms, using a matched sampling method based on the number of household residents.

The questionnaires were developed by experts in clinical medicine, public health, animal health and rural Chinese healthcare systems. Insights gained from four focus group discussions held in other villages in the study region earlier in 2015 were also used. The questionnaire (Appendix 1) included 95 items, including socio-demographics; health status; and knowledge, attitudes and practices towards antibiotic use and antibiotic resistance. Of the 769 rural residents who participated in the questionnaire (**Paper III**), 271 had pigs in a backyard pig farm at the time of the study. These respondents were asked additional questions about their knowledge, attitudes and practices towards antibiotic use in their pigs (**Paper IV**). In addition, respondents were asked to show data collectors which medicines they were storing in their households for use in humans and in pigs (**Paper III and IV**). For each medicine observed, the data collectors recorded the name and whether the respondent thought it was an antibiotic. The questionnaires were developed in English, translated into Mandarin Chinese, piloted in ten households, revised, and back-translated into English.

Households were visited in July 2015, and one resident per household was interviewed by a data collector. For households with backyard pig farms, the person who worked most closely with the pigs was prioritised to be invited. The data collectors were all students studying human or animal healthcare courses at master's level at local collaborating universities and they attended a training day on interviewing skills, which included practising using the questionnaire tool. The questionnaire data were double-entered in Microsoft Access in simplified Chinese, translated into English, and exported into a Microsoft Excel database.

3.2.3 Data management and analyses

*Coding of prescribed medicines (**Papers I and II**) and stored medicines (**Papers III and IV**)*

All antibiotics were coded according to the Anatomical Therapeutic Chemical (ATC) classification system [165] or ATCvet [166], and categorised by class and substance. In **Papers II-IV**, other types of medicine were also coded into single high-level categories: anti-inflammatories and analgesic medicines; traditional Chinese medicines; anti-parasitics; and other medicines (i.e. medicines that could not be identified or that did not belong to any of the other categories).

*Coding of diagnoses (**Papers I and II**)*

For **Paper I**, all prescriptions containing a single diagnosis of "Gan mao" (common cold) were identified and included in further analyses. For **Paper II**, all unique diagnoses were translated from Chinese into English and coded where possible according to the International Classification of Diseases, 10th Revision (ICD-10) by an independent researcher. A category of *likely viral acute upper respiratory tract infections (AURI)* was created by grouping two diagnoses: J00 (acute nasopharyngitis [common cold]) and J06.9 (acute upper respiratory infection, unspecified).

*Grouping of prescribers and prescriptions (**Papers I and II**)*

For **Paper I**, comparisons were predominantly made between the different levels of healthcare facility (i.e. village clinic, township health centre and county hospital). For **Paper II**, both aggregate and individual prescriber-level analyses were conducted. The prescriber-level analyses were limited to doctors with ≥50 prescriptions containing a diagnosis of likely viral AURI during the study period. An error was identified in the coding of one of the doctors responsible for prescriptions at village clinic 1, so all 433 prescriptions from this clinic were excluded from the prescriber-level analyses.

*Grouping of rural residents (**Papers III and IV**)*

For **Paper III**, participants were divided into two groups to assess the impact of experience with backyard pig farms on knowledge, attitudes and practices concerning antibiotic use in humans: "Backyard pig farmers" was used to collectively refer to the 330 participants who either had a backyard pig farm at the time of the study (271 participants) or within the previous five years (59 participants). The 439 "Other residents" were considered to not have any recent experience of backyard pig farming. Since **Paper IV** focused on respondents' current practices in their backyard pig farms, it only included the 271 participants that had pigs at the time of study.

3.2.3.1 Statistical analyses

Analyses were conducted in Excel, SPSS, Stata and R. All studies include descriptive analyses, such as frequencies and percentages for categorical variables, and mean and standard deviations for continuous variables. All statistical tests were two-tailed and were considered statistically significant if $p < 0.05$.

For Paper I, categorical data were compared using chi-square tests, with comparisons made against village clinics.

For Paper II, antibiotic prescribing patterns were analysed for village doctors using three indicators:

a) antibiotic prescribing rate (APR) = number of prescriptions including at least one antibiotic / total number of prescriptions X 100%

b) multiple antibiotics prescribing rate (MPR) = number of prescriptions including at least two antibiotics with different ATC codes / total number of prescriptions including at least one antibiotic X 100%

c) parenteral antibiotics prescribing rate (PAPR) = number of prescriptions including at least one parenteral antibiotic / total number of prescriptions including at least one antibiotic X 100%

The Kruskal-Wallis H-test was used to assess whether there were statistically significant variations between the individual doctors in terms of antibiotic prescribing rates for likely viral AURIs [119]. Pairwise Mann-Whitney U-tests were used post-hoc to assess for differences in all pairwise comparisons between doctors, using the Benjamini-Hochberg procedure [167] to control the false discovery rate for multiple comparisons. Comparisons were also made against antibiotic prescribing quality indicators developed in Europe [168] for a subset of clinical diagnoses and patient age groups.

For Paper III, a multivariable logistic regression model was used to identify socio-demographic factors associated with knowing what antibiotics are, and with correctly identifying antibiotics from a list of medicines.

For Paper IV, adjusted odds ratios were calculated to identify factors associated with household storage of at least one antibiotic for use in pigs. Independent variables included socio-demographic and farm characteristics, as well as knowledge, attitudes and practices towards antibiotic use in pigs. Adjustments were made for the sex, age and education level of respondent, but there was no attempt to adjust for clustering at the village level.

4 ETHICAL CONSIDERATIONS

Ethical approval was obtained for **Paper I** from the School of Public Health, Shandong University, China (permit number 20111202). Ethical approval was obtained for **Papers II-IV** from the first Affiliated Hospital, College of Medicine, Zhejiang University, China (reference numbers 2015#185 and 2015#283).

Individual participation in all studies was voluntary, and informed consent was obtained from participants immediately prior to their responding to questionnaires. Consent was given in writing if possible (otherwise verbally), and participants were made aware that they could withdraw at any point without negative consequences.

The following are reflections according to four common medical ethical principles [169].

Doing good
A central purpose of the studies in this thesis is to develop an understanding of the local context of antibiotic use and its determinants in order to design interventions to improve how antibiotics are used. It is possible that our educational interventions will help the study participants to improve certain practices (e.g. hand washing) which could reduce the incidence of infectious diseases and spread of resistant bacteria, thereby directly benefiting them. If these pilot interventions are successful, they may be scaled up throughout other areas in rural China.

Do no harm
Our studies are unlikely to have caused significant harm to participants, but there will have been some costs from participating. For example, rural residents spent approximately one hour answering the questionnaires in **Papers III and IV**, which meant that they could not work during this time. The majority of participants were farmers who looked after their own animals and vegetables, so most are unlikely to have directly lost income through participating. All participants were given a small gift (washing powder).

Some of the questions in the surveys in **Papers III and IV** asked for sensitive information, such as income, recent illnesses, and household storage of medicines. Similarly, the prescriptions collected from healthcare facilities in **Papers I and II** included doctors' names, patients' names, and clinical diagnoses. We informed participants that data would be stored confidentially and that there would be no judgments or consequences for them based on their individual responses. We strove to maintain confidentiality by replacing names with codes in the databases to de-identify individual participants, and further by limiting the sharing of data files. Only anonymised data were analysed in Sweden.

Respect autonomy
The studies included in this thesis may have impacted on the autonomy of individuals, in particular in the broader context of the research programme in which they were situated. After the baseline data collection presented in **Papers III and IV**, half of the participants were allocated to the intervention group for a pilot package of interventions to improve antibiotic use and hygiene practices. These interventions required a time investment from the individuals, for example, attending quarterly presentations at a village clinic and reading a booklet. Participation was voluntary for all intervention components, but there is cultural pressure placed on individuals to participate, and this explains why response rates in Chinese

studies (and other Asian countries) are often extremely high. For example, the participants were invited to join the study by an administrator in the village, and this person was “higher” in the social hierarchy than they are, so it could have been hard for them to decline. To address this, we routinely emphasised during data collection that participation was voluntary and that participants could withdraw without negative consequences.

Justice

We used scientific objectives to determine which healthcare facilities and individuals would be selected for our studies, and these objectives were articulated in the publications resulting from the research. For example, in **Papers III and IV** we purposefully over-sampled rural residents in the study villages who had backyard pig farms, in order to assess differences in the knowledge, attitudes and practices concerning antibiotics between residents with and without backyard pig farms, and in order to include a sufficient number of households with backyard pig farms for the pilot interventions. Overall, our research findings are intended to be of benefit for all rural residents, not any particular privileged groups.

5 MAIN FINDINGS

5.1 ANTIBIOTIC PRESCRIBING AT HEALTHCARE FACILITIES

5.1.1 What are the characteristics of the doctors who work at the healthcare facilities?

Table 4 summarises the sex, age and work experiences of the doctors who replied to the questionnaire in **Paper I,** and who worked at the village clinics where prescriptions were sampled in **Paper II**. A bachelor's degree was held by 77% of the doctors working at the county hospitals, 33% of the doctors at the township health centres, and 0% of the village doctors at village clinics in **Paper I**. Seventeen per cent of the village doctors had a junior high school education and 83% had a senior high school education at the village clinics included in **Paper II**.

Table 4. Sex, age and working experiences of doctors at selected healthcare facilities

	Paper I			Paper II
	County hospital	**Township health centre**	**Village clinic**	**Village clinic**
No. of doctors	60	98	30	23
Male (n (%))	26 (43)	49 (50)	22 (73)	19 (83)
Mean age (years)	35	36	48	52
Mean work experience (years)	11	14	26	32

5.1.2 What conditions are doctors prescribing antibiotics for?

Overall, 40.3% of prescriptions (5833/14471) from village clinics in **Paper II** contained one or more antibiotics. Respiratory tract infections accounted for 68.4% (3991/5833) and gastrointestinal conditions for 14.0% (815/5833) of all prescriptions containing at least one antibiotic (Table 5). A total of 5,177 prescriptions were categorised as *likely viral acute upper respiratory tract infections*, and 62.5% (3237/5177) of these prescriptions contained at least one antibiotic, accounting for 55.5% (3237/5833) of all antibiotic-containing prescriptions.

Table 5. Infection-related diagnoses and antibiotic prescription rates at village clinics in Paper II

Body system (No. of prescriptions)	Diagnosis	ICD-10 code	Antibiotic prescribing rate n/N	%
Respiratory (6183)	Acute nasopharyngitis [common cold][+]	J00	3034/4938	61.4
	Bronchitis*	J40	408/522	78.2
	Acute upper respiratory infection[+]	J06.9	203/239	84.9
	Acute pharyngitis	J02.9	160/190	84.2
	Acute tonsillitis	J03.9	68/73	93.2
	Rhinitis*	NA	31/67	46.3
	Cough	NA	23/65	35.4
	Pneumonia	J18	40/51	78.4
	Bronchopneumonia	J18.0	15/19	78.9
	Acute laryngopharyngitis	J06.0	8/14	57.1
Gastrointestinal (1642)	Gastritis	K29.7	258/856	30.1
	Gastroenteritis	A09	496/717	69.2
	Diarrhoea	NA	61/69	88.4
Dental (222)	Chronic periodontitis	K05.3	100/131	76.3
	Gingivitis and periodontal diseases	K05	61/72	84.7
	Pulpitis	K04.0	19/19	100.0
Urogenital (84)	Inflammatory disease of prostate	N41.9	23/45	51.1
	Urethritis and urethral syndrome	N34	23/24	95.8
	Urinary tract infection	N39.0	15/15	100.0
Eye (101)	Conjunctivitis	H10	9/101	8.9
Ear (11)	Otitis media	H66.9	7/11	63.6

Footnote: *Not specified as acute or chronic; [+]Categorised as *likely viral acute upper respiratory tract infections*; NA = no ICD-10 code allocated

Nineteen percent of prescriptions (1590/8400) collected at the healthcare facilities in **Paper I** contained a single diagnosis of common cold. Over half of these common cold prescriptions (55%, 869/1590) included at least one antibiotic. Table 6 summarises the antibiotic prescribing rates for the common cold across healthcare facilities in **Paper I** and at village clinics for likely viral AURIs in **Paper II**.

Table 6. Antibiotic prescribing rates at selected healthcare facilities for common cold (Paper I) and likely viral acute upper respiratory tract infections (Paper II)

	Paper I				**Paper II**
	CH	**THC**	**VC**	**Total**	**VC**
Total no. of prescriptions sampled at facilities	1303	4799	2298	8400	14471
Prescriptions for common cold or likely viral AURI (n (%))	122 (9)	839 (17)	629 (17)	1590 (19)	5177 (36)
Antibiotic prescribing rate for common cold or likely viral AURI (n (%))	57 (47)	366 (44)	446 (71)	869 (55)	3237 (63)

Footnote: CH = County hospital; THC = Township health centre; VC = Village clinic; AURI = acute upper respiratory tract infections

5.1.3 Which antibiotics are being prescribed for AURIs?

Similar classes of antibiotics were prescribed for common colds at the healthcare facilities in **Papers I** and for likely viral AURIs at village clinics in **Paper II** (Table 7), with the three most common classes being identical (J01D Other beta-lactam antibacterials; J01F Macrolides, lincosamides and streptogramins, J01C Beta-lactam antibacterials, penicillins). The mean number of antibiotics on antibiotic-containing prescriptions for common cold diagnoses at healthcare facilities in **Paper I** was 1.12, and the mean number for likely viral AURI diagnoses at village clinics in **Paper II** was 1.18. A quarter of the prescriptions for likely viral AURI diagnoses in **Paper II** included at least one parenteral antibiotic (24.3%, 785/3237).

