

INTERACTIONS BETWEEN INTENSIFYING LIVESTOCK PRODUCTION FOR FOOD AND NUTRITION SECURITY, AND INCREASED VULNERABILITY TO AMR AND ZOOSES

Jonathan Rushton, Will Gilbert, Lucy Coyne, Lian Thomas with Gina Pinchbeck and Nicola Williams (Institute of Infection and Global Health, University of Liverpool)

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ABBREVIATIONS

AGP	Antimicrobial Growth Promoters
AHPA	Animal Health and Products Association (Thailand trade association for veterinary pharmaceuticals)
AMR	Antimicrobial resistance
AMU	Antimicrobial use
APHCA	Animal Production and Health Commission for Asia and Pacific
ASF	Animal Source Foods
CDC	Centers for Disease Control and Prevention
CGIAR	Consortium of International Agricultural Research Centers
CIVAS	Center for Indonesian Veterinary Analytical Studies
DALYs	Disability Adjusted Life Years
DLD	Thai Government Department for Livestock Development
ECDC	European Centre for Disease Prevention and Control
ESVAC	European Surveillance for Veterinary Antimicrobial Consumption
EU	European Union
FAO	Food and Agricultural Organisation
FAOSTAT	Food and Agricultural Organisation Statistics
GAP	Good Agricultural Practices
GDP	Gross Domestic Product
HIC	High Income Country
HIV-AIDs	Human immunodeficiency virus infection and acquired immune deficiency syndrome
HPAI	Highly Pathogenic Avian Influenza
HP-CIAs	Highest Priority Critically Important Antimicrobials
ILRI	International Livestock Research Institute
IMF	International Monetary Fund
LMIC	Low and Middle Income Country
MARD	Ministry of Agriculture and Rural Development (Vietnam)
MDR	Multi Drug Resistance
MIC	Minimum Inhibitory Concentration
MOH	Ministry of Health (Indonesia)
MRSA	Methicillin Resistant <i>Staphylococcus aureus</i>
NTS	Non-Typhoidal <i>Salmonella</i>
OECD	Organisation for Economic Co-operation and Development
OIE	World Organisation for Animal Health
USA	United States of America
USD	United States Dollar
WHO	World Health Organisation
WAHIS	World Animal Health Information Database Interface
WTO	World Trade Organisation

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INTRODUCTION

Human society has changed more quickly over the last fifty years than at any other time in history due to technical innovations that have led to better sanitation and health provision, and greater and more stable supplies of food. The supply of food has been transformed with adoption of new crop and livestock systems. Livestock production systems have become more intensive in many regions in the use of land, water and feed in order to increase production overall and generate greater productivity in terms of output per animal, land and labour units. These factors have been the basis of very fast population growth, particularly in lower and middle-income countries during this period, with many of these new people being located in urban areas.

Yet despite these advances existing issues are not being resolved, and new issues are emerging. In the case of food and nutrition security: (1) there continues to be a major group of people who do not have enough food; (2) there is a rapidly emerging group who consume too many calories; and (3) there are others who have a limiting access to micronutrients. This triple burden can exist in different populations, yet the rural to urban transition has been so rapid that it has also been observed in the same family and in some extreme cases, even in the same individual (Keino *et al.*, 2014; Dominguez-Salas *et al.*, 2016). These nutrition-related problems are creating new health challenges in non-communicable diseases (NCDs) which are rising both in total case numbers and their relative importance (Murray *et al.*, 2012; Black *et al.*, 2013). The problems of NCDs in LMICs are of greatest relevance in urban centres. While this paper will not address NCDs directly, it will highlight that this is an area that needs to be thought through carefully when considering livestock food systems.

The intensification of livestock production has also created challenges of emergence and re-emergence of pathogens. Many of these pathogens are solely related to infections in animals, with some having impacts on food supply due to their infectious nature (Knight-Jones and Rushton, 2013; Knight-Jones, McLaws and Rushton, 2017), the losses they cause, and the responses to manage the disease (Rich and Wanyoike, 2010; Bett *et al.*, 2017). However, other pathogens have a major impact on human health as they can move between species: they are zoonotic. Zoonotic diseases may transmit through contact with animals and their products, such as the influenza viruses (Rushton *et al.*, 2005), or through consumption of contaminated food, leading to food borne infections (Havelaar *et al.*, 2015). When managing these pathogens in people, the effectiveness of pharmaceutical products can be compromised if the animals they come from have already been treated with certain types of antimicrobials, where selection pressures can lead to the emergence of antimicrobial resistance (AMR) (Aarestrup, Wegener and Collignon, 2008; Marshall and Levy, 2011a).

This paper will examine the context of intensifying livestock systems with reference to the zoonotic pathogens present in the associated value chains. It will then provide information on the increased risk of AMR development and zoonoses transmission from these systems. In this process it will help guide how the Consultative Group for International Agricultural Research (CGIAR) can help to address current problems and prevent the emergence of future issues while maintaining safe and stable supplies of livestock products through research innovation and policy influence.

Definitions

Food and nutrition security

Food Security is considered “*adequate access to food for all people at all times for an active, healthy life*”; where food is defined as a substance drunk or eaten in order to maintain growth and life. However, nutrition security is considered to go beyond this simple definition. Nutrition security is only considered to be achieved if there is sufficient food available, in an accessible form, which can be utilized by all individuals at all times, in order to live a healthy and happy life (Gross *et al.*, 2000). It is more than food being available, it is about there being sufficient accessible food which can be utilized by a population in order to maintain positive health. The World Food Summit (1996) captured this with the following statement “Food security exists when all people, at all times, have physical and economic access to sufficient, safe and nutritious food that meets their dietary needs and food preferences for an active and healthy life”.

Intensification of livestock systems

Intensification of livestock systems is the increased use of external inputs and services to increase the output quantity or value per unit for livestock production (Bebe, Udo and Thorpe, 2002). In reality, this usually means applying specialised management skills including changes in housing, feeding and husbandry in order to increase production per animal and per labour unit. This is typically driven by an increased consumer demand for meat, eggs and dairy products (Udo *et al.*, 2011).

Vulnerability

Vulnerability is the extent to which an individual, organisation or population is unable to anticipate or cope with, resist and recover from the impacts of disasters either a natural or man-made. This is a dynamic process and is frequently associated with poverty.

Food chain/food system

A food chain or food system is defined by the FAO as ‘*the full range of farms and firms and their successive coordinated value-adding activities that produce particular raw agricultural materials and transform them into particular food products that are sold to final consumers*’ (FAO, 2014a).

Antimicrobials and AMR

Antimicrobials are agents which kill or inhibit the growth of microorganisms such as bacteria, viruses, fungi and parasites. Antimicrobial resistance (AMR) occurs when these microorganisms change in ways which mean that antimicrobial agents are no longer effective in these actions. AMR is considered to be a natural adaptation mechanism for microbes, however the chances of resistance occurring are increased by the indiscriminate use and overuse of antimicrobials. The consequence of AMR is therefore that infections are increasingly difficult to treat and cure, resulting in higher morbidity and mortality in human and animal species. Consequently, this can have negative effects on livelihoods and food security and can result in increasing costs for healthcare.

Antibiotics are antibacterials which kill or inhibit the growth of bacteria; therefore, antibiotic resistance specifically refers to bacterial resistance (FAO, 2016; WHO, 2018).

Zoonoses and food borne diseases

A zoonotic disease is one which is naturally transmitted between people and vertebrate animals, including wildlife, livestock or domestic pets (WHO, 1959). It is estimated that such diseases represent 58% of all human pathogens and over 60% of all emerging diseases (Jones *et al.*, 2013). A foodborne disease is one caused through ingestion of

contaminated foodstuffs, be that by a parasite, viral or bacterial pathogen or chemical agent (Tauxe *et al.*, 2010). Foodborne diseases were estimated to be responsible for 33 million DALYS lost in 2010, of which over half were attributable to diarrheal causing agents (Havelaar *et al.*, 2015).

Animal welfare

Animal welfare refers to the state of an animal and how it is adapting to the conditions within which it lives. Animal welfare is considered to be of a sufficient standard if the animal is healthy, safe, has appropriate nutrition, is able to express natural behaviours and is free from pain, fear and distress. Maintaining positive animal welfare requires disease treatment and prevention, appropriate housing, management and nutrition with humane handling and slaughter (OIE, 2016a).

Problem and potential solutions

Intensifying livestock product systems and their associated value chains provide supplies of livestock products for growing human populations and particularly for urbanising populations. These systems generate significant benefits in terms of food security and nutrition, yet pose threats in terms of zoonotic disease emergence and re-emergence and antimicrobial resistance.

These problems need to be managed and minimised through smart research on pathogen and AMR mitigation measures and implementation of these through well-directed strategy discussions with the public sector, and policy engagement with the private sector. The objectives of such activities need to be optimisation of food security and nutrition and minimisation of the risks of zoonoses and AMR from the intensifying livestock systems.

Structure of the document

The document will cover the context in which the intensifying livestock systems are emerging and then examine the current levels of knowledge of zoonoses and AMR. This followed by looking at how the CGIAR are working in this area and how this can be linked to policy initiatives more broadly. The concluding section looks at specific recommendations.

THE CRITICAL DRIVERS OF CHANGE TO LIVESTOCK PRODUCTION AND THE POSITIVE AND NEGATIVE IMPACTS AT A GEOGRAPHICAL LEVEL

Introduction

The intensification of livestock systems and their associated value chains is the result of demand and supply factors that are described in this section. The positive and negative implications of this process are also covered with some indication of how they have been managed to date.

Global trends in population, urbanisation and incomes

The intensification of food systems follows predictable patterns which develop in response to the changing demands of a growing population and shifting demographic profiles. It is therefore necessary to look at global trends in population to understand the likely direction of development for livestock systems across the globe.

The human population of the planet has grown exponentially from 2.5 billion in 1950 to 7.4 billion in 2015, and is expected to approach 10 billion in 2050. The rate of change over this time period has been most rapid in middle income countries (Figure 1) and while growth in upper-middle income countries has been strong since 1950, these populations are expected to stabilise in the next 30 years; lower-middle and low income countries will then contribute the bulk of the global population increase between the present and 2050 (Gerland *et al.*, 2014).