Table 7. Antibiotic classes prescribed at selected healthcare facilities for common cold (Paper I) and likely viral acute upper respiratory tract infections (Paper II)

	Paper I				**Paper II**
	CH (n (%))	**THC (n (%))**	**VC (n (%))**	**Total (n (%))**	**VC (n (%))**
J01D Other beta-lactam antibacterials	22 (38)	156 (37)	210 (43)	388 (40)	1130 (30)
J01F Macrolides, lincosamides and streptogramins	31 (53)	158 (37)	145 (29)	334 (34)	859 (22)
J01C Beta-lactam antibacterials, penicillins	3 (5)	76 (18)	77 (16)	156 (16)	1153 (30)
J01M Quinolone antibacterials	1 (2)	14 (3)	30 (6)	45 (5)	443 (12)
J01X Other antibacterials	1 (2)	18 (4)	18 (4)	37 (4)	63 (2)
J01E Sulfonamides and trimethoprim	0 (0)	3 (1)	6 (1)	9 (1)	1 (0)
J01G Aminoglycoside antibacterials	0 (0)	1 (0)	7 (1)	8 (1)	166 (4)
J01A Tetracyclines	0 (0)	1 (0)	0 (0)	1 (0)	3 (0)

Footnote: CH = County hospital; THC = Township health centre; VC = Village clinic

5.1.4 How does the antibiotic prescribing compare with quality indicators?

We compared antibiotic prescribing patterns for selected respiratory tract infections at the village clinics in **Paper II** against published European quality indicators [168] for outpatient antibiotic prescriptions (Table 8), and found that each indicator lay outside of the recommended range.

Table 8. Antibiotic prescribing quality indicators for selected respiratory tract infections

Diagnosis	Patient age (years)	APR n/N, (%)	Antibiotic class prescribed		
			J01M n/N, (%)	J01CE n/N, (%)	J01AA or J01CA n/N, (%)
AURI	≥2	3236/5172, (62.6)	436/3236, (13.5)	49/3236, (1.5)	NA
Target		*0-20%*	*0-5%*	*80-100%*	
Tonsillitis	≥2	68/73, (93.2)	15/68, (22.1)	2/68, (2.9)	NA
Target		*0-20%*	*0-5%*	*80-100%*	
Pneumonia	18-65	22/30, (73.3)	11/22, (50.0)	NA	2/22, (12.8)
Target		*90-100%*	*0-5%*		*80-100%*

Footnote: Target ranges and categorisation of diagnoses is as previously published [168]; NA = no target set; APR = Antibiotic prescribing rate; AURI = Acute upper respiratory tract infection; J01M is the ATC code for Quinolone antibacterials, J01CE is the ATC code for Beta-lactamase sensitive penicillins, J01AA is the ATC code for Tetracyclines, J01CA is the ATC code for Penicillins with extended spectrum

5.1.5 Is there significant variation between doctors?

In **Paper I** we found that prescriptions with a diagnosis of the common cold were more likely to contain an antibiotic if they were from a village clinic than if they were from a township health centre or county hospital (71% vs. 44% and 47%, both $p < 0.001$).

In **Paper II** we analysed individual village doctors' prescribing patterns. We found that individual antibiotic prescribing rates for likely viral AURIs were relatively stable during the study period (i.e. highly correlated between 2015 and 2016 [$r = 0.646$]), but that there was widespread variation between prescribers (Figure 6). For likely viral AURIs, village doctors' APRs ranged from 33% to 88%, multiple antibiotics prescribing rate (MPR) from 1% to 60%, and parenteral antibiotics prescribing rate (PAPR) from 3% to 62%. Village doctors' APRs were positively correlated with their MPRs ($r = 0.472$, $p = 0.048$) and PAPRs ($r = 0.544$, $p = 0.02$).

The Kruskal-Wallis H-test showed that the variations in antibiotic prescribing rates for likely viral AURIs were statistically significant among the 18 prescribers ($\chi^2 = 426$, df = 17, $p < 0.001$). Pairwise Mann–Whitney U-tests were used as post-hoc tests to assess for differences in all possible pairwise comparisons between prescribers. This involved 153 pairs of prescribers, and the difference was statistically significant in 93 of these.

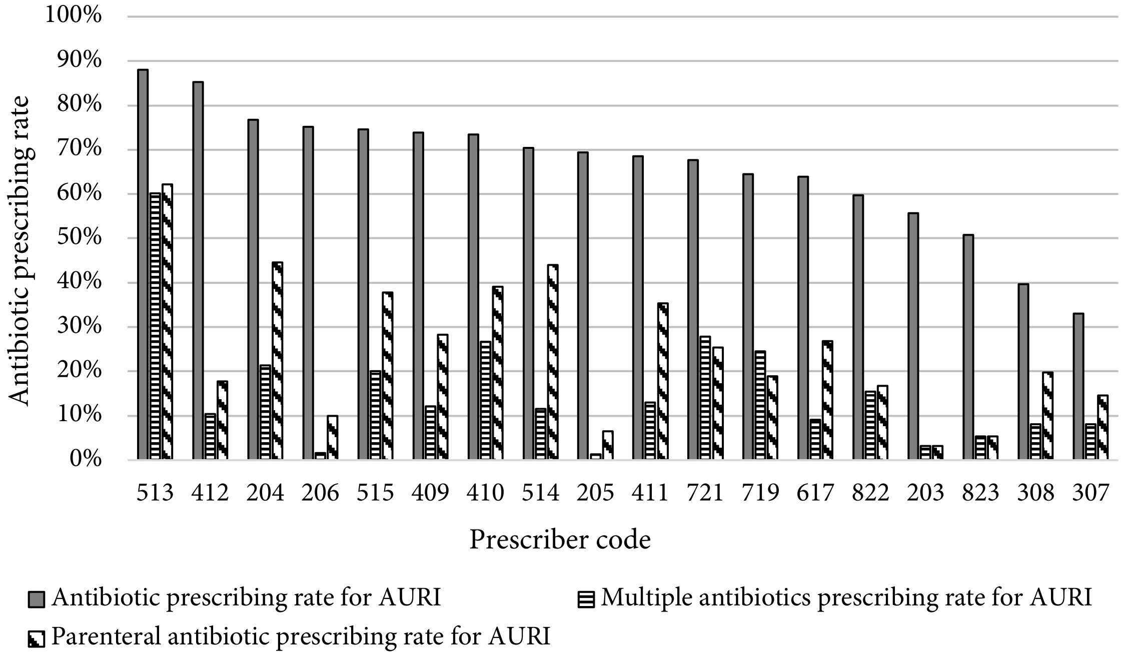


Figure 6. Antibiotic prescribing rates for likely viral AURIs for individual doctors

The village doctors each used between 11 and 21 different antibiotic agents for patients with diagnoses of likely viral AURIs. Amoxicillin was the most commonly prescribed agent for 13/18 doctors; the most commonly prescribed agents for the remaining doctors included levofloxacin (two doctors), amikacin (one doctor), lincomycin (one doctor) and azithromycin (one doctor). For each doctor, their three most commonly prescribed antibiotic agents accounted for a mean of 64% (range 45% to 86%) of all the antibiotics they prescribed for likely viral AURIs.

The village doctors also varied in the frequency with which they used other types of medicine for the patients that they diagnosed with likely viral AURIs (Figure 7). The most common choice was to use only an antibiotic (14/18 doctors); the four remaining doctors most commonly chose to use only analgesic or anti-inflammatory medicines.

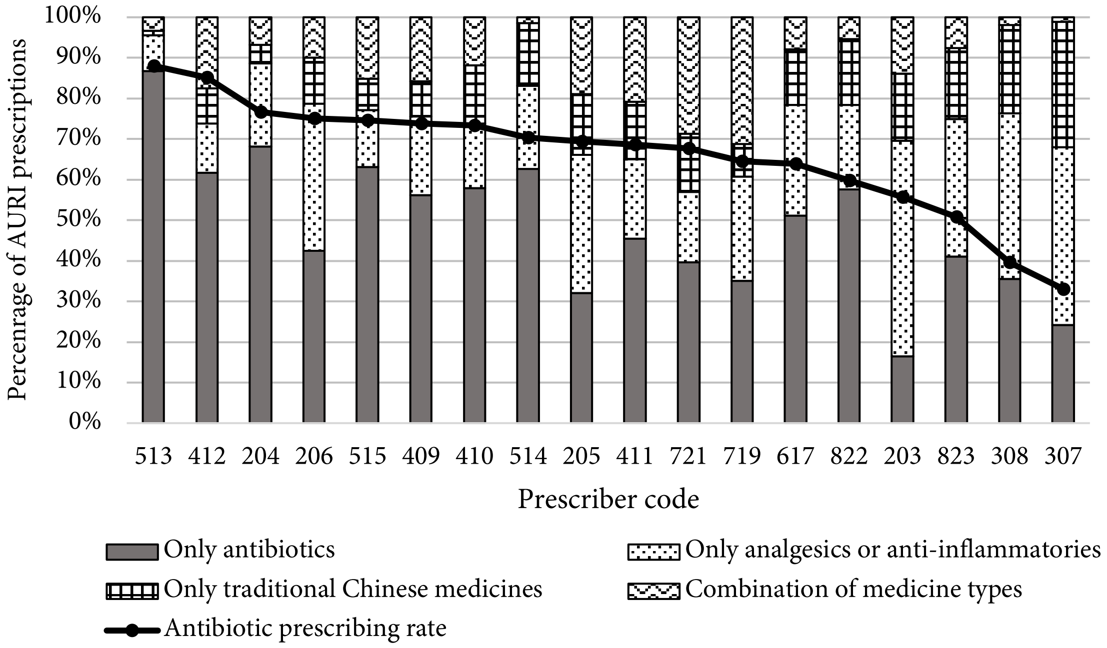


Figure 7. Prescribing of different medicine types for likely viral AURIs

We further compared selected indicators between the four village doctors with the highest (doctors 513, 412, 204 and 206) and lowest (doctors 203, 823, 308, 307) antibiotic prescribing rates for likely viral AURIs (Table 9).

Table 9. Comparisons between high and low antibiotic prescriber groups

Indicator	**High APR group (%)**	**Low APR group (%)**	**p-value**
Mean APR for likely viral AURIs	81.3	44.8	<0.001
Mean MPR for likely viral AURIs	23.4	6.2	<0.001
Mean PAPR for likely viral AURIs	33.6	10.7	<0.001
Mean prescribing rate of only antibiotics for likely viral AURIs	40.6	18.3	<0.001
Mean prescribing rate of only analgesics or anti-inflammatory medicines for likely viral AURIs	10.6	26.2	<0.001
Mean APR for AURI with potential bacterial causes*#	89.1	72.4	0.001
Mean APR for gastritis, gastroenteritis and diarrhoea#	85.0	68.3	0.002

Footnote: The high APR group contained the four village doctors with the highest antibiotic prescribing rates for likely viral AURIs, and the low APR group contained the four doctors with the lowest antibiotic prescribing rates for likely viral AURIs; APR = Antibiotic prescribing rate; MPR = Multiple antibiotics prescribing rate; PAPR = Parenteral antibiotics prescribing rate; *AURI with potential bacterial causes = prescriptions with a upper respiratory tract infection diagnosis of pharyngitis, tonsillitis or laryngopharyngitis; #These comparisons were restricted to village doctors in each group who had at least ten prescriptions containing a relevant diagnosis

5.1.6 What are the knowledge and attitudes of doctors concerning antibiotic use?

We examined the knowledge and attitudes concerning antibiotic use of doctors working at different healthcare facilities in **Paper I**. Most doctors did not think that newer antibiotics are more effective than older ones (98%, 182/186), nor that broad-spectrum antibiotics are more effective than narrow-spectrum ones (87%, 156/179). For patients with symptoms of the common cold, most doctors reported that that they would recommend drinking water and rest (80%, 150/187). Many doctors reported they would use analgesics, antipyretics or antivirals (67%, 126/187) whereas extremely few stated that they would prescribe antibiotics (2%, 3/187), and the majority reported that they would still not prescribe antibiotics if a patient insisted on receiving them (87%, 156/179). There were no major differences between doctors depending on the type of healthcare facility at which they worked.

Most doctors (83%, 149/180) reported having participated in some training on antibiotic use since starting to work as a doctor. This was within the previous three years for almost all (97%, 112/116) of those who could provide dates for the training. Doctors who had attended training were less likely to report that they would give antibiotics to a patient with symptoms of the common cold who was demanding them (29% vs. 14%, $p < 0.001$).

5.2 SURVEYS AMONG RURAL RESIDENTS AND BACKYARD FARMERS

5.2.1 What are the respondents' socio-demographic characteristics?

A total of 769 rural residents completed the questionnaire in **Paper III**, of whom 271 had backyard pig farms at the time and so also answered questions on antibiotic use in pigs (**Paper IV**). A further 59 of the 769 respondents had had a backyard pig farm within the previous 5 years and so were considered to be "backyard pig farmers" when assessing the impact of backyard pig farming experience on knowledge, attitudes and practices towards antibiotic use.

Table 10 summarises the socio-demographics of all respondents. The median age of the respondents was 54 years and the median number of household occupants was two. Backyard pig farmers were slightly younger on average than other residents and were more likely to have attended middle school. The median annual household income was 20,000 RMB (5,600 Intl$), with an interquartile range of 8,000 to 30,000 RMB (2,200 to 8,400 Intl$).