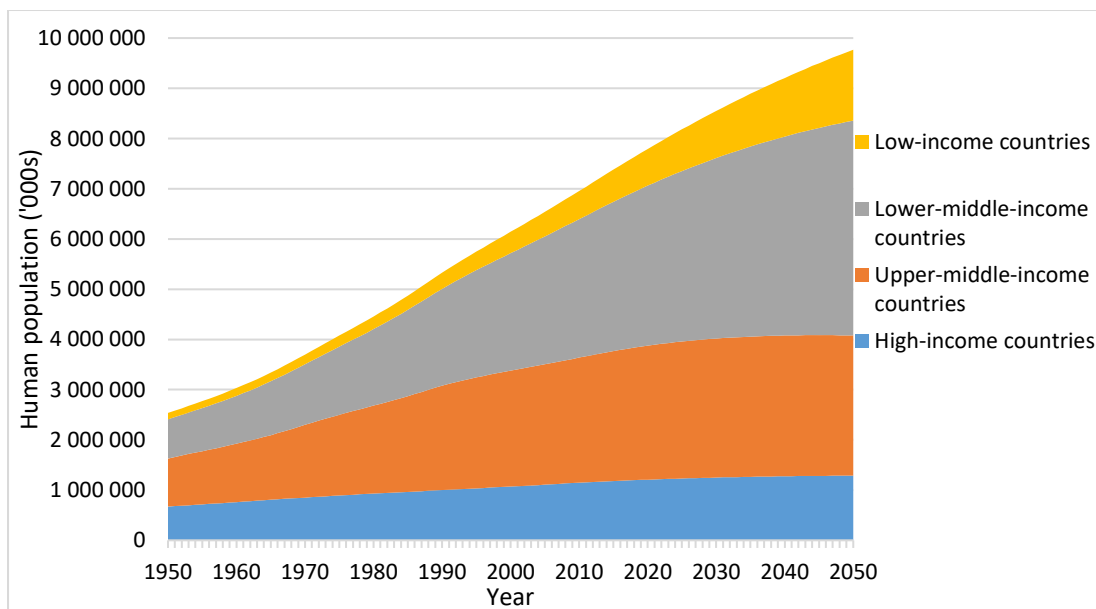


Figure 1. Global population by region 1950-2015 with projection to 2050. Groupings are defined by World Bank atlas classification on income. **Data source:** United Nations.

Over the same period, the world's population is becoming increasingly urbanised. Urbanisation is defined by an increase in the proportion of a population living in urban areas. There are three mechanisms by which this can take place, firstly the net of births and deaths in urban areas is greater than in rural areas, secondly migration from rural to urban areas increases as labour availability begins to exceed opportunities for employment (Satterthwaite, McGranahan and Tacoli, 2010). The urban population may then increase more rapidly than the rural population. Thirdly rural areas may reach

sufficient population density to cause them to be reclassified as urban (Rogers, 1982). Between 1990 and 2015, the proportion of the world's population living in urban areas increased from 42.9% to 53.8% (World Bank, 2018a); again, the greatest contribution to this change has come from middle income countries (Figure 2). Urbanisation is linked to economic growth, increased productivity, and rising incomes by a variety of mechanisms (Quigley, 2007).

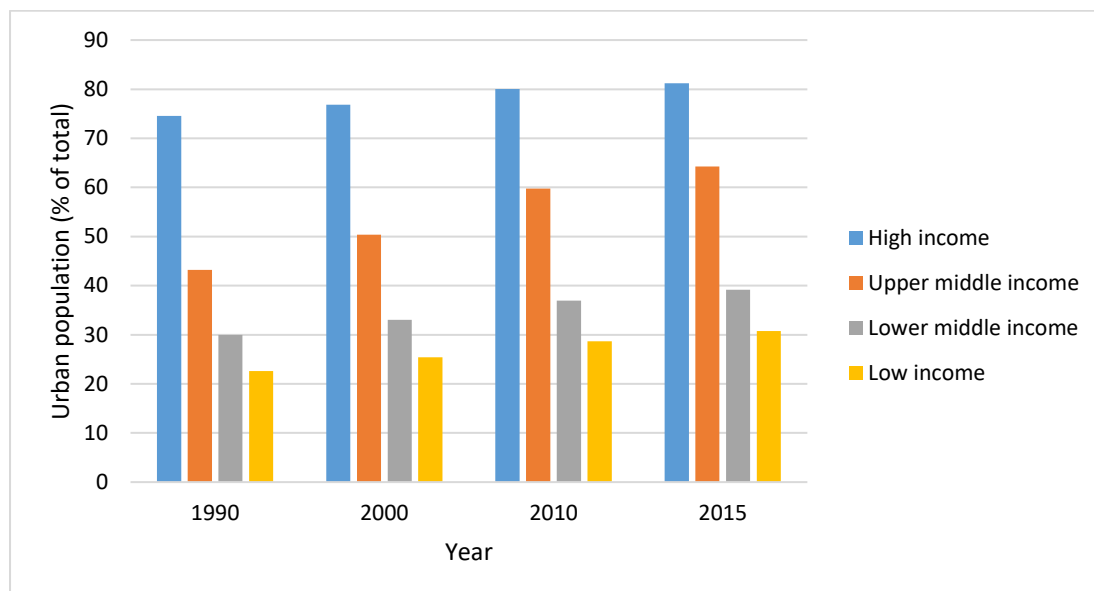


Figure 2. Urban populations as percentage of country total, 1990 to 2015, according to World Bank income classifications. **Data source:** World Bank.

Simultaneous to the growth in world population and urbanisation, approximately 25% of the population has risen out of the extreme poverty bracket since 1990. This increase in incomes has been particularly strong in lower and upper-middle income countries, which have experienced a period of sustained growth in GDP per capita since the 1990s. Perhaps more importantly for the development of food systems, the last 30 years have seen a rapid increase in incomes in upper middle income countries which has resulted in the appearance of what has been called a “global middle class” (Kharas, 2010). It is estimated that between 1990 and 2005, 1.2 billion people joined this middle class stratum, 80% of which were in Asia, 50% in China alone (Ravallion, 2010). The middle class, characterised by a proportion of disposable income, are able to discriminate purchases of goods on the basis of quality (Banerjee and Duflo, 2008).

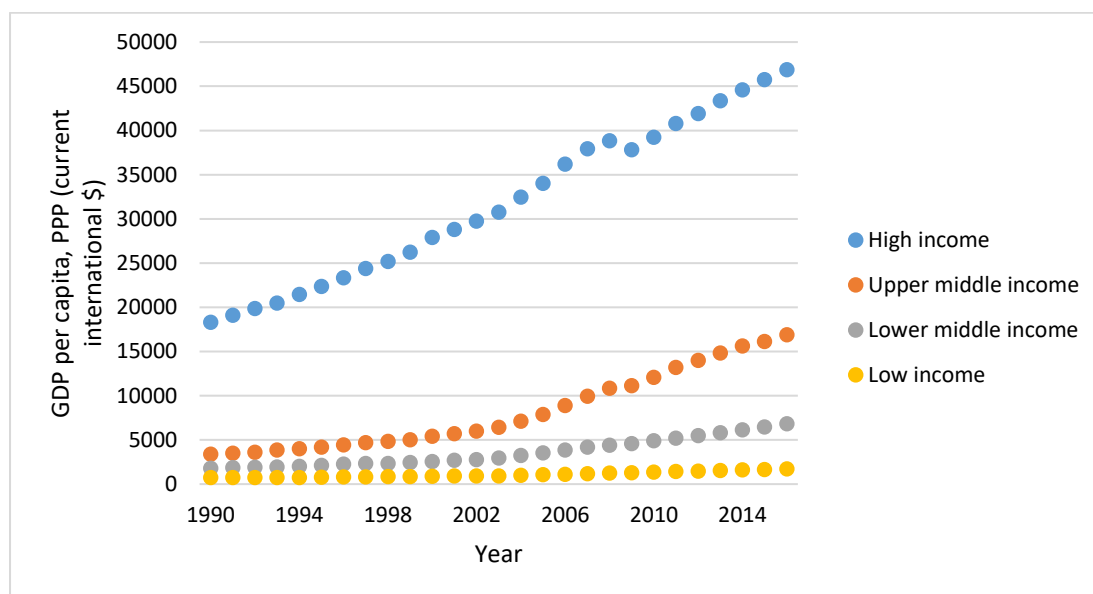


Figure 3. GDP per capita change over time in countries by World Bank income classification, 1990 to 2016.

Data source: World Bank

Implications for food system development

On the demand side, the proliferation of increasingly wealthy consumers located in urban centres is a key driver of demand for animal source foods (ASFs), demand which drives the development of food systems. First and foremost, income increases allow a shift toward better tasting food once basic needs energy requirements are met (Deaton, 1997). The intrinsic qualities of ASFs in terms of taste and perceived nutritional value appeal to consumers making this income transition, and demand for ASFs contains significant income elasticity (Cornelsen *et al.*, 2016). Increasing income therefore results in a shift toward increased intake of ASFs.

Gerbens-Leenes, Nonhebel *et al.* (2010) demonstrate a non-linear relationship in this shift, with the move to ASFs being most rapid at incomes below \$12,500 per capita, slowing thereafter. While it has been proposed that meat consumption will decline in affluent societies as consumers become increasingly aware of the long-term health risks associated with excessive consumption and the environmental risks associated and livestock production systems, empirical evidence suggests the threshold value at which this transition occurs is at an income approaching \$50,000 per year (Cole and McCoskey, 2013). Indeed, projections show only modest increases in demand for animal source foods in developed countries suggesting this saturation point is being reached (Alexandratos and Bruinsma, 2012), accompanied by a shift in preference from red to white meat, particularly poultry, due to health concerns (Daniel *et al.*, 2011). In the developing economies, growth in demand for meat and other ASFs has been strong in the past, driven by rapid growth in consumption in Brazil and China. In total, global meat consumption increased by 59% between 1990 and 2009 (Henchion *et al.*, 2014), however projections indicate consumption is likely to increase by between 1 and 2% for dairy products per annum and 1 and 3% for meat across the developing world for the next 30 years (Alexandratos and Bruinsma, 2012).

The effect of urbanisation on demand for ASFs cannot always be disentangled from the effect of increased income, however a number of studies have shown an increased meat consumption effect that is independent of increased income in urban areas (Rae, 1998; Maltoglou, 2007; Betru and Kawashima, 2009). Explanations for this phenomenon include the expansion of food retail businesses such as supermarkets in these environments, access to power allowing refrigeration of products, and changes in lifestyles leading to increased opportunity to eat meat away from home and consume convenience food (Liu and Deblitz, 2007; Kanerva, 2013).

On the supply side, production systems have been developed based on monogastric species; with their high reproductive rate and more efficient feed conversion they are able to deliver value to consumers in terms of price per consumption unit. These systems are based on the availability of cheap feed grains and oilseed cakes, and were initially developed in North America and adopted in OECD countries. More recently there has been widespread exposure to these systems in LMICs, both through adoption of the systems themselves and through import of the products they produce. Necessary elements for the development of these systems, such as access to cheap feed grains, are not, however, present in all LMICs. There is an interaction between local geographic, cultural or religious considerations which influences species and systems selection both within and between countries. This can inhibit growth in consumption of certain products despite rising incomes, hindering the ability to compare consumption patterns and food system development directly without consideration of these extrinsic variables. Also of note is the growth in global aquaculture as a provider of ASFs since the 1980s. Global per capita fish consumption has grown from 13.5kg per year in 1990 to over 20kg per year in 2016, with this increased demand almost entirely met by growth in aquaculture (FAO, 2018). China has been the major contributor to this growth, producing more than 50% of farmed fish globally. Aquaculture production is expected to grow by 37% globally to 2030, with the most rapid expansion in LMICs.

Satisfying increasing demand can be done in one of three ways, increasing food imports, through agricultural development by extensification: the turning of more land over to food production, or intensification: achieving higher yields per unit of input. While extensification does not demand technological change, intensification is strongly linked to increasing technological inputs to agricultural systems. A critical factor in determining whether food demand is satisfied by intensification or extensification is population density (Boserup, 2005). While rural populations grow under conditions of low density, extensification can satisfy increases in demand; however, land is a finite resource and once population density reaches a critical point, further land cannot be put into production at the same level of intensity. Put simply, increasing population density reduces the land available per farm, leading to intensification in input use: initially through labour, and subsequently through capital, to maintain total yields (Masters *et al.*, 2013). This pattern is detectable in empirical studies (Josephson, Ricker-Gilbert and Florax, 2014; Ricker-Gilbert, Jumbe and Chamberlin, 2014).

Intensified systems offer considerable advantages as compensation for their increased input use. Internal economies of scale allow labour specialisation, increased purchasing power to negotiate better input prices, and greater access to capital, therefore increasing access to technological interventions requiring capital investment. External economies of scale result from the collocation of similar enterprises, allowing the sharing of supporting services, such as transport, veterinary services and slaughter facilities, further reducing production costs. While transport costs remain high, livestock production systems tend to localise in close proximity to markets (Gerber *et al.*, 2010). Subsequent changes in land value and consideration for environmental impacts tend to drive livestock out of urban centres; however, up until this point there is still considerable reliance on livestock located within urban and peri-urban settings to meet local demand. Within such an environment there is noted risk of contact between livestock, livestock waste, wildlife and people (Mougeot, 2000).

These conditions raise the risk of externalities associated with livestock production systems being generated. Examples of such externalities include:

- Animal welfare. Considered a public good, poor animal welfare presents a case for intervention to internalize societal costs (FAWC, 2011).
- Environmental impact, particularly in relation to disposal of excreta. Traditional farming systems utilised animal waste as manure, cycling nutrients back into crop yield. If the nutrient content of waste exceeds the absorption capacity of available land, run-off into water systems can cause numerous negative consequences (Reid *et al.*, 2010).
- Risk of zoonotic disease transmission as intensive systems create high density populations of low genetic diversity which favour disease transmission (Jones *et al.*, 2013).

- AMR development, as intensive systems are the most intensive users of antimicrobials per unit of output (Van Boeckel *et al.*, 2015).

Livestock productions externalities raise the issue of regulation and governing institutions. The institutions responsible for imposing regulation and monitoring compliance are in a constant cycle of revision and restructuring as they seek to limit societal exposure to externalities, while optimising food supply and the benefits this creates in terms of food security and nutrition. In industrialised countries, where intensive livestock systems have been the norm for a longer period, governments still play a strong part in regulating to minimise public health or environmental risks, as well as imposing minimum standards on welfare and management of food safety; this is achieved through risk analysis and policy development. Additional standards are imposed by supranational organisations, such as the European Union (EU) and World Trade Organisation (WTO) in the public sector, and in the private sector through the International Organisation for Standardisation (ISO). Further standards relating to product quality, animal welfare and input use are also used to define product characteristics and differentiation (for example organic or free-range products). The frequency with which food safety scares and scandals are reported in the media illustrate the difficulty in successfully enforcing regulation and keeping pace with technological developments, even where resource allocations to regulating agencies are relatively generous (Knowles, Moody and McEachern, 2007; Bánáti, 2011). In addition, the instruments and policies used to internalise externalities in livestock systems can drive structural changes in livestock industries. Cases in point are provided by the reactions to BSE emergence in the UK in the 1980's and 1990's, and the avian influenza epidemic in Thailand in the 2000's which served to increase transaction costs facing producers and processors of beef and poultry products respectively (Loader and Hobbs, 1996; McLeod, Thieme and Mack, 2009).

Investigating how the regulatory agencies in LMICs are coping with the pace of change in livestock systems is compromised by the poor quality of data available. However there are significant efforts being made to address this issue, one such source of data on the performance of state veterinary services. Veterinary services are essential as an executive agency to enforce regulation as it pertains to livestock farming and animal health, particularly with reference to the occurrence of zoonotic disease in livestock populations and the supply and use of antimicrobial products. One source of information on veterinary services is provided by the OIE Performance of Veterinary Services (PVS) programme. This programme is aimed at capacity building within veterinary services, exploring the political and legislative structures in which veterinary services are embedded, as well as resource allocations, technical capabilities, and stakeholder engagement (Schneider, 2011). A review published in 2012 by Weaver *et al.* (2012) aggregated the results of 14 PVS evaluation reports from developing countries across the Americas, Africa and Asia. Classifying results on each criterion of evaluation by levels, ranging from “no significant activity” to “Good progress toward international best practice”, key deficiencies in capacity were identified in every one of the countries analysed. A summary of the report is presented in Table 1, illustrating the challenges facing veterinary services in developing countries. These challenges therefore relate directly to countries' capacity to regulate the supply and use of antimicrobial products, and act on zoonotic disease risks.

Table 1. Summary of findings relating to veterinary service evaluation in 14 developing countries as reported by weaver et al. (2012), assessed by OIE PVS GAP analysis.

Area	Definition	Result
Chain of command	Strength of authority from central government down to regional, district and local level.	Often decentralised with autonomy at district level. Lack authority to control or co-ordinate with other agencies.
Legislation	Specifies organisational structure, budget support, technical authority, obligations and responsibilities.	Often inadequate or outdated, fails to keep pace with changes in environment. Lobbying power is limited to push change. Lack of clear mandate for veterinary services. Organisational structures and responsibilities poorly defined. Lack of registration of veterinary professionals. Weak system of control for medications and biologicals.
Technical Competence	An assessment of the human capital within the system in terms of technical expertise and proficiencies.	Lack of management for professional standards means technical competence is unmeasured and unregulated.
Technical Independence	The ability to base decision making on technical matters on objective evaluation without bias or self-interest.	Inadequate information collected on which to base decisions. Processes not standardised. Bias, self-interest and political interference all documented. Insufficient remuneration of technical staff undermines independence.
Communications	Strength of communication within veterinary systems and between systems and stakeholders.	Lack of dedicated communications staff with specific budget. Lack of representative stakeholder groups within industry restrict communication opportunities.
Joint programmes	Jointly developed plans between veterinary services and other stakeholders.	Lack of public-private partnership in disease control. Lack of preparedness for disease incursion where co-ordination is required across livestock sector.
Technical policies and programmes	Core activities of veterinary services relating to animal health, livestock and public health.	Weaknesses in border control and quarantine including lack of staff, of data recording; limited use of risk analysis principles in resource allocation, low levels of co-ordination with neighbouring countries. Limited control over slaughter processes and post-slaughter distribution of products. Limited or no control over distribution and use of veterinary pharmaceuticals and biologicals.
Funding	Funding is adequate and sustained to allow forward planning.	Resources limited to the extent that baseline activities are compromised. Competition for resources with other departments, veterinary services are not seen as a priority. Reliance on foreign aid.

Summary

The development of intensive livestock production systems and their associated value chains is being driven by a combination of demand, through greater numbers of people in urban areas who are wealthier, and supply, through innovation in livestock food systems that allow more intensive systems of production, processing and distribution. This

has created a situation where ASF are more widely available and accessible than in the past with the result of positive impacts on food security and nutrition. Yet there are significant externalities with these intensifying systems in terms of the environment, welfare, zoonotic diseases and AMR. These require strong institutional responses and combined action from the public and private sectors to optimize food supply and minimize the externalities. So far the response in LMICs has been variable, and it is indicated that this is in part due to competition for resources and lack of institutional capacity. The following section will examine the state of knowledge on zoonoses and AMR with regards the intensifying livestock systems.

THE STATE OF KNOWLEDGE OF THE LIVESTOCK FOOD PRODUCTION, ZOOZOSES AND AMR

Introduction

The previous section described the situation in livestock systems in environments undergoing rapid economic and population growth and urbanisation. Now it is necessary to ask what characteristics of these systems produces changes in risk with respect to the emergence of antimicrobial resistance and zoonotic disease transmission? This section will therefore explore the theory and empirical evidence linking the process of intensification with changes in these risks. In doing so, the quality and quantity of data collection on antimicrobial use (AMU) globally will be explored and case studies in two LMICs presented.

Linking AMU, AMR and zoonoses

The drivers of AMR are complex and multifactorial; however, the exposure to antimicrobial drugs is believed to be key in providing selective pressure under which AMR becomes more common within populations. Logically following from this, the quantity, quality and frequency of exposure to AMs creates an environment under which the prevalence of AMR can be promoted. It has been estimated that in human medicine up to 50% of antimicrobial prescriptions are considered to be unnecessary (CDC, 2013) and this indiscriminate use has been directly linked with the development of resistance (Aiken *et al.*, 2014; Holmes *et al.*, 2016). This link is further confirmed by the modest reduction in AMR identified following a reduction in antimicrobial prescriptions in humans (Livermore *et al.*, 2013).