The median number of pigs in the backyard pig farms was 14. There were 29 households with more than 49 pigs at the time of the study, and responses from these households were included in all analyses. The backyard pig farmers had been raising pigs for a mean duration of 11 years. Eighteen percent (49/271) reported that they had had training about raising pigs, including from relatives, neighbours or friends (8%, 21/271), professional courses (7%, 20/271), or a mixture of the two (3%, 8/271).

Table 10. Socio-demographics of rural residents (Papers III and IV)

Respondent socio-demographics (N = 769)		**n**	**%**
Sex	Male	450	59
Age	≤54 years old	407	53
Residents in household	Two or fewer residents	390	51
Children in household	One or more children under 5 years old	70	9
Duration of formal education	0-6 years	435	57
	7-9 years	261	34
	≥10 years	80	10
Current occupation	Household animal farmer	329	43
	Household farmer (not animals)	351	46
	Other	89	12
Backyard pig farm characteristics (N= 271)			
Number of pigs	≤14 pigs	140	52
Type of pigs raised	A) Sows, with piglets raised to slaughter	164	61
	B) Sows, with piglets that are sold after weaning	40	15
	C) A mixture of A) and B)	42	15
	D) Piglets that are bought and raised to slaughter	16	6
	E) Other	9	3

5.2.2 What are rural residents' knowledge and attitudes towards antibiotic use in humans?

The majority of participants (70%, 542/769) stated that they did not know what antibiotics are, and a similar proportion (63%, 487/769) could not identify a single antibiotic from a list of commonly used medicines. In univariable analyses, backyard pig farmers were more likely to know what antibiotics are than other rural residents (36% vs. 25%, $p < 0.001$), and to identify at least two antibiotics on the medicines list (31% vs. 21%, $p < 0.01$). In multivariable analysis, respondents were more likely to report knowing what antibiotics are if they were male, under 54 years old or had higher levels of education (Table 11).

Table 11. Socio-demographic factors associated with reporting knowing what antibiotics are in multivariable logistic regression

Factor		OR (95% CI)	p-value
Sex	Male	2.56 (1.74 – 3.81)	0.001
Age	≤54 years old	3.04 (2.08 – 4.47)	<0.001
Duration of formal education	0-6 years	1 (Reference)	<0.001
	7-9 years	1.20 (0.70 – 2.04)	0.51
	≥10 years	3.55 (2.05 – 6.17)	<0.001
Backyard pig farm now or in past five years	Yes	1.39 (0.98 – 1.97)	0.06

Footnote: OR = odds ratio

Participants were asked how often they thought antibiotics are needed for certain common conditions in humans. Differences existed between backyard pig farmers and other residents (Table 11). Residents with higher education levels and higher household incomes were more likely to correctly think that antibiotics are less often or never needed for the common cold (Figure 8).

Table 11. Perceived needs for antibiotics for common conditions in humans

Conditions	Always or usually needs antibiotics: Backyard pig farmers N=330 (n (%))	Always or usually needs antibiotics: Other residents N = 439 (n (%))	p-value
Common cold	99 (30)	105 (24)	0.09
Sore throat	102 (31)	101 (23)	0.02
Pneumonia	106 (32)	92 (21)	<0.001
Urinary tract infection	86 (26)	70 (16)	0.001
Hypertension	20 (6)	26 (6)	1.0
Diabetes	20 (6)	18 (4)	0.28

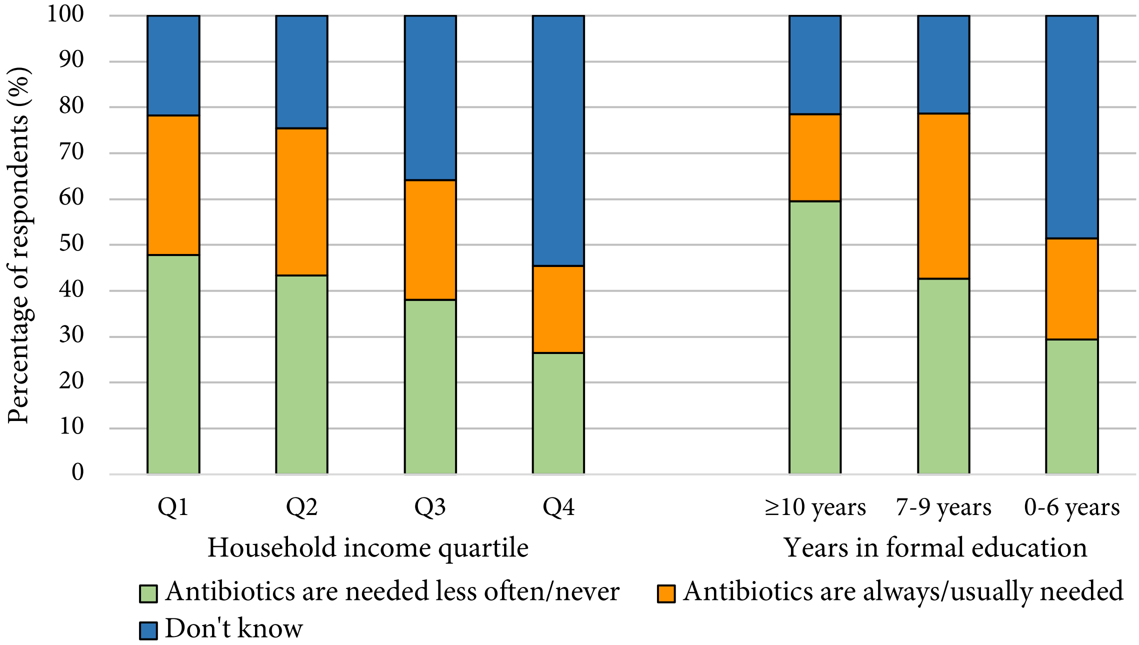


Figure 8. Variations between education and income quartile groups in how often antibiotics are perceived to be needed for the common cold

Footnote: Q1 = >30,000 RMB/year; Q2 = 20,001 to 30,000 RMB/year; Q3 = 8,001 to 20,000 RMB/year; Q4 = ≤8,000 RMB/year

5.2.3 What are backyard pig farmers' knowledge and attitudes towards antibiotic use in pigs?

Backyard pig farmers were asked to suggest up to two pig diseases that they thought should normally be treated with antibiotics. Thirty percent of participants (80/271) provided suggestions. The most common answers were diarrhoea (75%, 60/80) and respiratory tract infections (29%, 23/80). Other responses included foot and mouth disease (19%, 15/80), when a pig stops eating its feed (3%, 2/80), and bacterial infections (3%, 2/80). Figure 9 shows participants' attitudes towards using antibiotics in pigs on their farms.

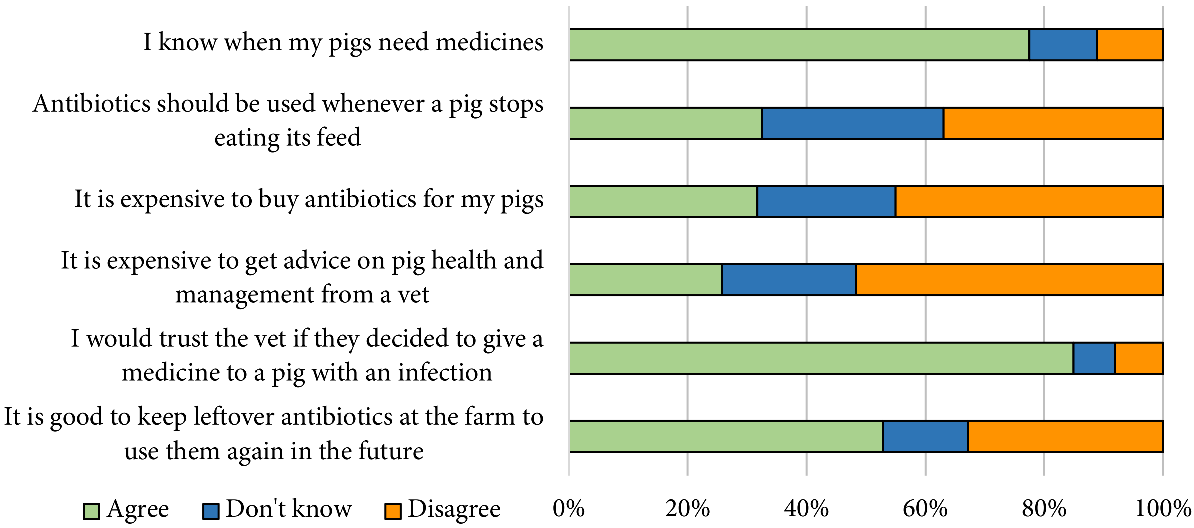


Figure 9. Backyard pig farmers' attitudes towards using antibiotics on their farms

5.2.4 What knowledge and attitudes do rural residents have towards antibiotic resistance?

Rural residents were equally likely to believe that bacteria can become resistant to antibiotics (26%, 201/769) as they were to think that humans (29%, 220/769) or animals (27%, 210/769) can become resistant to antibiotics. Just under a fifth of participants (19%, 145/769) felt that their own actions were important for controlling antibiotic resistance. Participants were much more likely to think that their individual practices were important if they had earlier reported knowing what antibiotics are and had also correctly identified two antibiotics on the list of medicines (49% vs. 12% for other participants, $p < 0.001$).

5.2.5 How are rural residents using antibiotics in humans?

Thirty-one percent of participants (238/769) stated that they had bought antibiotics for human use from a pharmacy during the previous year. Most of these respondents (85%, 202/238) reported that they did not have a prescription for at least one of the antibiotics that they had purchased. A half of all respondents (48%, 372/769) reported that they had stored leftover antibiotics in the previous year, and almost all (92%, 343/372) had either already used or planned to use these stored antibiotics.

5.2.6 How are backyard pig farmers using antibiotics in pigs?

Participants' self-reported practices towards antibiotic use for their pigs are shown Table 12. Thirty percent (82/271) of backyard pig farmers reported that they had bought antibiotics in the previous year without first speaking with a veterinarian.

Table 12. Backyard pig farmers' self-reported practices towards antibiotic use

Practices	n	%
I use antibiotics:		
Always or often in feed to keep pigs healthy and prevent diseases	48	18
For all pigs in a pen when some are sick	75	28
Only in pigs that are showing disease	137	50
No response provided	11	4
When my pigs are sick, I seek advice from:*		
A veterinarian	163	60
An animal pharmacy	56	21
Other farmers	70	26
Nobody	45	16
I usually buy antibiotics for my pigs from:*		
A veterinarian	117	43
An animal pharmacy	157	58
A human pharmacy	4	2
Other	20	7

Footnote: *Multiple responses could be selected.

5.2.7 Are rural residents storing antibiotics in their households?

Rural residents were asked to show data collectors which medicines they were storing in their households for human use and for pig use (Figure 10).

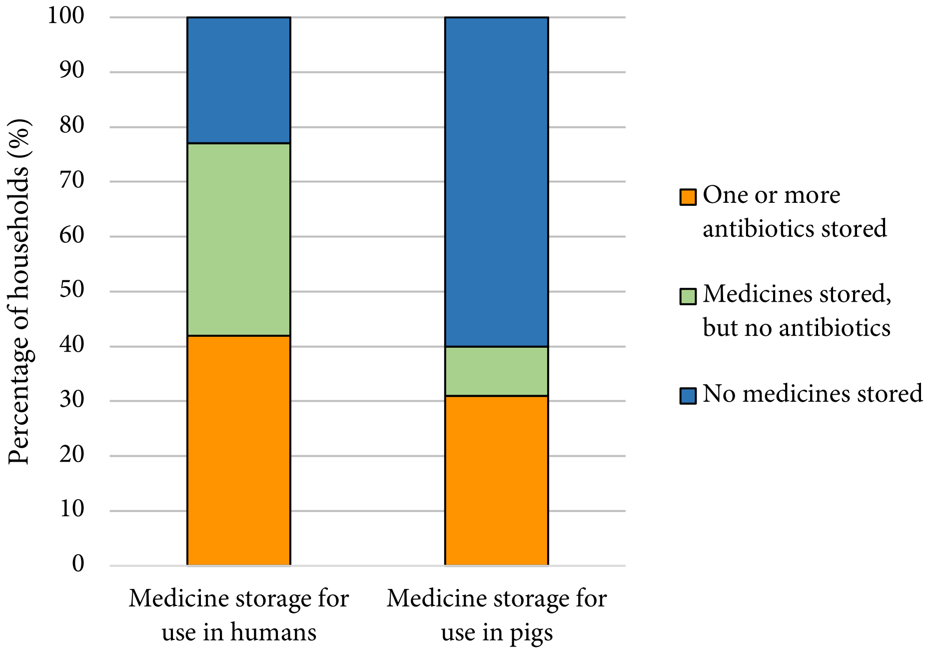


Figure 10. Observed household storage rates of medicines for use in humans and pigs

Antibiotics for human use were observed in 42% of households (321/769), with a median of one antibiotic stored per household (range one to six). Anti-inflammatory and analgesic medicines (46%, 357/769) and traditional Chinese medicines (48%, 371/769) were also frequently stored in households. The three most common antibiotic agents were J01CA04 amoxicillin (present in 139 households), J01DB01 cefalexin (58 households), and J01DB09 cefradine (39 households).

Antibiotics for use in pigs were observed in 31% of households with backyard pig farms (83/271), with a median of two antibiotics stored per household (range one to nine). Traditional Chinese medicines accounted for 23% of all stored medicines for use in pigs (81/358). Anti-parasitic medicines (8%, 29/358), anti-inflammatory and analgesic medicines (3%, 12/358), and other medicines (11%, 39/358) were also observed. The three most common antibiotic agents were (Q)J01CA04 amoxicillin (present in 20 households), (Q)J01FF02 lincomycin (20 households) and (Q)J01AA06 oxytetracycline (15 households) and (Q)J01BA90 florfenicol (15 households).

Seventy percent of participants (226/321) from households in which antibiotics for human use were being stored were not aware that any of the medicines stored were antibiotics. Similarly, 55% of farmers (46/83) from backyard pig farms in which antibiotics were being stored were not aware that they were storing any antibiotics.

Table 13. Five most common antibiotic classes stored for use in humans and pigs

	ATC code	Antibiotic class	n	% of stored antibiotics
Antibiotics for human use (N = 526)	J01D	Other beta-lactam antibacterials	163	31
	J01C	Beta-lactam antibacterials, penicillins	148	28
	J01M	Quinolone antibacterials	73	14
	J01F	Macrolides, lincosamides and streptogramins	65	12
	J01X	Other antibacterials	28	5
Antibiotics for pig use (N = 197)	(Q)J01C	Beta-lactam antibacterials, penicillins	37	19
	(Q)J01F	Macrolides, lincosamides and streptogramins	28	14
	(Q)J01M	Quinolone antibacterials	25	12
	(Q)J01A	Tetracyclines	22	11
	(Q)J01D	Other beta-lactam antibiotics	19	10

5.2.8 Is there an association between backyard pig farmers' knowledge, attitudes and practices towards antibiotic use in humans and their knowledge, attitudes and practices towards antibiotic use in pigs?

Backyard pig farmers who stated that they always or often add antibiotics into their pig feed were more likely to believe that antibiotics can prevent common colds in humans from becoming more a severe disease such as pneumonia (52% vs. 32% for the group of farmers who reported only using antibiotics if their pigs have signs of disease, $p < 0.001$). Backyard pig farmers who reported that they know when their pigs need medications were more likely than other farmers to expect a doctor to prescribe them antibiotics when they feel they are needed (38% vs. 24%, $p < 0.001$).

Backyard pig farmers who reported that they had bought antibiotics in the previous twelve months without consulting a veterinarian were more likely than other farmers to report having bought antibiotics for human use at a pharmacy in the previous year without a prescription (49% vs. 25%, $p < 0.001$). Backyard pig farmers who believed it was good to store leftover antibiotics for pig use were more likely to be observed to be storing antibiotics for use in pigs (41% vs. 20%, $p < 0.001$) and also for use in humans (47% vs. 32%, $p < 0.01$). There was also a trend for farmers who were observed to be storing antibiotics for use in pigs to be more likely than other farmers to be storing antibiotics for use in humans (48% vs. 35%, $p = 0.06$).

6 DISCUSSION

The aim of the thesis was to assess how antibiotics are being used for humans and on backyard pig farms in a rural region in China. This was addressed through studies of antibiotic prescribing at healthcare facilities, and surveys of the knowledge, attitudes and practices of doctors, rural residents and backyard pig farmers.

The main findings are:

1. Doctors, rural residents and backyard pig farmers are often misusing and overusing antibiotics
2. There is significant variation in the antibiotic prescribing practices of individual doctors and between healthcare facilities
3. Doctors have gaps between their knowledge and attitudes about rational antibiotic use, and their actual practices
4. Rural residents and backyard pig farmers' knowledge, attitudes and practices could lead to inappropriate antibiotic use
5. Backyard pig farmers' knowledge, attitudes and practices towards antibiotic use in humans and towards antibiotic use in pigs are interconnected

The discussion begins with an interpretation of the findings, structured according to the research questions. This is followed by methodological considerations and lessons for assessing antibiotic use in other regions, as well as future recommendations for policy, practice and research.

6.1 INTERPRETATION OF FINDINGS

6.1.1 Antibiotics are frequently being misused and overused

6.1.1.1 Prescriptions at healthcare facilities

In China, almost all outpatient encounters include a prescription, in part because this is a way in which reimbursements are calculated and administered. We found that 40% of prescriptions from village clinics in **Paper II** contained at least one antibiotic, implying that a large proportion of outpatient appointments result in antibiotic use. This rate is slightly lower than previously published studies for outpatients in China, which have tended to be around 50% [66,117,119,135]. The government set a target in 2012 for secondary level and higher hospitals to prescribe antibiotics for fewer than 20% of outpatient encounters [170,171], but there is currently no corresponding target for village clinics. Although variations in case mix and patient health-seeking behaviours mean that it is difficult to make international comparisons, the WHO has previously recommended that the antibiotic prescription rate for outpatient encounters should not be higher than 30% [172], which suggests that antibiotics are being overused in our study setting.

We investigated which clinical diagnoses antibiotics were being prescribed for by village doctors in **Paper II**, in order to assess whether antibiotics are being used responsibly. Although antibiotics can be appropriate therapies for several of the diagnoses (for example, urinary tract infections, prostatitis), the vast majority of antibiotics were prescribed for conditions for which there is little evidence of benefit (for example, upper respiratory tract infections, diarrhoea).

We focussed in more detail on how antibiotics were being prescribed for the common cold (**Paper I**) and for likely viral acute upper respiratory tract infections (**Paper II**). These are self-limiting conditions caused by viruses, for which antibiotics have not been shown to have clinical benefit [173–175]. Prescribing antibiotics to patients for these conditions therefore leads to the intrinsic negative consequences of using antibiotics (effects on microbiome, risks of adverse events, increasing selection pressures for resistant bacteria [6,15,16]), without positive clinical benefit, and so is not considered to be a responsible use of antibiotics [50,173]. We found that an antibiotic was included on 55% of all prescriptions for the common cold at healthcare facilities in **Paper I**, and on 62.5% of all prescriptions for likely viral AURIs at village clinics in **Paper II**. These antibiotic prescribing rates are similar to previous studies in rural village clinics in western China [119] and Guanxi province in southern China [176], as well as to studies in rural India (81%) [177] and Malaysia (46%) [67], but are higher than rates observed in national-level studies in Sweden (8%), Belgium (19%) and Netherlands (38%) [178].

The patterns of antibiotic classes prescribed at healthcare facilities were quite similar in **Papers I and II**, although the studies were conducted four years apart and in different areas in Shandong province. Broad-spectrum and critically important antibiotics were commonly prescribed, in keeping with overall consumption levels that were recently reported in Shandong province using procurement data [85], and similar to previous studies conducted in village clinics in western China [119]. In general, broad-spectrum antibiotics are considered to pose a greater selection pressure for resistant bacteria and have wider impacts on the microbiome. Prescribing broad-spectrum antibiotics for clinical conditions where antibiotics have not been shown to have a clinical benefit is a particularly irresponsible practice. All but one antibiotic prescribed for likely viral AURIs at village clinics in **Paper II** were either present on the national essential medicines list [145], or on the list of supplemental essential medicines available in Shandong province; cefixime did not feature on either of these lists and accounted for 1.6% of all antibiotics prescribed for likely viral AURIs during the study period.

Outpatient antibiotic prescribing quality indicators have been developed in Europe to assess the decision to prescribe an antibiotic in specific clinical conditions, and the actual choice of antibiotic agent [168]. All of our results from the village clinics in **Paper II** lay outside of the recommended ranges. In particular, we found that the recommended narrow-spectrum J01CE beta-lactamase sensitive penicillins were rarely used (1.5% for acute upper respiratory tract infections, 2.9% for tonsillitis), whereas J01CA penicillins with an extended spectrum were used far more frequently. This finding is not unique to rural China: broad-spectrum penicillins such as amoxicillin are still commonly used worldwide for treatment of upper respiratory tract infections, with the notable exception of Scandinavian countries where narrower-spectrum penicillins are preferred [179].

Interestingly, we observed that antibiotics were used less frequently than recommended for adults diagnosed with pneumonia (73.3% compared with a target of 90-100% [168]). This potentially represents an underuse of antibiotics, but needs to be investigated further. We also found that urogenital infections and skin and soft tissue infections each accounted for less than 1% of all antibiotic prescriptions at the village clinics, whereas these conditions are typically the second and third most common reasons for antibiotic prescriptions in studies from highly developed countries [180]. In contrast, dental conditions were the third largest group of diagnoses for which antibiotics were prescribed in our study. This may reflect the extreme paucity of dentists in rural China [143], and is potentially an important and under-reported source of antibiotic overuse.

6.1.1.2 Practices of rural residents

We asked residents in twelve villages about their practices concerning antibiotics in **Paper III**, to assess whether they were using antibiotics responsibly. A quarter of respondents reported having bought antibiotics for human use at pharmacies without a prescription in the previous year. This is a behaviour that can easily lead to antibiotics being consumed when they are not clinically needed, or an inappropriate choice of antibiotic being used when they are clinically needed. Regulating over-the-counter accessibility of antibiotics is recommended in the WHO Global Action Plan, to the extent that it does not restrict access to effective therapy [4]. Since 2004, prescriptions have been legally required for obtaining antibiotics from pharmacies in China [61]. This regulation is incompletely enforced, however; a study in another province in China reported that 40% of parents had bought antibiotics without a prescription in the previous year [95]. Studies using simulated patient encounters in urban and rural pharmacies have also demonstrated that antibiotics are frequently dispensed by pharmacists without prescriptions, based on presentations of symptoms of clinical conditions for which they are not necessary (such as AURIs), and particularly if directly demanded by patients [181–183].

We found that household storage of antibiotics for human use was common, and similar to levels identified in previous studies in Asia [95,184]. The types of antibiotic stored were very similar to the patterns of antibiotics contained on prescriptions sampled from the village clinics serving the villages in which the rural residents live (**Paper II**), suggesting that the stored antibiotics may be leftover from earlier prescribed courses. Almost all participants had already used the stored antibiotics on a second occasion or planned to do so in the future. Self-treatment with leftover antibiotics is another behaviour that can easily lead to antibiotics being consumed when they are not clinically needed, or an inappropriate choice, dose or duration of antibiotic being used when they are needed [57,185].

6.1.1.3 Practices of backyard pig farmers

We asked farmers about their practices concerning antibiotics on backyard pig farms in **Paper IV**. We found that nearly a fifth of farmers reported always or often adding antibiotics to their pigs' feed to keep the pigs healthy, i.e. using antibiotics as growth promoters. This proportion is probably higher in reality, since three-quarters of farmers also reported using commercial feeds, and these may have contained antibiotics that the farmers were unaware of. It is currently still permitted to use antibiotics as growth promoters in China, although the use of specific antibiotics has been restricted in recent years, in particular those that are considered critically important for human health [134,154]. Using antibiotics as growth promoters may lead to small benefits in growth production rates, but it comes at the expense of exposing animals to large volumes of antibiotics throughout their lifespans, and increases their carriage of resistant bacteria [18,186]. This may in turn represent an important source of contamination of carcasses at slaughter [187], but the ultimate risk for human health remains unclear [188]. Nevertheless, using antibiotics as growth promoters has been banned in the European Union since 2006 [189], and the WHO Global Action Plan recommends that all Member States work to phase out their use worldwide [4].

A third of backyard pig farmers reported having bought antibiotics for their pigs in the previous year, without consulting with a veterinarian. This can lead to antibiotics being used when they are not clinically required, or an inappropriate choice, dose or duration of antibiotic being used when they are needed. We found that storage of antibiotics in households for pig use was common, and many of the stored antibiotics are classified by the WHO as critically important for human medicine [190], for example macrolides and quinolones (the second and third most frequently stored classes of antibiotics).

Household storage of antibiotics for pigs could be a less strong indicator of irrational use compared with storage of antibiotics for human use; it may be appropriate and financially beneficial for farmers to store bulk-purchased antibiotics for use under the guidance of a veterinarian. However, we found that backyard pig farmers who had stored antibiotics in their household were more likely than other farmers to report having purchased antibiotics in the previous year without consulting a veterinarian, which suggests that antibiotics are not being stored under their guidance. There was also a trend towards higher storage rates of antibiotics for pig use among farmers who reported always or often using antibiotics as growth promoters, and among farmers who thought that antibiotics should be used whenever pigs stop eating their feed. Both of these behaviours are unnecessary uses of antibiotics.

6.1.2 There is significant variation in the practices of doctors

6.1.2.1 Variation between healthcare facility levels

We compared antibiotic prescribing rates for common cold diagnoses at three different levels of healthcare facility in **Paper I**. Prescriptions were much more likely to contain an antibiotic if they were from village clinics, with township health centres and county hospitals having similar rates to each other. A previous systematic review similarly found that higher level hospitals in China tended to have lower overall antibiotic use rates for outpatients [135]. This might be considered a counterintuitive finding in terms of clinical need, since patients with more severe illnesses are generally referred (or self-refer) to higher level healthcare facilities. A possible explanation is that doctors in higher level healthcare centres are better at diagnosing and treating infections, leading to lower prescription rates of antibiotics for viral illnesses, and lower overall antibiotic consumption. As described earlier, the background educational levels of doctors normally vary across healthcare facilities in China. None of the village doctors in our studies had a bachelor's degree, compared with almost half of the doctors at county hospitals and a third of the doctors at township health centres. Although most village doctors reported in **Paper I** having recently attended training on rational antibiotic use it is likely that such training does not fully compensate for underlying differences in the education of doctors.