Whilst the link between antimicrobial use and resistance has a logical mechanism, the complexity of this association should also be considered. Factors such as pathogen-host and pathogen-drug interactions, horizontal gene transfer, the transmission rates of pathogens between humans, animals and the environment, and cross-resistance to different antimicrobials and classes need to be considered when AMR mechanisms are assessed. Other factors such as population vaccination rates, hygiene measures, migration, different healthcare settings and population densities also influence resistance prevalence (Turnidge and Christiansen, 2005; Grijalva, 2014).

The direct study of the relationship between exposure to antimicrobials and resistance development is problematic. Firstly, it is difficult to quantify the effects of specific antimicrobial use on resistance levels in a bacterial population. The literature documents that a number of factors have been associated with variability in AMR in populations of pigs, poultry and cattle. For example, differences in exposure to antimicrobials, variations in management practices that might contribute towards AMR and contrasts in the association between antimicrobial exposure and resistance have been demonstrated in these different livestock species (Akwar *et al.*, 2008; Thibodeau *et al.*, 2008; Morley *et al.*, 2011).

Secondly, the diverse methodologies by which AMR is tested can result in testing biases and data which cannot be easily compared, making meta-analysis difficult (Aarestrup, 2005). For example, results from some methodologies may be quantitative, such as Minimum Inhibitory Concentrations (MIC), whilst all tests can provide qualitative categorical

results such as susceptible, intermediate or resistant. Other tests such as disc diffusion testing also only provide categorical data (Jorgensen and Ferraro, 2009; Benedict *et al.*, 2014, 2015).

Nevertheless, potential pathways for the spread of resistance from organisms existing within animal populations to those of significance to human health are recognised, via both the zoonotic transmission of pathogens or through horizontal transfer of resistance genes. The use of antimicrobials in livestock is therefore considered to present a risk to human health, and although at present that risk is unquantifiable in a precise manner, isolated incidents of such transfer are described in the literature (O'Neill, 2016; Hadjadj *et al.*, 2017; Tang *et al.*, 2017; Aidara-Kane *et al.*, 2018). Research into intensive agricultural systems has identified that the intestinal microbiota of food producing animal species can act a source of resistant bacteria for those working and living in close proximity (Graveland *et al.*, 2011; Seiffert *et al.*, 2013; Patchanee *et al.*, 2014), and multi-drug resistant bacterial zoonoses have been identified and may represent major threat to public health (Zhu *et al.*, 2013; Jans *et al.*, 2017; Lugsomya *et al.*, 2017). In light of these early indicators of risk, it has been considered prudent that restrictions are placed on the use of antimicrobials in both veterinary and human medicine, with the aim of slowing the emergence of resistance (Aarestrup, 2005; Llor and Bjerrum, 2014; O'Neill, 2016).

Intensive livestock systems have traditionally been heavily reliant on non-therapeutic antimicrobials; particularly around production stages with high stress (Van Boeckel *et al.*, 2015). Non-therapeutic use includes both group administration for disease prevention and antimicrobial growth promoter (AGP) use; whereby sub-therapeutic doses are used in order to enhance growth and productivity. A study in Vietnam identified that 84% of farms used antimicrobials for disease prevention and that around a third of such usage was antimicrobial classes considered by the World Health Organisation (WHO) to be critical to human health (Carrique-Mas *et al.*, 2015). Despite many LMICs regulating and banning AGP use, it is often poorly enforced due to limited resources and insufficient funding (Schar *et al.*, 2018). The sub-therapeutic use of antimicrobials and their use as AGPs to meet the increased demand for animal protein increases the selection pressure for resistant bacterial strains to develop. Trade-offs also exist between the use of AGPs and the risk generated through their use. A study of production losses due to hypothetical global ban on AGPs estimated a reduction in the value of global meat production of between \$13 and \$44 billion (Laxminarayan, Van and Teillant, 2015). Reports from the Danish pig sector, which banned AGPs in 2006, indicate a rise in therapeutic use of AMs following, and no net change in AMR levels in environmental microorganisms (Jensen and Hayes, 2014). These studies indicate that such trade-offs must be considered in each individual context when setting policy.

Concern has been expressed over the use of AMs with human health significance in aquaculture systems (Marshall and Levy, 2011b). Aquaculture carries risk pathways for the development of AMR through the discharge of waste water and excreta into surface water bodies, and the accumulation of medicated feed in the environment (Samuelsen, Torsvik and Ervik, 1992; Sørum, 2008). Sediment deposit sampling in aquaculture farms has demonstrated that antimicrobial resistance genes can persist in the environment after selection pressure has been removed (Tamminen *et al.*, 2011). Significantly, studies indicate that the transfer of resistance genes between aquatic and terrestrial bacterial species including human pathogens is possible in aquatic environments and indeed may have occurred (Aedo *et al.*, 2014; Tomova *et al.*, 2015). Although some countries, such as the UK and Norway, have taken significant steps to reduce AMU in aquaculture, other major producers, such as Chile and China, are still some way behind on this issue (Pruden *et al.*, 2013; Mo *et al.*, 2017). As aquaculture systems across Asia, South America and Africa continue to intensify, the continued use of antimicrobials, including as prophylactics, is expected to continue to present risks in terms of AMR emergence (Cabello *et al.*, 2016; Santos and Ramos, 2018).

While the focus of this document is on the links between agricultural intensification, AMU and AMR, it is also worth noting that the problems associated with AMU are not unique to intensive systems. There are limited data on antimicrobial use in smallholder systems in LMICs however, published studies suggest that antimicrobial use may be high and include use of antimicrobial classes considered to be of critical importance to human health (WHO, 2017), with similar drivers for use such as increased growth and productivity (Nguyen *et al.*, 2015; Bernadether *et al.*, 2016;

Lowenstein *et al.*, 2016; Ström *et al.*, 2017). There are even fewer studies which explore the potential effects on human health from livestock carrying antimicrobial resistant bacteria in smallholder systems. For example, a small study in Peru and Panama identified chicken faeces as a major source of AMR genes, with human and chicken resistomes sharing 10 common AMR-encoding proteins (Pehrsson *et al.*, 2016). Additionally, a small study in Ecuador identified an increased risk of carrying AMR determinants in households which raised chickens in comparison to those which did not (Moser *et al.*, 2018). Nevertheless, the focus on intensive systems is justified by virtue of their scale, the trend toward their proliferation in LMICs, and their greater reach in terms of product distribution.

In relation to zoonotic disease, the majority of high impact novel diseases in human medicine emerge from livestock species, with an estimated economic burden of 80 billion USD from six major zoonotic outbreaks between 1997 and 2006 (World Bank, 2012). It is likely, however, that the health burden from neglected endemic zoonoses surpasses that of novel diseases; many of these are also associated with livestock (Grace *et al.*, 2012). Animal source foods (ASFs), while critically important as a dietary source of protein and micronutrients (Neumann, Harris and Rogers, 2002), are considered to be the major food category responsible for foodborne disease. It has been suggested that the human health burden for foodborne disease is comparable to the 'big three' diseases (malaria, HIV-AIDs and tuberculosis) which demand the greatest health budget in Low and Middle Income Countries (LMICs) (Havelaar *et al.*, 2015). The threat from zoonotic diseases is predicted to increase exponentially over time with an estimated 60% of global emerging infectious diseases being of zoonotic origin (Jones *et al.*, 2008). This has to be balanced by the positive benefits derived from livestock products in addressing malnutrition, which contributes to wasting and stunting and has an impact on cognitive development. The impacts of these issues are both short and long term (Neelsen and Stratmann, 2011; Péter *et al.*, 2014).

The pathogens which spark the greatest concern for zoonotic transmission through livestock or food to humans include *Campylobacter*, pathogenic *Escherichia coli* and non-typhoidal *Salmonella species* (NTS) (WHO, 2014). Using the Disability Adjusted Life Years (DALYs)¹ measurement, these zoonotic pathogens are causative in 30% of diarrhoeal diseases in LMICs with an estimated overall cost of 27 million DALYs annually. By comparison, hepatitis is estimated to cost an estimated 13 million DALYs per year. Other key zoonotic pathogens include *Vibrio* species from seafood, and *Listeria monocytogenes* from meat and dairy products (Grace, 2015). The rise of importance of problems such as campylobacteriosis is a combination of better reporting of this problem, a change to urban-style living and food systems, and the intensification of the production systems, particularly chicken meat production. Detailed studies in Kenya on the broiler and layer systems indicate problems across the intensified livestock food systems (Carron *et al.*, 2017; Onono *et al.*, 2018) and the risks that this transfers in terms of the changing patterns of consumption towards chicken meat (Carron *et al.*, 2018).

Planning, implementing and evaluating restrictions on AMU requires firstly benchmarking of current AMU and AMR prevalence, and secondly, surveillance systems which allow the ongoing collection and analysis of both AMU and AMR data over time. Furthermore, determining the value derived from such restrictions requires an understanding of the societal impacts of changes in livestock management aimed at reducing AMU, where societal goals in terms of food availability and security must be evaluated concurrently with benefits to human health risk reduction.

The case for better measurement and better management

While the risks posed by AMR have been recognised, the data required to quantify these risks globally is to a large extent missing, as data collection has been beset by an absence of standardised testing and reporting metrics and lack of institutional capacity to perform such operations. In recent years there have been attempts to improve the collection of

¹ The Disability Adjusted Life Year (DALY) is a widely used global metric of human sickness and death. One DALY can be thought of as one lost year of "healthy" life.

data on livestock systems by international organisations (Seré and Steinfeld, 1996; Steinfeld *et al.*, 2006; Robinson *et al.*, 2011; Fetzel *et al.*, 2017). At a country level, data are usually collected by species, sometimes with a further level of resolution by product produced; however, even these newer classification systems rarely consider further detail on the organisation of livestock systems. For example, in the Sere and Steinfeld (1996) classification, chickens are classed as ‘landless livestock’ as opposed to standard more standard classification system, which divides the chicken population into breeding birds, broilers (meat birds) and layers (eggs). This can result in data which are difficult to interpret in the context of antimicrobial use and zoonotic disease risk, for example where different production types within the same species produce different risks, e.g. dairy versus beef cattle, or egg-laying versus meat chickens.

International efforts to estimate livestock populations at a regional or country level have most commonly relied on FAOSTAT data rather than field level data (Sumption, Rweyemamu and Wint, 2008; Thornton, 2010), thus there are queries over data accuracy, such as in South America where inconsistencies in livestock populations at a local, national and international level have been identified (Rushton and Viscarra, 2004). These issues are currently being considered by the OIE in the development of their World Animal Health Information Database Interface (WAHIS) system (OIE, 2013).

Interpreting animal population and production data are essential in the context of AMU in order to quantify relative use with regards to species, production systems and animal biomass; thus, enabling the interpretation of antimicrobial use, antimicrobial residue and AMR data and allowing the development of appropriate targeted interventions to control AMR.

To illustrate, it is worth describing the work published by a study that estimated the consumption of antimicrobials in livestock through the use of data from a limited number of countries, and subsequent extrapolation to those countries without data. The data used to generate the model were provided entirely by countries within the OECD, where a linear relationship between intensity of livestock production and AMU was observed. Coupled with trends in increasing intensification within LMICs, this relationship was then extrapolated globally and projected into the future. This represents a best estimate for global AMU given knowledge at the time. As such, consumption of antibiotics in livestock was projected to increase from 63,151 tons in 2010 to 105,596 tons in 2030, excluding aquaculture. The principle contribution to this total was judged to come from chicken and pig production in intensive systems. Geographically, the most intense use of AMs was identified in areas with the greatest concentration of intensive livestock farming (Figure 1). Usage in BRICs countries is estimated to increase by 99% in this period, as production systems continue to intensify.

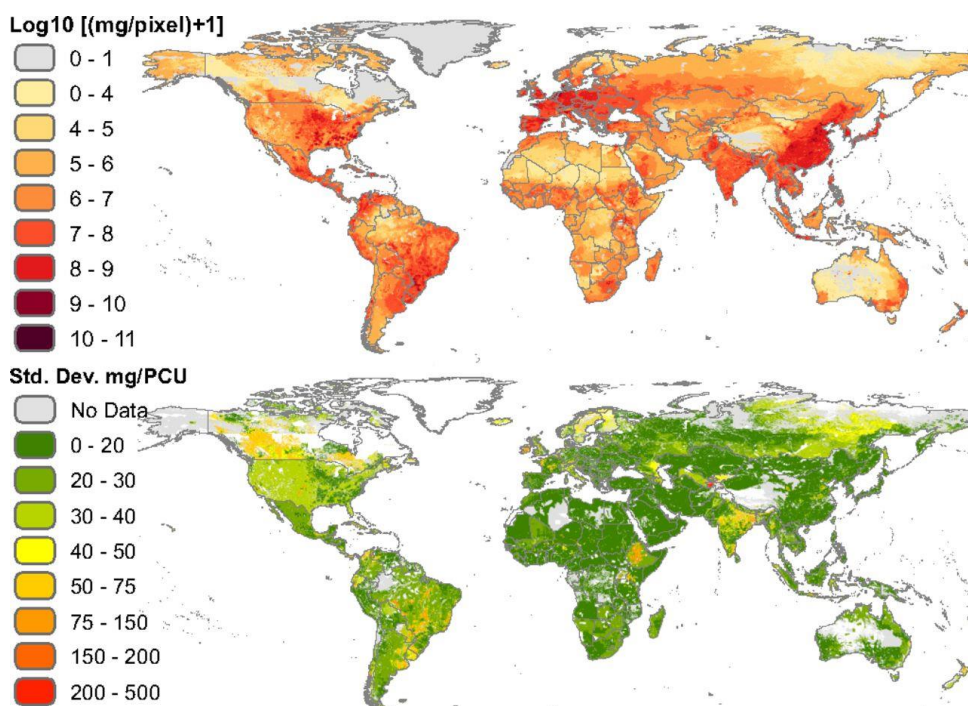


Figure 4. Global antimicrobial consumption estimates for livestock in milligrams per 10 km² pixels (top) and average SD of estimates of milligrams per PCU (bottom). From (Van Boeckel et al., 2015).

Similar techniques based on extrapolation have also been employed in other studies (Krishnasamy, Otte and Silbergeld, 2015; Laxminarayan, Van and Teillant, 2015). In 2015, 54 (73%) of the LMICs reporting data to the OIE were able to provide some data on antimicrobial consumption in livestock; however, 20 (27%) were not able to provide any data at all. Much of the data was qualitative and therefore difficult to quantify in terms of animal species, production setting and reason for use. Thus far, pigs, cattle and poultry have been identified as key species for high antimicrobial use (Grave, Torren-Edo and Mackay, 2010; Grace, 2015); however, other species have historically been neglected.

These findings have prompted action to address the gaps in available data. The need to quantify antimicrobial use in human and animal health is the aim of the Global Action Plan on AMR (WHO, 2015) and compliments work by the FAO and OIE (FAO, 2016; OIE, 2016b). Country level surveys of AMU are now beginning in LMICs. As an example, limited data are available from Thailand from the Animal Health and Products Association (AHPA), the trade association for veterinary pharmaceuticals. These data identified pigs to be the species with the highest consumption, with a value of 238 mg/PCU in fattening pigs in comparison to 16 mg/PCU in broiler chickens in 2016 (AHPA, 2017). These data are presented using the European Surveillance for Veterinary Antimicrobial Consumption (ESVAC) metric of mg of antimicrobial per population correction unit (mg/PCU) (European Medicines Agency, 2014). A contemporaneous study found a high prevalence of multi-drug resistant *Salmonella* in pigs, pork and human samples in Thailand and Laos (Sinwat et al., 2016). Lukkana et al. (2016) showed a prevalence of 78% for resistance to the fluoroquinolone enrofloxacin in a study examining *Streptococcal* pathogens in tilapia farming in Thailand. This coupled with the frequent use of enrofloxacin in aquaculture identifies tilapia production as a potential public health concern (Rico et al., 2013; Lukkana, Jantrakajorn and Wongtavatchai, 2016). Some of this major institutional work is being supported by the UK's Fleming Fund which aims to improve surveillance of AMU and AMR in both human and animal health with some input into environmental health.

Two case studies are now presented which illustrate the linkages between intensification, AMU and AMR, demonstrating the gains in understanding possible through improving data collection in LMICs. Firstly, a study of pork

production in Vietnam shows the risks presented by the emergence of AMR in *Salmonella* species pathogens in an environment where AMU is poorly regulated. The second case study presents risk pathways both for zoonotic *Escherichia coli* transmission in urban and peri-urban Nairobi, and the emergence of AMR via poorly managed use of antimicrobials.

Case Study: Pig production in Vietnam

Vietnam is an excellent example of the trends in income growth, ASF consumption and intensification of livestock systems in LMICs. With an estimated population of 93.6 million people in 2017, Vietnam is the 14th most populated country in the world. It has a rapidly growing economy, with a GDP in the region of 220.4 billion USD in 2017 and an estimated growth of around 7% in that year (IMF, 2018; World Bank, 2018b). Alongside the growing economy there has been increasing urbanisation, with 34% of the population living in urban areas in 2016, in comparison to 28% in 2006. Currently, around 70% of Vietnam's population are under 35, and with the growing economy there is a rapidly expanding middle class population which accounts for around 13% of the populace. Alongside this growth there has been an increase in demand for animal source foods, with a 21% increase in pork consumption from 23 Kg per capita in 2006 to 29 Kg in 2016 (World Bank, 2018b). This increase in the number of middle and high income households has been identified as being behind the shift towards greater meat consumption (Hoang, 2018).

Industry Structure

There has been a trend towards intensification across the pig industry in Vietnam, with the development of vertically integrated production; however, at present the majority of the pig population are still housed on smallholder and small commercial units. In 2010, 83% of pigs were housed on farms with less than 99 pigs, and commercially available mixed feeds accounted for 45% of all feed consumed by the national herd (Dzung and TuLiem, 2014).

Pork now accounts for 76% of meat consumed in Vietnam, highlighting pig production as the key livestock sector (Dzung and TuLiem, 2014), and since 2000 there has been a steady increase in both the national herd and the amount of pork produced in Vietnam (Dzung and TuLiem, 2014). The majority of pork is still purchased by consumers from local markets (Lapar, 2010). Slaughterhouses in Vietnam are primarily small and owned by the private sector. They are numerous but most are small-scale with manual equipment and poor hygiene (Dzung and TuLiem, 2014).

Antimicrobial Use and Resistance

Antimicrobials are the most frequently registered veterinary drugs in Vietnam (An, 2009). The limited data available on antimicrobial use in pig production suggest that use is high, with frequent use of the WHO highest priority critically important antimicrobials (HP-CIAs) (Belton *et al.*, 2011; Dang *et al.*, 2013; Carrique-Mas *et al.*, 2015; WHO, 2017). A study by Van Cuong *et al.* (2016) identified that 55% of commercially produced pig feed was found to contain at least one antimicrobial (Van Cuong *et al.*, 2016). Dang *et al.* (2013) identified that growth promotion was the most frequently reported reason for use, followed by treatment and disease prevention. This study also demonstrated farmers' poor compliance with antimicrobial withdrawal period regulations and administering of sporadic doses and variable course lengths (Dang *et al.*, 2013). AGP use has been prohibited in Vietnam since 31 December 2017 (Ward, 2016); however, there are concerns that the government does not have sufficient resources to enforce or monitor the effects of this ban. The national action and containment plan for AMR outlines a program to undertake surveillance of AMR and antimicrobial use in livestock, but at present this is still a future goal (MARD, 2017).

Given the lack of surveillance systems, studies from similar and neighbouring LMICs may offer further insight into probable antimicrobial use behaviours and patterns. Research into antimicrobial use in commercial pig production in Thailand identified that antimicrobial use may be lower in smallholder and smaller scale commercial production systems. Smallholders were also more likely to use antimicrobials in response to disease rather than for prevention (Love

et al., 2015; Lugsomya *et al.*, 2017); thus, evidence from Thailand suggests that smallholder production may have lower antimicrobial use when compared with larger scale commercial systems.