These variations in antibiotic prescribing rates between healthcare facility levels may also reinforce socioeconomic inequalities in healthcare. In general, the village clinics serve residents who live in the villages, whereas the township health centres and county hospitals serve people who live in more developed areas (such as towns), as well as those who live in villages but who are willing to travel further and to pay more for the care they receive. Choice of healthcare facility is at least partly related to patients' socioeconomic status. Our results suggest that within rural areas, people living in poorer areas (villages) are more likely to be unnecessarily exposed to antibiotics for the common cold, through being more likely to attend lower level healthcare facilities where antibiotics are more frequently overused.

6.1.2.2 Variations between individual doctors

Our study design for **Paper II** enabled us to investigate variability in antibiotic prescribing at the prescriber-level whilst keeping several factors relatively constant: the villages served by the village clinics were limited to a small geographical region and were quite homogeneous in terms of socioeconomic levels; the patient populations in the villages were likely to have had similar consultation behaviours when ill, particularly for a common diagnosis such as an AURI; the doctors all had the same medical qualifications and at least 14 years of clinical experience; the village clinics were all subject to the same regulations concerning antibiotic use and reimbursement systems [138,146]. It could be hypothesised that little variation would exist in the prescribing practices of the village doctors, given these similarities. Our results, however, revealed substantial differences between doctors in antibiotic prescribing rates for likely viral acute respiratory tract infections, as well as for the use of multiple antibiotics and injectable antibiotics.

Few previous studies have assessed variations between individual prescribers, with most studies analysing aggregated data and presenting averages. A study in 2005 found that antibiotic prescribing rates for upper respiratory tract infections among 84 primary care doctors in the Netherlands ranged from 15% to 27% [191]. Among our considerably smaller group of 18 doctors, this rate ranged from 33% to 88%.

Individuals who had higher antibiotic prescribing rates for likely viral AURIs were also more likely to prescribe multiple antibiotics and injectable antibiotics for these conditions. We found that the quartile of village doctors with the highest antibiotic prescribing rates for likely viral AURIs were more likely to prescribe antibiotics for diagnoses of gastritis, gastroenteritis and diarrhoea than the lowest quartile of antibiotic prescribers for likely viral AURIs. This suggests that for some village doctors, overuse of antibiotics is not limited to specific clinical conditions but may be a general pattern of behaviour. Uncertainty avoidance is a factor that has been linked with overuse of medicines, including antibiotics [65]. In keeping with this, these high antibiotic prescribers were also more likely than the low antibiotic prescribers to prescribe antibiotics for the subgroup of respiratory tract infections that have potential bacterial causes, i.e. where antibiotics are more likely to be clinically indicated.

We also found significant variation within the high-prescriber group, demonstrating the additional information that can be gained from individual-level analyses: patients with likely viral acute respiratory tract infections who visited village doctors 513 and 412 were equally likely to be prescribed an antibiotic (mean antibiotic prescribing rate of 87%). However, those who visited doctor 513 were six times more likely to be prescribed two or more antibiotics, three times more likely to be prescribed a parenteral antibiotic, and a third less likely to be prescribed an analgesic or anti-inflammatory medicine; furthermore, the choice of antibiotic prescribed was likely to be an aminoglycoside, a third generation cephalosporin or a fluoroquinolone (all broad-spectrum antibiotics), compared with amoxicillin, a first-generation cephalosporin, or a macrolide (slightly narrower-spectrum antibiotics).

Individual-level analyses are often cautioned against due to the difficulties in accounting for variations in patient case mix. This is particularly relevant when attempting to compare studies conducted in settings where patients exhibit different health-seeking behaviours and have different patterns of co-morbidities. However, evidence is increasingly suggesting that differences in patient case mix may not explain a large amount of the variability in prescribing patterns for antibiotics [192]. Importantly, choosing to not investigate variations between individual prescribers causes us to subtly obscure the responsibility of the individual decision-maker, as well as the elevated risks that individual patients are exposed to when they consult with individuals who overuse antibiotics. Indeed, this is a compelling example of why antibiotic stewardship is often advocated to be viewed in terms of patient safety [193].

Promisingly, a recent US study showed that monthly peer comparison of antibiotic prescribing rates, combined with baseline education, was able to reduce rates of unnecessary antibiotic prescribing among high prescribers for acute respiratory tract infections [194]. Similarly, a study in Anhui province, China, demonstrated that just-in-time information and individualised feedback to village doctors can improve their antibiotic prescribing practices for respiratory tract infections and gastrointestinal tract infections [195].

6.1.3 Knowledge and attitudes of doctors, rural residents and backyard pig farmers towards antibiotic use and resistance

6.1.3.1 Doctors have gaps between their knowledge and attitudes and their actual practices

We asked doctors at different healthcare facilities about their knowledge and attitudes towards antibiotic use in **Paper I**, using a limited set of questions. Their responses were consistent with using antibiotics responsibly. For example, most doctors reported that they did not believe that newer antibiotics are more effective than older ones, nor that broad-spectrum antibiotics are more effective than narrow-spectrum ones. Concerning the use of antibiotics for patients with symptoms of the common cold, extremely few doctors reported that they would consider prescribing antibiotics, even when pressured by patients; most doctors said they would recommend using non-antibiotic measures instead. In practice, however, we found that at least one antibiotic was present on over half of all prescriptions for patients with a common cold diagnosis at the facilities these doctors worked in, and these were frequently broad-spectrum antibiotics. There is therefore a significant discrepancy between reported knowledge and attitudes, and actual practices.

In a separate study [196], we interviewed fifteen of the village doctors who worked at the village clinics from which prescriptions were collected in **Paper II**. These doctors reported that patients frequently demand antibiotics, and that they would simply buy them at pharmacies if the doctors refused to prescribe them. Reynolds *et al.* previously carried out semi-structured interviews with doctors at healthcare facilities in another province in southern China [61]. Their findings suggested that doctors know that antibiotics are not needed for the common cold, but they often still prescribe them under the belief that they might speed recovery, and in response to patient expectations. A further driving factor for antibiotic overuse may be financial incentives: at the time of the study reported in **Paper I**, doctors were able to make a profit from prescriptions, and this may have stimulated over-prescribing of antibiotics [137].

6.1.3.2 Rural residents and backyard pig farmers' knowledge and attitudes may lead to inappropriate antibiotic use

Overall, rural residents appeared to have low levels of knowledge about what antibiotics are and when they should be used, as well as about antibiotic resistance, as found in previous studies in China [95,124,125]. Over two-thirds of residents reported that they did not know what antibiotics are, and a large proportion responded "Don't know" to questions concerning the need for antibiotics in common illnesses; these responses were also more frequent among respondents with lower education levels and from households with lower incomes. Rural residents more frequently thought that antibiotics are needed for infectious conditions (pneumonia, common cold) than for non-infectious conditions (hypertension). They did not, however, differentiate significantly between infections caused by bacteria, where antibiotics may be needed, and those caused by viruses, where they are not. A quarter of respondents thought that antibiotics were always or usually needed for a common cold, and nearly a third thought antibiotics can prevent a common cold from becoming a more severe illness. We found similar over-expectations for antibiotics in another study in Shandong province, in which respondents commonly thought that antibiotics are needed when children have a stuffy nose (32%) or a sore throat (36%) [125]. It is possible that these over-expectations for antibiotics are a result of the frequent prescribing of antibiotics by doctors for patients with AURIs, as seen in our prescription analyses (**Papers I and II**); it is also possible that patient expectations for antibiotics are influencing prescriber behaviour, and so are themselves a driver for antibiotic overuse [61,197].

We found that backyard pig farmers also had low levels of knowledge about antibiotic use in pigs. These knowledge levels are similar, however, to other studies conducted among animal farmers in low-and middle-income countries including Sudan [198], Ghana [199], Cambodia [200]. These low knowledge levels are not unexpected, since very few farmers reported having had any form of training on raising pigs, and only 10% had attended professional courses. Backyard pig farmers most likely gain their knowledge from conversations with other farmers and family members, and from their own practical work experience. Of note, only 30% of farmers were able to provide suggestions for which pig diseases usually require antibiotic treatment, with most responding "Don't know". The most frequently mentioned disease was diarrhoea. Several common diarrhoeal diseases in pigs are caused by bacteria (e.g. neonatal diarrhoea, weaning diarrhoea, swine dysentery and porcine proliferative enteritis). However, viruses are also a common cause of diarrhoea in pigs, so consulting a veterinarian to reach an aetiological diagnosis is important for deciding whether antibiotics are indicated, and if so, which antibiotic should be used [201]. Positively, the backyard pig farmers in our study had high trust levels in veterinarians, and most farmers did not consider it to be expensive to consult veterinarians. Despite this, 40% reported that they do not usually seek advice from veterinarians when their pigs are sick.

Foot and mouth disease was the third most common suggestion by backyard pig farmers of a disease that requires antibiotic treatment. This is perhaps surprising since foot and mouth disease is a highly epidemic viral disease with strict national and international regulations, such as culling of affected animals, and vaccination of animals at nearby farms. It is possible that farmers are aware that injections are needed to prevent foot and mouth disease, but that they do not know that this is a vaccine, not an antibiotic.

6.1.4 Backyard pig farmers' knowledge, attitudes and practices towards antibiotic use in humans and antibiotic use in pigs are interconnected

Due to their practical experience of treating pigs on their farms, we hypothesised that backyard pig farmers might have slightly different patterns of knowledge, attitudes and practices concerning antibiotic use in humans, compared with other residents. We found that backyard pig farmers were indeed more likely to report knowing what antibiotics are and to correctly identify antibiotics from the list of medicines commonly used in humans. Backyard pig farmers were also more likely to think that antibiotics are always or usually needed for specific infectious illnesses in humans. These differences remained significant after adjusting for socio-demographic differences (age, sex and education) between backyard pig farmers and other residents, as well as for self-reported knowing what antibiotics are.

We also found that backyard pig farmers' attitudes and practices towards medicine use in pigs had some parallels with their attitudes and practices towards medicine use in humans. For example, farmers who reported always adding antibiotics to pig feed to keep pigs healthy were more likely to believe that antibiotics could have a prophylactic effect in humans (stopping a cold becoming more severe). Similarly, farmers who reported that they had bought antibiotics for their pigs in the previous year without speaking with a veterinarian were also more likely to report having bought antibiotics for themselves in the previous year without a prescription. We also found that farmers who thought it was good to store leftover antibiotics for pigs were more likely to be storing antibiotics for human use in their household.

Together, these findings suggest that backyard pig farmers develop common attitudes towards antibiotic use that translate into similar behavioural patterns when using antibiotics in pigs and for themselves. Indeed, during a focus group discussion we held with backyard pig farmers in a nearby village, one participant said *"It is basically the same between humans and pigs. If they have a fever, I use penicillin"*. To our knowledge, such associations have not previously been investigated. They may be widely relevant, however, in the many other resource-limited settings where small-scale food animal production is common [39]. These associations highlight the importance of a One Health perspective, including recognising that interventions may have consequences across sectors: changing farmers' antibiotic use practices on their backyard farms may affect how they use antibiotics for themselves, and vice versa.

6.1.5 Antibiotics are not being used responsibly enough

Overall, the work in this thesis strongly suggests that antibiotics are not being used responsibly enough for humans and on backyard pig farms in the study region. This is both in terms of individual uses of antibiotics, and in terms of the broader context in which antibiotics are being used [50]. We identified several individual practices of antibiotic overuse and misuse, including doctors prescribing antibiotics for conditions for which they are not necessary; rural residents using leftover antibiotics and obtaining antibiotics without prescriptions; and backyard pig farmers giving antibiotics to healthy pigs. The types of antibiotics that were being prescribed unnecessarily by doctors were frequently broad-spectrum, as were the antibiotics stored in rural residents' households that they reported to have self-treated with. Similarly, many of the antibiotics stored for use in pigs are considered to be critically important antibiotics for human medicine [190].

More broadly, rural residents and backyard pig farmers had poor knowledge of which conditions require antibiotics, yet antibiotics for use in both humans and pigs appeared to be readily accessible without needing to consult doctors or veterinarians. Doctors had access to training on antibiotics and appeared to know that antibiotics were not needed for common colds, yet no mechanisms were in place to help ensure that their practices reflected this knowledge. Furthermore, wide variations in prescribing rates and patterns were permitted to exist, and many doctors were underusing symptom-relieving alternatives to antibiotics for acute respiratory tract infections, such as anti-inflammatory and analgesic medicines.

The specific consequences of the level of antibiotic overuse and misuse in the study region are unknown. However, as described earlier, these will likely include negative health and economic consequences for individuals and the healthcare system through being an inefficient use of resources and through unnecessarily exacerbating the burden of antibiotic resistance. Other parts of the IMPACT research programme from which **Papers II-IV** originated have demonstrated the high prevalence rates in the region of resistant bacteria in humans [202], animals [157,158] and the environment [159,160], as well as the common presence of antibiotic residues in a number of water sources [203]. The data presented in this thesis on antibiotic use patterns, and the knowledge, attitudes and practices of doctors, rural residents and backyard pig farmers complement these data and contribute towards a more holistic One Health understanding of antibiotic use and resistance in the region.

6.2 METHODOLOGICAL CONSIDERATIONS

The studies in this thesis used two main methods: analyses of prescriptions from healthcare facilities (**Papers I and II**), and surveys of knowledge, attitudes and practices of doctors (**Paper I**), rural residents (**Paper III**) and backyard pig farmers (**Paper IV**).