In addition, research in Thai pig production also identified an association between the use of in-feed antimicrobials and higher AMR levels on farms. Lugsomya *et al.* (2017) identified multi-drug resistance commensal *Escherichia coli* on all study farms but identified a greater range of resistance in farms routinely using tiamulin and amoxicillin for disease prevention than farms which did not use them. In parallel, Love *et al.* (2015) identified greater AMR in *Salmonella* species, *Escherichia coli*, and *Enterococcus faecalis* in farms buying commercially formulated feed when compared to farms home-mixing feed. Studies have also linked herd size with AMR, identifying greater levels of multi-drug resistant (MDR) bacteria on larger farms (Love *et al.*, 2015; Strom *et al.*, 2017). A move towards more intensive pig production with an increased use of commercial feeds, larger herd sizes and increased productivity demand on the pigs is suggested, resulting in a greater risk of AMR in the agricultural environment with an increased risk of zoonotic disease spread to humans.

The potential AMR risk to human health from pig production in Vietnam

Multi-drug resistant bacteria of *Campylobacter*, *Escherichia coli* and *Salmonella* species have been found in both farms and fresh meat samples in Vietnam (Thai *et al.*, 2012; Carrique-Mas *et al.*, 2014; Nguyen *et al.*, 2016). Nguyen *et al.* (2016) identified widespread resistance to antimicrobials considered classed as the highest priority clinically important antimicrobials (HP-CIAs) by the WHO (colistin and fluoroquinolones), both of these antimicrobials classes have been cited as being commonly used in pigs in Vietnam (Dang *et al.*, 2013; Nguyen *et al.*, 2016; Van Cuong *et al.*, 2016).

A detailed overview of the pig supply chain in Vietnam is shown in Figure 5, which identifies the potential highest risk value chain for human health from antimicrobial use. Smallholder and small-medium commercial production systems were identified as being the highest risk; these systems account for 83% of production (Dzung and TuLiem, 2014). There are an estimated 4 million full time workers in the pork supply chain with smallholders and small-medium commercial farms relying heavily on family labour. Thus, this sector offers the largest population at risk from antimicrobials along the supply chain (Son *et al.*, 2006, Tisdell, 2010). In addition, these systems most frequently slaughtered pigs through small independent abattoirs which are often poorly regulated, and have poor food safety standards (Dzung and TuLiem, 2014).

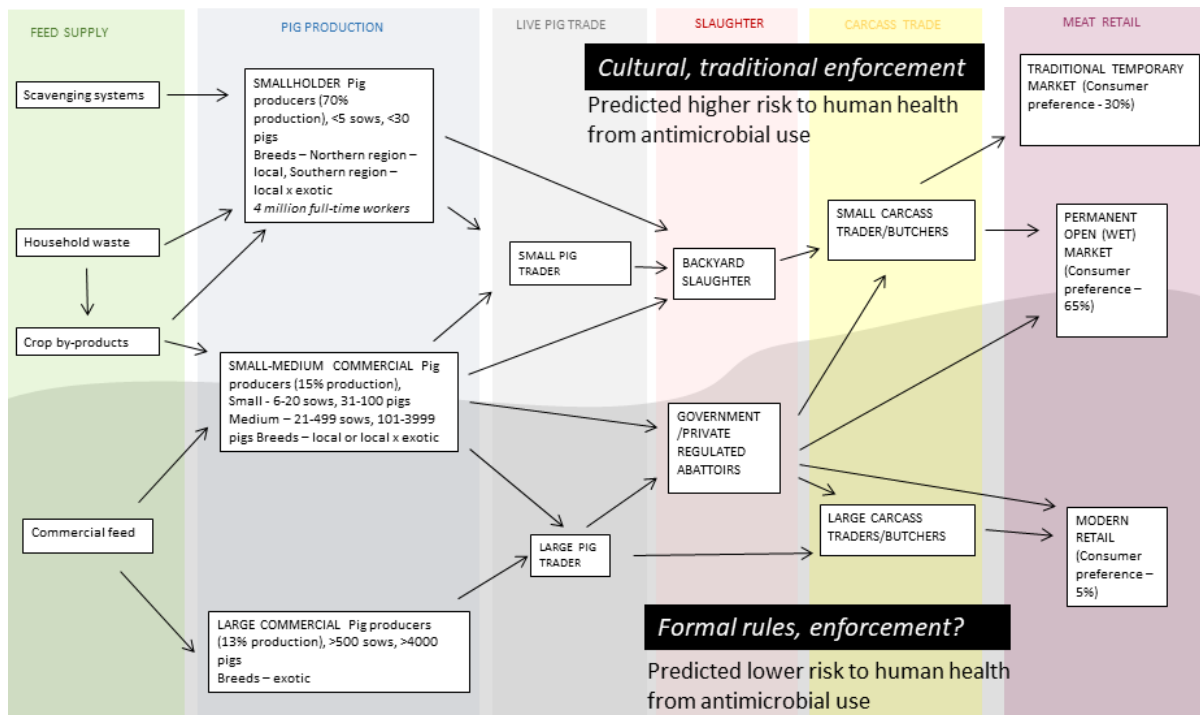


Figure 5. The pork supply chain in Vietnam and the potential risk to human health from antimicrobial use in pigs

Salmonella as a zoonotic risk from pig production

Non-typhoidal Salmonellas are one of the most important zoonotic disease pathogens in Vietnam (Havelaar *et al.*, 2015). Whilst salmonellosis most commonly causes a self-limiting gastroenteritis, it can cause complications and severe morbidity in older, younger and immunosuppressed patients (Pegues and Miller, 2009).

Invasive NTS (iNTS) infections are becoming common in sub-Saharan Africa, comprising 50% of blood borne bacterial infections. They affect predominately children and HIV-positive individuals, and are associated with a mortality rate of 22-25% (Gordon, 2011). A study in Vietnam suggest that iNTS are not as common, but are still an important infection in immunocompromised adults, with a similar mortality rate of approximately 25% (Phu Huong Lan *et al.*, 2016). Several isolates of *S. choleraesuis*, were identified in this study, a species highly associated with consumption of pork and pork products (Phu Huong Lan *et al.*, 2016). A study by Dang-Xuan *et al.* (2017) found a *Salmonella* prevalence of around 40% in pork carcasses and an estimated that the probability of acquiring salmonellosis from consumption of boiled pork was as much as 17.7% per person per year.

Table 2 provides a summary of the available data, challenges for Vietnam and future research areas for *Salmonella* in pig production in Vietnam.

Table 2. Summary of available data, challenges for Vietnam and future research areas for *Salmonella* in pig production in Vietnam adapted from Carrique-Mas and Bryant (2013)

Human data	Data on animal reservoir	Challenges for Vietnam	Suggested areas of research
Data suggests it may be responsible for up to 7% of diarrhoea in children under 5. There are limited data on serovars but carriage in the adult population is suspected to be high	High prevalence found in pork 37-69% (Dang-Xuan <i>et al.</i> , 2017)	Opening up the pig production value chain to export will require greater surveillance and control of <i>Salmonella</i>	Studies to explore source of Salmonellosis in humans, effects of urbanisation and smallholder production on human immunity, AMR levels, levels of non-typhoidal <i>Salmonella</i> in intensive versus smallholder systems

Case study: The Urban Zoo

Nairobi represents an ideal case study of the consequences of rapid urbanisation on disease emerging in the African context. A CGIAR affiliated project, ‘UrbanZoo’ investigated routes of zoonotic pathogen emergence through the study of microbial transmission across a network of interfaces within the urban and peri-urban landscape. The interfaces considered by the project included the physical boundaries across which pathogens are exchanged and the social and policy interfaces which influence these. Networks of scales from the household to the city level were considered and populations of humans, domestic livestock, and wildlife were included within the scope of the project and *Escherichia coli* was used as an exemplar pathogen to better understand the connectivity within and between networks. The drivers of spill over relevant to zoonosis and AMR are shown in Figure 6.

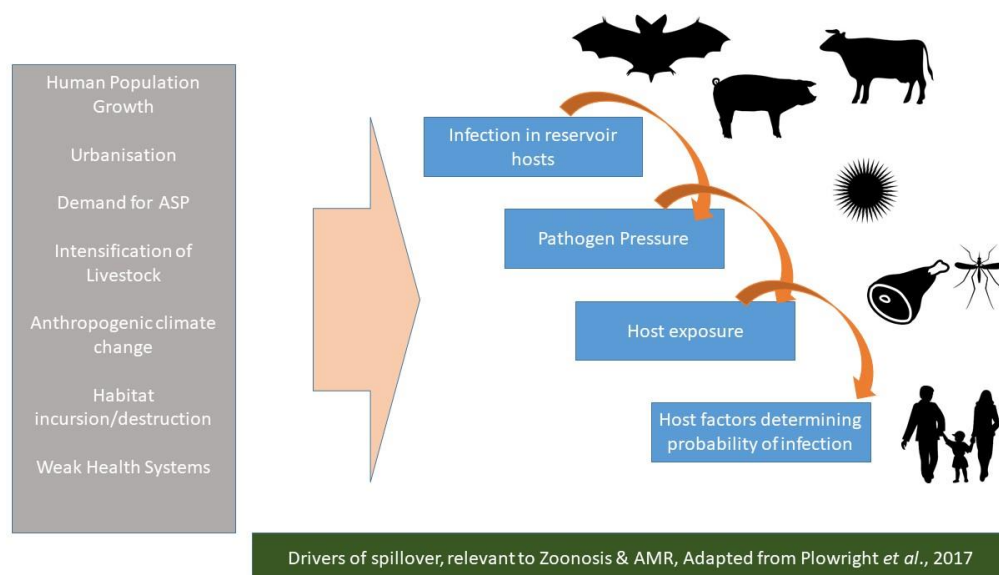


Figure 6. Drivers of spillover to zoonosis and AMR, adapted from (Plowright *et al.*, 2017)

Nairobi has a population of approximately 3.5million people (2018), is one of the fastest growing cities in Africa and the demand for animal source protein in the city is increasing year on year, although food consumption inequities remain high (Cornelsen *et al.*, 2016; Alarcon *et al.*, 2017). In response to an increase in demand for ASF and the need of diverse

sources of income, urban and peri-urban agriculture, despite being prohibited within the city boundaries, is a rapidly transforming and growing industry (Kang'ethe *et al.*, 2012; Alarcon *et al.*, 2017). There is a great diversity of livestock systems found across Nairobi including poultry (broiler, layers & 'Kienyeji'), pigs, small ruminants, dairy cattle and rabbits, with the vast majority of producers being small scale, with short, and often informal, value chains (Alarcon *et al.*, 2017). An overview of the dairy and small ruminant food systems in Nairobi can be found in Figure 7 (Alarcon *et al.* 2017). Focusing on the dairy sector, an ILRI-led project has identified several public health hazards present in the urban setting including; the risk of exposure to E.coli O157:H7, cryptosporidiosis, bovine tuberculosis and brucellosis from urban dairy cattle (Kang'ethe, Ekuttan and Kimani, 2007; Kang'ethe, Ekuttan, *et al.*, 2007; Kang'ethe, McDermott, *et al.*, 2007; Kang'ethe, Onono, *et al.*, 2007; Grace *et al.*, 2008), the presence of antimicrobial residues in milk (Ekuttan *et al.*, 2007) and of aflatoxins in animal feed and milk (Kang'ethe, M'Ibui, *et al.*, 2007). High-risk activities related to zoonotic disease and AMR emergence have been identified across each of the livestock systems in Nairobi. Particular activities include the sale and consumption of sick or dead animals, indiscriminate use of antimicrobials, lack of adherence to withdrawal times, and poor reporting of disease events to the government veterinary officers (Alarcon *et al.*, 2017). A particular challenge to the mitigation of these risks in the urban environment was the perception by small farmers that they are 'not responsible for food safety' (Alarcon *et al.*, 2017), though opportunity has been demonstrated for the carefully tailored dissemination of public health messages to particular 'at risk' groups (Kang'ethe *et al.*, 2012). The CGIAR (via ILRI) has been central to the understanding of the livestock systems and associated risks within Nairobi. They are now uniquely positioned to build upon the current knowledge, collaborations and trust engendered with this community to develop mitigation strategies in this dynamic ecosystem.

In a study of the emergence of pathogens, a complete assessment of the livestock food systems was carried out with an example of the maps produced shown in Figure 7(Alarcon *et al.*, 2017), alongside very detailed work on urban planning and a thorough assessment of the flows of *E. coli* and risks in 99 study households. These households represented different socio-economic strata of urban and peri-urban dwellings across Nairobi, and a landscape genetics approach has allowed the pathways of transmission between wildlife, domestic animals and people to be documented, and the importance of wildlife and domestic animal species in the transmission of gastro-intestinal pathogens to be understood. Work on linking this household study to the wider food system and the urban planning context is ongoing and needs further support.

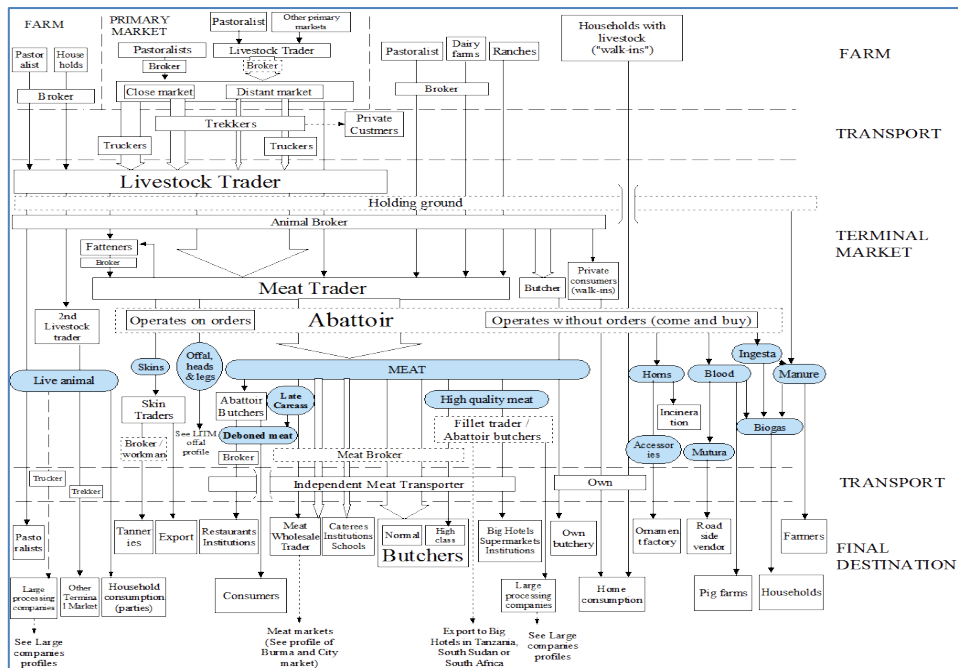


Figure 7. Cattle and small ruminant food system in Nairobi from (Alarcon et al., 2017)

Summary

The use of antimicrobials within livestock systems applies selective pressure which drives the development of resistance. Data from OECD countries suggests the use of antimicrobials is highest in intensive systems. Historically, the data on AMU in LMICs has been sparse, although this is now being addressed. Such data as have emerged suggest the lack of regulation, or enforcement of regulation in these countries, combined with rapid economic, demographic and population changes is creating particularly high-risk environments for the development of resistance and the spread of zoonotic disease.

This situation is exemplified in Nairobi, Kenya, where urbanisation and demand for ASFs have brought livestock and large human populations into close proximity, resulting in numerous pathways to the risk of zoonotic disease transmission and the spread of antimicrobial-resistant bacteria. In Vietnam, rapid economic growth has driven an increased demand for animal source proteins in the form of pig meat and significant zoonotic disease risks exist due to poorly regulated and unhygienic production and slaughter processes. In addition, the use of several HP-CIAs within animal production and the detection of multi-drug resistant bacterial species compound the risk of zoonotic disease transmission presented.

MAPPING CURRENT CGIAR ACTIVITIES RELATED TO DRIVERS OF ZOO NOTIC DISEASE & AMR EMERGENCE

Introduction

Before considering recommendations for action on AMR and zoonotic disease risk, due consideration should be given to activities already being undertaken by CGIAR in this domain. Provided here is a brief summary of current projects supported by CGIAR.

Current CGIAR activities

Current CGIAR activities relating to Zoonoses and AMR emergence fall predominately within the Agriculture for Nutrition & Health (A4NH) CRP and specifically within the flagship programs 3 & 5 on 'Food Safety' and 'Improving Human Health' as well as within the LIVESTOCK CRP within the flagship project 'Livestock Health'. Table 3 provides summaries of the relevant ongoing projects to 2022.

Table 3. Summary of CRP agriculture for nutrition and health (A4NH) research on zoonoses and AMR.

Flagship	MARLO Project (Project leader)	Project summary
A4NH		
3 – Food Safety	399 (Delia Grace) Better evidence on foodborne disease in target regions	This project focuses on generating evidence for better action on FBD. It covers W3/bilateral funding sources, such as SafePork, ICAR projects, MyDairy 2, Zimbabwe mycotoxin surveillance, and the garnering of evidence from previous projects. Methods that will be used for research include: 1. Systematic literature reviews 2. Literature reviews 3. Synthesis of information 4. White paper(s) 5. Conceptual papers: food safety and SDG 6. Development of food safety system performance tool 7. Small to moderate hazard prevalence, risk factor and risk studies 8. Experimental assessments of promising technologies This is food safety work that generates new information, evidence, syntheses, technologies, approaches and tests and delivers them as appropriate but which does not specifically aim to reach millions to tens of millions of consumers of fresh foods in wet markets.
	340 (Delia Grace) Technological and institutional innovations for assessing, communicating and mitigating	This project focuses on gathering evidence that will support the scaling up of training, certification and marketing (TCM) (based on the past Training and Certification - T&C) intervention and also prospects for scale in development projects. It draws mainly on "MoreMilk: making the most of milk" project. The project aims to reach millions to tens of millions of consumers of fresh

	food safety risks designed and tested, with capacity building	foods in informal markets in the short to medium term. The methods are set out in the Trader ToC working paper (Johnson et al.). To support further research and, eventually, delivery at scale, this paper develops a theory of change for how the intervention is expected to contribute to better nutrition and health outcomes for consumers. The outcomes along the pathway from intervention to impact are identified, along with the underlying causal assumptions. For each assumption, the existing evidence is summarized and assessed.
	341 (Delia Grace) Policy engagement to build awareness of opportunities in informal markets	This project focuses on policy engagement at 3 levels: a) international (FAO, WHO, OIE); b) regional (AU, EAC, ASEAN etc.); c) CRP L&F value chains and site integration countries. It covers GLAD, USAID White Paper, World Bank and other projects. The project is linked to both evidence that counts and impact that scales projects.
5 – Improving Human Health	353 (Jo Lines) Mapping & analysis of changing agro-ecosystems and health outcomes	Desk based study reviewing evidence of agro-ecosystem change across Africa, and the impacts on human health that result from these changes. Will employ a structured approach to reviewing both published and grey literature, and will be written as a landscape analysis of the field (less stringent inclusion criteria than are required for a systematic review).
	354 (Jo Lines) Evidence base on farming practices which reduce health risks	This project will explore how to minimize health risks to humans by adapting agricultural practices. An initial particular focus will be practices that reduce the breeding potential of insect vectors of malaria and zoonotic arboviruses.
	355 (Eric Fèvre) Evidence base on the benefits of joint agriculture and health interventions against zoonotic disease	Using empirical data from a number of zoonotic infections, this project will identify through empirical data and modelling, the impact of livestock-targeted interventions on human health. A significant focus of activity will be cysticercosis control, generating evidence through large scale interventions in both humans and domestic pigs
	356 (Eric Fèvre) Portfolio of validated methods for alternative surveillance and control options of animal and human disease, particularly in higher-risk areas.	This project will undertake to implement, develop and deploy improved diagnostic tools for infections that cross the livestock-human interface, and will optimize the delivery of surveillance. For some diseases (such as cysticercosis) it will involve the development of a completely novel diagnostic. For others, like brucellosis, it will prepare the policy framework for national guidelines for diagnostics. More generally, a formal human-animal health surveillance system will be established and deployed.
	357 (Barbara Wieland) Characterize and manage risks for public health from agricultural	The project will explore antimicrobial drug use in agriculture and by people in associated food systems in LMICs, and the impact on detectable levels of resistance. In several country-