6.2.1 Analyses of prescriptions

6.2.1.1 Strengths

In **Paper I** we investigated how frequently antibiotics were prescribed for patients with the common cold at different types of rural healthcare facility. These facilities were selected from three different counties, in order to increase representativeness of rural Shandong province. Within each county, the same procedures were used for selecting participating facilities and for sampling prescriptions. Prescriptions were all collected over the same one-month period, to reduce the impact of seasonal variation in antibiotic prescribing rates on comparisons between the facilities.

In **Paper II** we investigated how frequently village doctors prescribed antibiotics for likely viral acute upper respiratory tract infections, and how much variation there was between individual prescribers. The prescriptions contained the clinical diagnoses, the medicines prescribed and the doctors' names, which allowed us to describe the prescribing patterns of individual doctors for specific clinical diagnoses, and to assess the use of antibiotics as well as other medicines (e.g. anti-inflammatory and analgesic medicines). We collected data over a long time period, and we made comparisons between years which showed that doctors' practices were generally stable across the study period. We coded all clinical diagnoses according to ICD-10 codes to facilitate comparisons with other studies. We limited the prescriber-level analyses to doctors with ≥50 AURI prescriptions during the study period.

6.2.1.2 Limitations

Selection bias

Selection biases are introduced when the study population does not represent the target population [204]. Healthcare facilities were selected from three different counties in Shandong province in **Paper I**; within each county, facilities were selected at random. Although we have no reasons to believe that the selected facilities differed substantially from others in rural Shandong province, we did not collect information on the size of the facilities or patient mixes, which might have allowed comparisons to be made. For **Paper II**, all village clinics within the study area were included. In both studies it is possible that patients attended healthcare facilities and received diagnoses, but were not given prescriptions; however, this would be very unusual in this setting, in part because prescriptions are a way in which reimbursements for healthcare expenditures are calculated and administered.

Information bias

Information biases are introduced during data collection when there are systematic differences in the way data on exposure or outcome are obtained from differing study groups [204]. We had no way to clinically validate the diagnoses included on the prescriptions in

Papers I and II, so it is possible that misclassifications occurred, and potentially at different rates between facilities. To focus on antibiotic overuse we used a very conservative definition for *likely viral acute upper respiratory tract infections* in **Paper II**, rather than including other acute upper respiratory tract infections which may be caused by bacteria (e.g. pharyngitis), and where antibiotic use is more likely to be warranted for a proportion of patients. These likely viral AURIs accounted for an average of 86% of all respiratory tract infection diagnoses in **Paper II**, but this ranged from 58% to 100% for individual doctors. This wide range suggests that there were variations in how village doctors classified infections, and/or in their diagnostic abilities. A recent study has highlighted variability in diagnostic ability as an important driver of unnecessary antibiotic prescriptions in clinics in rural China [205].

Additional limitations
Our data sources were prescriptions; it is possible that there are systematic differences between the healthcare facilities and patient populations that affect the likelihood that a prescribed antibiotic is ultimately consumed. We used a few indicators that have been used in previous studies of antibiotic prescriptions. However, due to the formatting of the exported prescriptions, we were not easily able to assess the duration or dosing of antibiotics prescribed. We therefore could not express antibiotic use in terms of Defined Daily Doses, which would have enabled more accurate comparisons with international studies of antibiotic consumption intensity. We also did not have access to data that could account for variations in the workload of individual doctors, or to control for patient co-morbidities. A broader limitation to assessing antibiotic use on backyard pig farms in the study region was our complete inability to assess the prescribing patterns of veterinarians, due to a lack of access. Similarly, we were unable to involve pharmacies in our studies; these may have been able to provide complementary information on over-the-counter purchasing patterns for antibiotics for use in both humans and animals.

6.2.2 Surveys of knowledge, attitudes and practices

6.2.2.1 Strengths
In **Paper I** we assessed doctors' knowledge and attitudes towards antibiotic use. We had a very high participation rate with all doctors who were working on the day when the questionnaire was distributed at each facility completing the survey.

In **Papers III and IV** we assessed rural residents' and backyard pig farmers' knowledge, attitudes and practices towards antibiotic use and resistance. A local administrator visited each selected household the day before data collection to remind residents that someone should be at home for the data collection visit. In total 769 responses were included (**Paper III**) from an original target of 780. Participants were interviewed in their own homes, which provided a more natural setting than in studies conducted at healthcare clinics. This also allowed us to directly observe storage of antibiotics and other medicines, rather than using self-reports with their potential for reporting bias, and further to assess if participants were aware that they were storing antibiotics.

6.2.2.2 Limitations
Selection bias
For **Paper I**, the same biases as described above are relevant here. It should also be noted that respondents at the three included county hospitals were from the departments of internal medicine, surgery, paediatrics and obstetrics & gynaecology; these respondents were

therefore more specialised, and their responses may be less directly comparable with the more generalist doctors working at township health centres and village clinics.

For **Papers III and IV**, we purposefully over-sampled backyard pig farmers compared with their prevalence in the villages. We found differences between backyard pig farmers and rural residents without backyard farms, which suggests that for certain outcomes a weighted method of aggregating the responses from different participant types might be needed to most accurately represent these villages. We also ultimately included 29 households that had more than 49 pigs in a backyard farm at the time of data collection. We decided to still include these households in our analyses since almost all had fewer than 100 pigs, and there were no significant differences in a subgroup analysis.

Information bias
All of the surveys may have suffered from reporting and recall bias, as well as bias due to social expectations. Rural residents and backyard pig farmers may not have been willing to show which medicines they were storing in their households, but we have no reason to believe that they would specifically conceal storage of antibiotics. It is possible that medicines intended for use in other animals were shown and/or recorded by the data collectors in **Paper IV**, although respondents were asked to only show the medicines that they were storing for use in pigs. We did not record the locations or conditions in which medicines were stored, nor whether they were within their expiration dates. Data collection occurred at a single time point for **Papers III and IV**, and storage rates of antibiotics may have differed at other times in the year.

Confounding
The regression models presented in **Papers III and IV** may be subject to confounding, when an observed association is distorted because the exposure is correlated with another risk factor, which is in turn associated with the outcome, but independently of the exposure under investigation [204]. For example, residents' knowledge of what antibiotics are (**Paper III**) and rates of storing antibiotics for pig use (**Paper IV**) could be related to household income, but this factor was not included in the regression models due to a high frequency of missing data. Of note, there did not appear to be any major clustering at the level of villages for responses to the knowledge, attitudes and practices questions in **Papers III and IV**.

6.2.3 External validity of the studies

External validity deals with the degree to which research findings can be generalised to other groups or populations [206]. We believe that our main findings described above are mostly transferrable to other parts of rural eastern China, to which our study region is broadly similar in terms of population socio-demographics and educational levels [131,207]. Shandong province has previously been used as a representative of eastern coastal and northern provinces both for studies involving backyard pig farms [150] and antibiotic use in human healthcare [66,163]. Within human healthcare, all rural areas are subject to the same regulations, such as the zero mark-up policy at village clinics and public primary care facilities. Backyard pig farms are quite homogenous, and previous studies in rural China have often collected data from a small number of sites [150,151].

Several specific results, for example in terms of the types of antibiotics stored, are likely to be less generalisable to other countries in the region. This is because the behaviours of doctors, residents and backyard pig farmers will likely be influenced by local antibiotic use regulations, market availability of antibiotics, cultural health-care seeking patterns, and other economic factors.

6.2.4 Lessons for assessing antibiotic use in other regions

As antimicrobial resistance rates continue to rise, and as new antibiotic classes are yet to reach market availability, it is critical that we assess how we are using our existing antibiotics. The WHO Global Action Plan recognises this, and assessments of antibiotic consumption in humans and animals are commonly featured in countries' National Action Plans on antimicrobial resistance [4,148,208]. To date, there have been very few examples of comprehensive assessments of antibiotic use and resistance within a single region [81,209,210], highlighting the substantial challenges involved in such work [80,211]. The results presented in this thesis, and the experiences involved in designing and conducting the studies [80], provide lessons that may be valuable for other regions.

Purpose: A critical initial step is deciding on the purpose of assessing antibiotic use, since this directly affects which data should be collected, how it should be collected, and how it should be analysed. In resource-limited community settings where little existing data is available, purposes might include: identifying where the majority of antibiotics are being obtained (e.g. pharmacies vs. healthcare facilities; private vs. public healthcare facilities); identifying the most common clinical reasons for unnecessary and inappropriate antibiotic use; identifying how frequently antibiotics are being used in the absence of consultations with human or veterinary healthcare professionals.

Coverage: In some countries, existing systems in human medicine are able to provide representative coverage of which antibiotics are being used and for which clinical diagnoses, at national levels [180]. Comparatively, equivalent systems are in veterinary medicine [79,208]. In resource-limited settings it may only be feasible to collect data in a small number of areas, and at a limited number of time points. Whilst these samples may not produce nationally representative consumption data, they may still produce valid insights into the reasons for overuse and misuse of antibiotics within a country, and these may actually be more relevant to improving antibiotic use than accurate consumption data. It may therefore be more strategic to invest in conducting high quality assessments at a small number of study sites than in attempting to capture overall antibiotic consumption across larger areas.

Working across sectors: Cross-sectoral work is needed to understand the total antibiotic use within a region, and consequently the overall ecological pressure placed on bacteria [78,79]. This is particularly important for countries such as China where antibiotics that are originally manufactured for human use are frequently used in animals, either as growth promoters in feed, or for veterinary purposes [134]. Working across sectors may also help to identify strategic intervention points where antibiotic use can be improved in both humans and animals, such as limiting over-the-counter availability of antibiotics.

Investigate variations: It is valuable to assess the extent of variations in antibiotic use practices. If there is little variation, then interventions to improve antibiotic use (such as education for doctors and the public) may be able to focus on a limited number of key messages and be widely applicable; if there are widespread variations, however, interventions may need to be much more targeted, such as individualised feedback to doctors on choices of antibiotic agents. Assessing variations can also help identify individuals and facilities that consistently appear to be using antibiotics responsibly. A more in-depth follow-up with these "bright spots" may then help to identify barriers and facilitators to responsible antibiotic use.

Include qualitative assessments: We conducted focus group discussions with residents before we designed the questionnaire used in **Papers III and IV**. This was an important phase to develop initial ideas about how and why rural residents might be overusing or misusing antibiotics, which we could then assess with a larger number of respondents. These focus group discussions were also helpful for developing the pilot interventions in the IMPACT research programme, such as highlighting the importance of patient expectations for antibiotics. Qualitative work with doctors can also be a useful way to further explore findings from quantitative assessments of antibiotic consumption, for example to find explanations for variations seen between prescribers.

Involve the public: There can be a need to survey the public in settings where antibiotics are routinely accessed over-the-counter (for use in humans or in animals), because antibiotic consumption data from healthcare facilities may provide limited insights into total antibiotic consumption. Involving the public can also provide information about adherence to antibiotic courses prescribed by doctors and veterinarians, and on the frequency of self-treatment with leftover antibiotics.

7 CONCLUSIONS

The main conclusions to be drawn from the work in this thesis are:

- Doctors, rural residents and backyard pig farmers in rural Shandong province are frequently overusing and misusing antibiotics. The majority of antibiotics prescribed at human healthcare facilities are prescribed for conditions that do not require them. In addition, rural residents are commonly acquiring antibiotics without prescriptions and using leftover antibiotics, and backyard pig farmers are often using antibiotics in healthy pigs when they are not needed.

- There are widespread variations in the antibiotic prescribing practices of individual doctors and between healthcare facilities, within a relatively homogenous setting in rural Shandong province. This is a barrier to equitable access to healthcare, and the differences in prescribing rates between village clinics and higher-level healthcare facilities may exacerbate inequalities in health through disproportionately exposing poorer individuals to unnecessary antibiotic use.

- Doctors have gaps between their knowledge and attitudes concerning antibiotics, and their actual prescribing practices. This is despite a majority having recently attended training on rational antibiotic use. There is a need to investigate which additional drivers are causing doctors to overuse and misuse antibiotics despite knowing that they are not needed.

- Rural residents and backyard pig farmers have low levels of knowledge about what antibiotics are and when they should be used. Their knowledge and attitudes may contribute to overuse and misuse of antibiotics through promoting self-treatment and through creating expectations to receive antibiotics from healthcare professionals in situations for which they are not clinically needed.

- Backyard pig farmers have differences in their knowledge, attitudes and practices towards antibiotic use in humans compared with other rural residents, and these appear to be inter-related with their knowledge, attitudes and practices towards antibiotic use in pigs.

- In resource-limited settings, high quality, cross-sectoral assessments of antibiotic use at a small number of study sites can provide valuable insights into how responsibly antibiotics are being used.

8 RECOMMENDATIONS

8.1 PRACTICE AND POLICY

It is clear that actions must be taken globally to improve how we use antibiotics [1,4,21,212]. These actions are needed to ensure that people and animals have access to effective therapy today, and so that we can preserve the effectiveness of our limited arsenal of antibiotics for the patients of tomorrow [42,50]. These actions include individual doctors and healthcare facilities, healthcare systems and politicians, and the general public: everyone needs to be involved, and everyone has a role to play [4,47].

A wide range of effective interventions for improving antibiotic use have previously been described [97,213–215], but these should be context-adapted to maximise their impact. Change on a large scale is possible in China, as evidenced by the rapid and sustained reductions in antibiotic use seen across many urban hospitals that have coincided with national campaigns [110]. The results in this thesis provide several suggestions for how to proceed to improve antibiotic use in rural Shandong province and in similar settings for humans and on backyard pig farms. These include:

Investing in education and public awareness

Healthcare professionals: Educating prescribers in human and animal healthcare about the rational use of antibiotics is a key goal of the Chinese National Action Plan on Antimicrobial Resistance [148]. Several studies, including in China, have demonstrated that educational interventions can be low cost, scalable and effective at improving antibiotic prescribing [97,216,217]. Within human healthcare, our results suggest that education may be needed to help doctors understand which clinical conditions require antibiotics, but perhaps more importantly, it must provide them with alternatives to prescribing antibiotics for when they are not needed. This could include training on medications that provide symptomatic relief for viral illnesses, such as anti-inflammatories and analgesics, and on communication skills to help doctors address patients' expectations without resorting to prescribing antibiotics. In China in particular, there may also be a role for promoting the use of traditional Chinese medicines.

Rural residents: Remarkably, despite no previous active efforts to educate the public in the region, half of the rural residents who knew what antibiotics are thought that their individual practices were important for controlling resistance. This suggests that public awareness campaigns will benefit from providing rural residents with a basic understanding of what antibiotics are, and from empowering them to know what actions they can take to keep antibiotics effective. These include visiting healthcare providers instead of using leftover antibiotics or purchasing antibiotics without a prescription. Furthermore, residents need to be more aware of which conditions do not need antibiotics, and of how their demands may result in prescribers and pharmacies providing them with antibiotics when they are not needed.

Backyard pig farmers: Farmers should be encouraged to seek advice from veterinarians and para-veterinarians when their pigs are ill, instead of self-treating with antibiotics. Promisingly, farmers had very high trust levels in veterinarians, and most did not think it was expensive to consult with them. Farmers should also be discouraged from adding antibiotics to feed as growth promoters.

Providing feedback to doctors
Electronic prescribing records are increasingly common in primary care facilities in rural China. These could be harnessed to provide timely individualised feedback to doctors on both the quality and quantity of their antibiotic prescribing, in particular for conditions where they are not needed [195]. Furthermore, given the variation in antibiotic prescribing observed between individuals, doctors could be encouraged to discuss their prescribing patterns with one another, to help better understand facilitators and barriers to responsible antibiotic use.

Restricting over-the counter access to antibiotics
The results of our studies suggest that antibiotics remain easily accessible over-the-counter, both for humans and animals. The Chinese National Action Plan includes a goal that antibiotics for human use should be prescription-only by 2020 [148], but recent studies suggest that this target is unlikely to be met [182,183]. Stronger efforts to enforce this regulation are needed.

Reducing fixed pack dispensing of antibiotics
Antibiotics are commonly dispensed in fixed pack sizes in China. Instead, providing only the number of antibiotics actually prescribed by a doctor could help reduce the number of leftover antibiotics, and in turn reduce the likelihood of patients self-treating [218].

Restricting the use of antibiotics as growth promoters
It is legal to use antibiotics as growth promoters in agriculture in China, although there are now restrictions on the types of antimicrobial agents that can be used [134]. International recommendations suggest that this use of antibiotics should be further curtailed [4,189].

8.2 FUTURE RESEARCH

Our study methodology and surveys provide a model for how similar investigations could be conducted to assess how antibiotics are being used in other resource-limited settings. Our findings also suggest several questions that future research could address:

- What are the underlying reasons behind the gaps between doctors' reported knowledge and attitudes towards antibiotic use, and their actual prescribing practices? Can addressing these reasons improve antibiotic prescribing?
- Why is there so much variation in practices between individual village doctors? How much of this variation can be explained in terms of patient-related factors?
- Why do some village doctors have very low rates of parenteral- and multiple-antibiotic use?
- Why are some patients that are diagnosed with pneumonia not being prescribed antibiotics?
- Is there a gradient across socioeconomic groups in terms of access to information about appropriate antibiotic use?
- Do interventions that target farmers' knowledge, attitudes and practices towards antibiotic use in animals also affect their knowledge, attitudes and practices towards antibiotic use in humans?

9 ABOUT THE AUTHOR

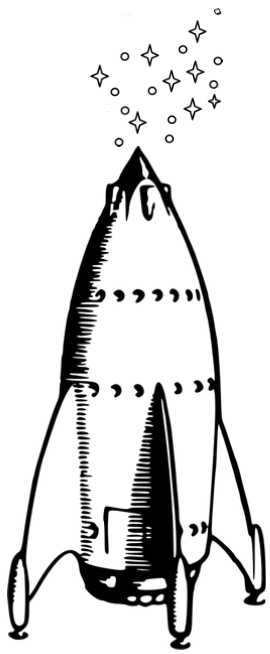
Om vi åker längre än längst,
högre än högst,
var hamnar vi då?

Den nattsvarta himlen är sån,
den tar aldrig slut.
Hur kan det vara så?

Universum,
ger mig svindel
Universum,
Oändligheten.

Hur många stjärnor finns det?
Vad är en evighet?
Finns det oändligt med platser
vi aldrig får se...

Och hur kan man veta det?



If we journey further than the furthest,
higher than the highest,
where do we end up?

The night black sky is like that,
it never ends.
How can that be so?

The universe,
it makes me dizzy,
The universe,
Infinity.

How many stars are there?
What is an eternity?
Is there endless space
we never get to see…

And how can we know that?

Lyrics to *Universum*, written by Madeleine Wittmark, Ensemble Yria

For as long as I can remember, there's always been a certain thrill in thinking about what we know, what we don't know, and how we might be able to get answers to the questions that we don't yet have the solutions to. I like to think of research as being a journey into outer space, to reach the frontiers of our current knowledge – and then exploring ways to go further. In school and at undergraduate level it was mostly about the first part, travelling increasingly deeper within known space. At a postgraduate level it became about pushing past the boundary that lies between the known and the unknown. As a doctoral student I have had the unique opportunity to take this trip full time, for which I am extremely grateful.

I first became interested in infections and microbiology in school. In the beginning it was viruses: I found something indescribably elegant in how simple they were, yet how successful they managed to be. One of my first jobs was in the science department at a local bookshop. This helped provide the resources to fuel my passion further, but unfortunately the employee discount on buying books proved to be such a strong incentive that I'm fairly sure I never actually made any money from all the hours I worked there. During my undergraduate years at medical school I specialized in infections and immunity, and then during my master's thesis I first had the chance to work with antibiotic resistance. I was hooked. This was a rapidly-evolving area of science that united several of my growing interests: global health, human behaviour, education, political actions, systems approaches, ethical dimensions, clinical relevance, and, of course, bugs.

I was fortunate over the following decade to be invited to go on journeys into the unknown together with several researchers spread across the globe – the most significant journey, of course, being the one described in these pages. These journeys are now slowly drawing to an end and I look forward to returning to clinical practice. I have learnt a lot from the time I have been a researcher, both about the world and myself. I am eagerly anticipating the journeys that are yet to come, whichever parts of our universe they end up involving.

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Teachers open the door, but you must enter by yourself.
Chinese Proverb

The question is not what you look at, but what you see.
Henry David Thoreau

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APPENDIX I: QUESTIONNAIRE FOR RURAL RESIDENTS AND BACKYARD PIG FARMERS

Research questionnaire of interaction, transmission and intervention of antibiotics resistance among animals and humans in the rural area of Shandong Province

Village: ______________ Name: ______________

No.: ____________ Date of investigation: _____Year____Month____Day

Data collector: __________

Data checker: _________

Section one: Basic information and life habits of individuals

No.	Question	Answer Type	Comments
1.1	Gender of respondent	①Male ②Female	
1.2	Age of respondent	________years old	
1.3	How many people live with you in the past 6 months.		
1.4	What are the ages of other people in the household?	①__________②_________③__________④___________⑤____________	
1.5	What are the relations to you of other people in the household?	①__________②_________③__________④___________⑤____________	
1.6	Does anyone in your household work outside the village?	① Yes, I do ② Yes, somebody else in my household does ③ No, nobody does	Tick all that apply
1.7	Education level of respondent	①illiterate/half illiteracy ②primary school ③middle school ④high school/technical school/technical secondary school ⑤college ⑥university or above	

1.8	Occupation of respondent	①farmer without a household farm ② small scale household farm ③ big scale commercial farm ④ worker (not on a farm) ⑤ administrator of village ⑥ teacher ⑦village doctor ⑧ student ⑨ military service ⑩ businessman (11) other（specify）	
1.8.1	Do you have any contact with animals on most days?	① Yes, I do ② No	
1.8.2	How often do you visit farms or households with animals, outside of your village?	① Every day ② At least once a week ③ At least once a month ④ At least once every six months ⑤ Less often than once every six months	
1.8.3	Does anyone in your household have any contact with animals on most days?	① Yes, I do ② Yes, somebody else in my household does ③ No	Tick all that apply
1.9	Are you covered by any medical insurance?	① New rural cooperative medical insurance ② Medical insurance for urban residents ③ Commercial medical insurance ④ At my own expense (no medical insurance) ⑤ Other (specify)	

<table>
<tr><td>1.10</td><td>Total (gross) yearly income of household during the last year</td><td colspan="5">________________RMB</td><td>Including job, income from farm</td></tr>
<tr><td>1.11</td><td>Do you eat meat?</td><td colspan="5">① Yes
② No (skip to 1.10)</td><td></td></tr>
<tr><td>1.11.1</td><td>Do you eat mostly market-bought meat or meat from home-raised animals?</td><td colspan="5">① Market-bought
② Home raised
③ About half and half</td><td></td></tr>
<tr><td>1.11.2</td><td>How many days do you eat pork in a week?</td><td colspan="5">_______ days</td><td>Write a number, not a range</td></tr>
<tr><td>1.11.3</td><td>How many days do you eat chicken in a week?</td><td colspan="5">_______ days</td><td>Write a number, not a range</td></tr>
<tr><td>1.12</td><td>How many days do you eat raw vegetables in a week? (e.g. lettuce, raw cucumber etc.)</td><td colspan="5">_______ days</td><td>Write a number, not a range</td></tr>
<tr><td rowspan="3">1.13</td><td rowspan="3">Where do you mostly get your daily-use water from?</td><td>1.13.1 Source of water for drinking</td><td>1.13.2 Source of water for washing and rinsing</td><td>1.13.3 Source of water for rinsing vegetables</td><td>1.13.4 Source of water for washing clothes</td><td>1.13.5 Source of drinking water for pigs</td><td>1.13.6 Source of water for cleaning pigs (e.g. for cleaning the pigsty)</td></tr>
<tr><td></td><td></td><td></td><td></td><td></td><td></td></tr>
<tr><td colspan="6">① Home tap water ② Private well ③ Shared well ④ River water ⑤ Other (specify)
⑥ Not relevant/I have no pigs</td></tr>
</table>

1.14	How often do you drink unboiled water taken directly from a tap or well?	①Every day ②At least once a week ③At least once a month ④Less than once a month ⑤ I never do this			Select one
1.15	Do you usually wash your hands:	1.15.1 Before meals	1.15.2 After going to the toilet	1.15.3 Before working with the pigs	1.15.4 After working with the pigs
		① Always ②Frequent ③Often ④Sometimes ⑤Never ⑥Not relevant			
1.16	How do you usually wash your hands: (for each option where the answer was Always, Often, or Sometimes to 1.13)	1.16.1 Before meals	1.16.2 After going to the toilet	1.16.3 Before working with the pigs	1.16.4 After working with the pigs
		① Wash with soap ② Wash with water only ③ Other (specify) ④Do not wash hands ⑤Not relevant/I have no pigs			
1.17	What kind of toilet do you mostly use?	① Self-owned toilette in the yard or outside of the house ② Toilet inside the house ③ Outdoor shared toilet			
1.17.1	Is the toilet with water-flush or aqua privies?	① Water-flush ② Traditional dry type			

1.18	What animals, and roughly how many of each, do you have in your household and household farm now?	chicken_______ duck_______ dog_______ cat_______ goat_______ sheep_______ cow_______ donkey_______ mink _______ other_______	
1.19	Do you use human faecal or animal manure as fertilizer?	① Human faecal ② Animal faecal ③ Human faecal and animal faecal ④ No	Tick all that apply

Section two: Household health status

No.	Question	Answer type			Comments
			01 Interviewee	02 Other members of household	
2.1	Have you used any medicines (including traditional Chinese medicines) to prevent infections in the past six months?	①Traditional Chinese products ②Western medicines ③No			Tick all that apply
2.2	Have you or your families taken any medicines during the last month (orally) due to newly emerged diseases, not including chronic diseases?	①Yes, in the past week ②Yes, in the past month ③No (skip to 2.3)			Select one
2.2.1	For what kind of disease did you take the medicine(s)?	Open (can include multiple)			
2.2.2	Which medicine(s)?	Write the name of medicine (can be multiple)			
2.2.3	Where did you obtain the medicine(s)?	①village clinic ②town clinic ③county hospital ④Pharmacy in village ⑤Pharmacy in town/city ⑥Other (specify)			Tick all that apply
2.3	Have you or your family had any IV infusions or injections in the past six months?	①yes ②no (skip to 2.4)			
2.3.1	When was the most recent IV infusion or injection?	①In the past week ②In the past month ③Over a month ago			Select one

2.3.2	Reason for the most recent IV infusion or injection	Open			
2.3.3	Place	①village clinic ②town clinic ③county hospital ④Other (specify)			Select one
2.3.4	Medicine(s) in the infusion/injection	Open			
Most recent stay in hospital					
2.4	Have you or someone in your family stayed overnight in hospital in the past year?	①yes ②no (skip to 2.5)			
2.4.1	When was your most recent hospital stay?	①In the past week ②In the past month ③Over a month ago			Select one
2.4.2	Reason for most recent stay in the hospital	Open			
2.4.3	Type of hospital	①Village clinic ②Town clinic ③County hospital ④Above county level hospital ⑤Other (specify)			Select one
2.4.4	Did you have an operation?	①yes ②no			
2.4.5	How many days did you stay in the hospital?				

Section three: Knowledge, attitude and practices towards use and resistance of antibiotics

No.	Question							Answer type	Comments
	Knowledge								
3.1	Do you know what antibiotics are?							①Yes (please describe) ②No	
3.2.1	Please point out which of the following drugs are antibiotics (maximum of three)?								
	3.1.1 Amoxicillin		3.1.2 Paracetamol		3.1.3 Simvastatin		3.1.4 Qingkailing Capsule		
	3.1.5 Erythromycin		3.1.6 Cephradine		3.1.7 Aspirin		3.1.8 Cephalexin		
	3.1.9 Dioctahedral smectite		3.1.10 Compound liquorice tablets		3.1.11 Ibuprofen		3.1.12 Compound acetaminophen		
3.2.1	Please point out which of the following drugs are anti-inflammatory drugs (maximum of three)?								
	3.2.1Amoxicillin		3.2.2 Paracetamol		3.2.3 Simvastatin		3.2.4 Qingkailing Capsule		
	3.2.5 Erythromycin		3.2.6 Cephradine		3.2.7 Aspirin		3.2.8 Cephalexin		
	3.2.9 Dioctahedral smectite		3.2.10 Compound liquorice tablets		3.2.11 Ibuprofen		3.2.12 Compound acetaminophen		
After 3.2.1, say to all participants: "As a reminder, antibiotics are medications that are used to treat bacteria that cause some infections/transmitted diseases"									
3.3	Antibiotics should always be used whenever an adult has a fever							①yes ②no ③I don't know	
3.4	Antibiotics should always be used whenever a child has a fever							①yes ②no ③I don't know	

3.5	Can taking antibiotics in advance protect people from the common cold?	①yes ②no ③I don't know	
3.6	Can antibiotics prevent a common cold developing into more severe disease such as pneumonia?	①yes ②no ③I don't know	
3.7	Do you feel that the same antibiotic has less effect than before if you use it again?	①yes ②no ③I don't know	
3.8	Bacteria can become resistant to antibiotics	①yes ②no ③I don't know	
3.9	Humans can become resistant to antibiotics	①yes ②no ③I don't know	
3.10	Animals can become resistant to antibiotics	①yes ②no ③I don't know	
3.11	Can bacteria which have resistance towards antibiotics infect you or your family?	①yes ②no ③I don't know	
3.12	Where do you mainly hear about antibiotics resistance?	①TV ②Radio ③Internet ④Conversation with other people ⑤Other (specify)	

	Attitudes		
3.13	Please let us know your attitude towards antibiotics if you or your families suffer from the following diseases:		
3.13.1	common cold	①have to use antibiotics every time ②have to use antibiotics most times ③have to use antibiotics sometimes ④there is no need to use antibiotics ⑤I don't know	
3.13.2	Sore throat	①have to use antibiotics every time ②have to use antibiotics most times ③have to use antibiotics sometimes ④there is no need to use antibiotics ⑤I don't know	
3.13.3	hypertension	①have to use antibiotics every time ②have to use antibiotics most times ③have to use antibiotics sometimes ④there is no need to use antibiotics ⑤I don't know	
3.13.4	pneumonia	①have to use antibiotics every time ②have to use antibiotics most times ③have to use antibiotics sometimes ④there is no need to use antibiotics ⑤I don't know	
3.13.5	Diabetes mellitus	①have to use antibiotics every time ②have to use antibiotics most times ③have to use antibiotics sometimes ④there is no need to use antibiotics ⑤I don't know	

3.13.6	asthma	①have to use antibiotics every time ②have to use antibiotics most times ③have to use antibiotics sometimes ④there is no need to use antibiotics ⑤I don't know	
3.13.7	diarrhea	①have to use antibiotics every time ②have to use antibiotics most times ③have to use antibiotics sometimes ④there is no need to use antibiotics ⑤I don't know	
3.13.8	urinary tract infection	①have to use antibiotics every time ②have to use antibiotics most times ③have to use antibiotics sometimes ④there is no need to use antibiotics ⑤I don't know	
3.14	Would you trust the village doctor if they give you medicines when you or your family are suffering from above diseases such as common cold, diarrhea or pneumonia?	①trust ②do not trust ③I don't know	
3.15	Would you trust the county/town doctors if they give you medicines when you or your family are suffering from above diseases such as common cold, diarrhea or pneumonia?	①trust ②do not trust ③I don't know	
3.16	Would you trust the staff working at the pharmacy if they give you medicines when you or your family are suffering from above diseases such as common cold, diarrhea or pneumonia?	①trust ②do not trust ③I don't know	
3.17	I expect the doctor to prescribe me antibiotics when I feel it is needed.	①agree ②disagree ③I don't know	

3.18	Antibiotic can only be purchased with prescriptions from doctors.	①agree ②disagree ③I don't know	
3.19	When taking antibiotics, even if you start to feel better, you should insist on taking the full course based on doctor's advice.	①agree ②disagree ③I don't know	
3.20	Do you worry about antibiotic resistance?	①Yes ②No ③I don't understand	
3.21	I believe that my own practices towards controlling antibiotics resistance is very important	①agree ②disagree ③I don't know	
	Reported practices		
3.22	Have you ever purchased antibiotics at pharmacy during the past year?	①yes ②no (skip to 3.24) ③I don't know (skip to 3.24)	
3.22.1	In what type of pharmacy store did you purchase antibiotics?	①pharmacy in the village ②pharmacy in the town ③pharmacy in the city	
3.22.2	What antibiotics did you purchase? (list up to three they can remember)		
3.22.3	Did you have a prescription from a doctor when you purchased the antibiotics?	① Yes, for all of them ② Yes, for most of them ③ Yes, for some of them ④ No, not for any	

3.22.4	What are the main reasons why you would take antibiotics without visiting the doctor?	①I won't do that ②I have no time to see a doctor ③I don't feel sick enough to see a doctor ④ I have leftover antibiotics from previous illness at home for similar symptoms ⑤ It's more convenient to buy drugs from pharmacy stores ⑥ I don't have money to visit a doctor ⑦other	
3.23	When do you normally stop taking antibiotics for an illness?	①when the symptoms start to disappear ②when I finish the amount of drugs that I was told to take ③other	
3.24	In the past year, have you stored any antibiotics that are left over after an illness?	①yes ②no ③I don't know	
3.24.1	Have you already, or will you use these left-over antibiotics again, when you become ill?	①yes ②no ③I don't know	

Section four: Prioritization during health seeking behavior

No.	Question	Answer type	Comments
4.1	Which of the following are important to you when you suffer from an infection such as common cold or pneumonia?	①getting better quickly ②knowing what caused the illness ③being able to work ④taking medicines ⑤cost of medicines ⑥others	Tick all that apply
4.1.1	Is there anything else that is important to you when you are suffering from an infection?	Open	
4.1.2	Which of these is most important to you?	Select the one that is most important from 4.1 or 4.1.1	
4.2	Which of the following are important to you when you visit the doctor and are suffering from an infection such as common cold or pneumonia?	①physical examination ②obtaining information about the cause of the illness ③obtaining information about the duration of the illness ④if the doctor is going to prescribe me any antibiotics ⑤obtaining information about self-management ⑥other (please specify)	Tick all that apply
4.2.1	Is there anything else that is important to you when you visit the doctor and are suffering from an infection?	Open	
4.2.2	Which of these is most important to you?	Select the one that is most important from 4.2 or 4.2.1	Tick all that apply

Section five: Farm characteristics and pig health

No.	Question	Answer type	Comments
5.1	Do you have pigs in your household now?	①Yes (skip to 5.1) ②No	
5.1.1	Have you had any pigs in your household in the past five years?	①Yes (skip to section 6, don't ask section 7) ②No (skip to section 8)	
5.2	How many years have you had pigs in your household for?	_____ years	
5.3	What type of pigs do you have?	① Sows, with piglets that I raise to slaughter ② Piglets that I buy and raise to slaughter ③ Sows, with piglets that I sell after weaning ④ a combination of 1) and 3) ⑤ Other (specify)	
5.4	How many pigs do you have now?	Numbers of piglets_____ Weaners____ Slaughter pigs (weaned pigs)____ Sows (for breeding) ____ Boars (for breeding)____	
5.5	Have you had any training about raising pigs?	① Yes, from a relative ② Yes, from another person in the village ③ Yes, at a professional course (Days_____) ④ Yes, other (specify) ⑤ No, learned by myself	Tick all that apply
5.6	What are the two most common diseases in your pigs?	Open	
5.7	Have any of your pigs been unwell in the past month?	① Yes, in the past week ② Yes, in the past month ③ No (skip to 5.8)	
5.7.1	What were the diseases in the past month?		

5.7.2	What were their symptoms?		
5.7.3	How many days on average were they ill for?	____days	____days
5.7.4	Did you give them any medication?	① Yes (specify) ② No	① Yes (specify) ② No
5.8	Have you given any healthy pigs any medications in the past month (including traditional Chinese medicines)?	① Yes (specify all medications given and why________) ② No	
5.9	Which of the following are important to you when your pigs are suffering from an infection, such as diarrhea?	① Knowing what caused the illness ② Knowing how severe the illness is ③ How long it takes them to recover ④ The cost of medicines ⑤ Preventing spread of the infection to other pigs ⑥ That I will lose all my possible profit from my pigs	Tick all that apply
5.9.1	Is there anything else that is important to you when your pigs are suffering from an infection?	Open	
5.9.2	Which of these is most important to you?	Select the one that is most important from 5.8 or 5.8.1	

Section six: Knowledge, attitudes and practices towards pig antibiotic use and antibiotic resistance

No.	Question	Answer type	Comments
	Start with introduction to antibiotics again:	As I said earlier, antibiotics are medications that are used to treat bacteria that cause some infections/transmitted diseases	
	Knowledge		
6.1	Can you mention two pig diseases that are normally treated with antibiotics?	Open	
6.2	Should antibiotics be used whenever a pig stops eating its feed	① Yes ② No ③ I don't know	
	Attitudes		
6.3	I know when my pigs need medications	①agree ②disagree ③I don't know	
6.4	It is good to keep left over antibiotics at the farm to use them again in the future	①agree ②disagree ③I don't know	
6.5	I would trust the vet if they decided to give a medication to a pig with an infection	①agree ②disagree ③I don't know	
6.6	It is expensive to get advice on pig health and management from a vet	①agree ②disagree ③I don't know	
6.7	It is expensive to buy antibiotics for my pigs	①agree ②disagree ③I don't know	
	Practices		

6.8	Do you usually seek advice from other people if your pigs are sick?	① Yes, from vet ② Yes, from animal pharmacy ③ Yes, from other farmers ④ Other (specify) ⑤ No	Tick all that apply
6.9	Do you have these behaviors when you use antibiotics?	① Always or often in feed, to keep the pigs healthy and prevent disease ② For all pigs in a pen, when some of the pigs in the pen are sick ③ Only in pigs showing disease	Select one
6.9.1	Are there any other reasons why you use antibiotics?	①yes ②no	
6.10	Where do you most commonly buy antibiotics for your pigs?	① From a vet ② From an animal pharmacy ③ From a human pharmacy ④ From the market ⑤ From another household farm ⑥ Other (specify)	Tick all that apply
6.11	What are the three antibiotics that you most commonly use for your pigs?	Open (list up to three)	
6.12	Do you use traditional Chinese medicines for your pigs?	① Yes ② No (skip to 6.13)	
6.12.1	What are the main reasons you use traditional Chinese medicines for your pigs?	Open	
6.13	In the past year, have you purchased antibiotics for your pigs without first speaking with a vet/?	① Yes ② No	
6.14	What are the main reasons why you would give antibiotics to your pigs without first speaking with a vet/animal health advisor?	Open	

Section seven: Biosecurity on household farms

No.	Question	Answer type	Comments
7.1	What feed do you use for your pigs?	1 Own feed 2 Feed from another farmer 3 Commercial feed 4 Other (specify)	Tick all that apply
7.2	Do you always clean the pens more thoroughly when they are empty?	1 Yes 2 No	
7.3	What do you clean the pens with when you clean them more thoroughly?	1 With water first, then disinfectant 2 With disinfectant only 3 With soap and water 4 With only water 5 Other (specify)	Select one
7.4	How often do you buy pigs?	1 Many times a year 2 Once a year 3 Once every two years 4 Less often than once every two years	Select one
7.5	Where do you normally buy pigs from?	1 My village 2 Another village 3 A mixture of villages 4 Other (specify)	Select one
7.5.1	What sort of place do you normally buy pigs from?	1 Village farm 2 Commercial farm 3 Market 4 Other (specify)	Y/N for each option
7.6	Do you keep newly bought pigs separate from other pigs for some time?	1 Yes (how long for ________) 2 No	
7.7	On average, how often do you sell animals?		

Section eight: Medicines currently in household

No.	Question	Answer type		Comments
8.1	Which medicines do you have in your home at the moment for you or your family?	Please write down ALL medicines (names only)	For each medicine, ask if they think it is an antibiotic and record Yes, No or Don't know	
8.2	Which medicines do you have in your home at the moment for your pigs?	Please write down ALL medicines (names only).	For each medicine, ask if they think it is an antibiotic and record Yes, No or Don't know	