	associated antimicrobial resistance in LMIC settings.	scale studies, this will be supplemented by empirical data collection to quantify resistance, quantify drug use, map resistance gene flow and link phenotypic markers of resistance to genetic profiles. The evidence generated will be used to design and evaluate interventions and engage policy makers and other stakeholders.
	358 (Jeff Waage)	Promote interactions of public health and veterinary sectors
CRP LIVESTOCK		
2-Livestock Health	P605 Activity 2.1.1 (Barbara Wieland) Development of tools for assessing socio-economic impact of diseases.	Develop or adapt gender sensitive assessment tools and frameworks to quantify disease impact. Conduct longitudinal studies to determine socio-economic impact of diseases in three countries.
	P606 Activity 2.1.2 (Barbara Wieland) Development livestock distribution and risk maps.	Assess risks for production systems, VCs and geography to produce risk models and maps
	P607 Activity 2.2.1 (Ulf Magnusson) Development and evaluation of herd health packages.	This project reviews and evaluates existing and novel interventions to improve herd health, considering biosecurity, infectious disease prevention, reproductive management, animal welfare, assessments of feed and genetic shortcomings and antimicrobial use. The project focuses on dairy, pig and small ruminant systems in Uganda, Tanzania, Ethiopia and Vietnam.
	P608 Activity 2.2.2 (Ulf Magnusson) Establish protocols for survey of antimicrobial use and for monitoring AMR.	This activity looks to move towards rational use of antimicrobials in livestock production through harmonisation of AMU data collection and engagement with policy makers.
	P609 Activity 2.3.1 (Lucilla Steinaa, Vish Nene) Developing improved diagnostics and diagnostic platforms	Currently focused on CBPP and small ruminant Mycoplasma
	P616 Activity 2.4.1 (Henry Kiara) Animal Health Service provision	The aim of this activity is to improve animal health service delivery models: Review experiences of users of different AH delivery models by considering gender implications, available AH products (vaccines and diagnostics, drugs) and manufacturing capacity. Develop networks to test new gender and youth sensitive models and capacity building for AH service providers. Optimize gender

		sensitive vaccine delivery; increase vaccination coverage for ECF in Mali in cattle and small ruminants.
	P748 Activity 5.4.2 (Isabelle Baltenweck) Optimal Herd Management Practices	Develop dynamic herd models that maximize productivity given climate variability and risk and test management options in different contexts

In several middle/low-income settings there is arbitrary and medically irrational use of antibiotics (e.g. Ström *et al.*, 2018) which contributes to the development and emergence of antibiotic resistance – not only among zoonotic microbes, but also for animal pathogens and commensal bacteria. The Livestock CRP approaches this complex issue in several ways: providing techniques for better diagnostics thereby giving the opportunity to increase therapeutic precision, developing vaccines that are preventive thereby replacing antibiotics; improving everyday herd health management thereby reducing the occurrence of endemic diseases which are significant drivers for antibiotic use, and improving the delivery of adequate animal health services products (like vaccines) in order to offer alternatives to antibiotic use. Besides these direct actions to reduce the emergence of antibiotic resistance for the sake of animal and public health, the CRP Livestock together with the CRP A4NH has developed a “universal” tool: AMUSE- Livestock. This tool is to be used to understand the rationale among farmers for using antibiotics, which is imperative for designing interventions and policy for reducing the excessive and irrational use of antibiotics in the livestock sector.

Many CGIAR activities pre-2018 have led directly to closing gaps in knowledge regarding the drivers and mitigating factors for zoonoses and AMR emergence. The transmission dynamics of zoonotic arboviruses in Vietnam and Kenya have been explored (Bett *et al.*, 2017; Lee *et al.*, 2017) and exposure to *Brucella species* in areas bordering a wildlife reserve in Kenya has been investigated (Enström *et al.*, 2017). These studies are assisting in building an evidence base for potential mitigation strategies to reduce exposure of humans to these pathogens in areas of ongoing land-use change. A conceptual framework exploring the linkages between nutritional outputs and food safety using a value chain approach has been developed which can guide the CGIAR in ways in which integrated nutritional and risk analysis may be performed (Häsler *et al.*, 2017). Knowledge of pathogens at the human – livestock interface and ways in which the spread of these may be mitigated is the remit of two projects based in western Kenya, the People Animals and their Zoonoses project and the ZooLinK project both led by Eric Fèvre (Fèvre *et al.*, 2017). One of the priority diseases identified in western Kenya was cysticercosis due to the zoonotic parasite *Taenia solium*, and joint veterinary and public health interventions to control this parasite are currently being developed in the light of increasing pork consumption in the region (Wardrop *et al.*, 2015; Thomas *et al.*, 2016, 2017; Trevisan *et al.*, 2017).

In 2017, as part of the A4NH CRP, under flagship program 5 (Improving human health), a workshop was held at the London School of Hygiene and Tropical Medicine. Seeking to further the development of harmonious metrics for antimicrobial use applicable in the livestock and human health sectors, this workshop brought together academic researchers, funding organisations and policy makers (Queenan, Chandler and Goodman, 2017). This workshop recognised the difficulties in collecting data on antimicrobial use with high resolution in LMIC settings and sought to build consensus on how this problem could be addressed in a manner that was congruent with stakeholders. It is noted that within the livestock sector, only one LMIC is currently reporting farm-level usage data, so considerable work is still required in this area to develop pathways to AMU data collection, and ensure these pathways lead to collection of data which is useful in informing policy and intervention design.

The effect of irrigation activities and land cover change on the risk of zoonotic pathogen infection were investigated in eastern Kenya. This area has experienced a dramatic reduction in vegetation cover over the last 25 years and an increase in irrigated crop-land. People in the irrigated areas were found to have higher seroprevalence of Rift Valley Fever, West

Nile virus and Dengue Fever Virus, though lower seroprevalence of the other non-arbovirus zoonotic pathogens studied. Possibly due to lower livestock densities in the cropped areas. This study highlighted some of the trade-offs occurring through increasing crop-production through irrigation in terms of increased risks to some zoonotic pathogens (Bett *et al.*, 2017).

Summary

CGIAR is already active in the area of zoonotic disease risk in LMIC settings, centred particularly in Kenya and East Africa. With respect to AMR, the opportunity for existing to projects to synergise with expanding interest in AMR is noted, given the fundamental linkages between zoonotic disease risk, changing livestock systems, economic development and antimicrobial use. The AMU/AMR complex in livestock is an area where there could be more emphasis and the need to tie this into the overall strategy of intensifying livestock systems to feed growing urban-based populations.

INSTITUTIONAL ENVIRONMENT – PUBLIC POLICY, PRIVATE SECTOR STRATEGY, CULTURE

Introduction

The policy environment in relation to AMU and zoonoses is by no means static, and despite the limitations described previously in terms of data availability, moves have been made to anticipate emerging risks with the introduction of new regulation or initiatives. It is therefore necessary to summarise the global trends in policy development, highlight key programmes that are active in this domain, and give due consideration to the challenges presented by the institutional environment in which these policies and programmes are operating.

Global Context

In 2012 the WHO published the NTD roadmap for neglected tropical diseases, with targets of control, elimination and eradication for each disease, with a major proportion of these being zoonotic and already targets of CGIAR activity (World Health Organization, 2012). The support for such work has come from initiatives such as the London Declaration 2012 which was signed by 80+ organisations, governments, NGOs, pharmaceutical companies etc., generating upward of US\$17bn in drug donations for combating NTDs. For the period of 2017 to 2024 there has thus far been US\$800m in funding pledged (Uniting to Combat NTDs, 2017). The progress on this work is well summarised by Molyneux *et al.* (2017) and has enabled the establishment of specific organisations to manage pathogens, including GARC which was established for rabies.

On an individual country level and with a specific focus on zoonoses, the UK research councils and DFID have a developmental research programme called Zoonoses and Emerging Livestock Systems (ZELS) that works across 11 countries in Africa and Asia and has £20 million committed. The scoping work for this project covered important aspects of zoonoses emerging (Jones *et al.*, 2013) and the institutional context of zoonosis management and emergence (Scott-Orr, Adams and Edwards, 2012). This recognised the need for a food system approach and the adoption of tools such as value chain analysis in order to address disease risk change and disease emergence, including zoonoses and AMR. This follows the major efforts on the management of highly pathogenic avian influenza, where the need to understand the poultry sector dynamics in order to implement cost-effective control measures was recognised (Rushton *et al.*, 2010; Taylor and Rushton, 2011; FAO, 2012).

These responses are in recognition that disease emergence and re-emergence from livestock systems has changed in terms of scale and impact, such as the food borne disease issues that were highlighted during the 1980s and 1990s with salmonella crisis in the UK, followed by the emergence of BSE. Combined, these generated the need for an institutional change in managing the food system and the formation of national level organisations, such as the UK's Food Standards Agency, and at the EU level the European Food Safety Authority. In the background has been the increasing use of risk analysis to determine critical points of societal management of the food system, and in the private sector an increasing use of HACCP, and implementation of standard operating procedures in slaughter of animals, processing and manufacture of food through ISO. The outbreaks of highly pathogenic avian influenza in the 2000s followed by the emergence of swine flu later in that decade have raised issues of the management of disease in the intensified livestock production systems, (Leibler *et al.*, 2009; Silbergeld, 2016) and the need to balance the positive outcomes from these systems in terms of nutrition and food security with the externalities outlined in section 2.

The recognition that there is a problem with antimicrobial use in livestock and patterns of change in AMR happened some years ago, yet the global response has hardened since 2012. Over the course of the past decade, action on AMR at the international level has coalesced from individual or small groups of countries acting unilaterally or in concert, to global multilateral initiatives (Gelband and Delahoy, 2014). China, for example, launched a National Action Plan on AMR in 2016, recognising both the need for cross-sectoral approaches to reducing AMU and international collaboration within the region on this issue (Xiao and Li, 2016).

At regional and country level however, continued international support for initiatives is required where partners are lack the capacity to act individually. A successful process of advocacy has raised concern over AMU in livestock to a level where it is no longer acceptable for animals to be given antibiotics for growth promotion, and in many countries there is legislation banning such use (see following sub-section on SE Asia). There has also been a successful message that antimicrobial use in animals has to be reduced which has been coordinated with a tripartite agreement between WHO, OIE and FAO². These messages and their implementation are slowly being backed with research demonstrating what this means in terms of food production. They are also being backed with initiatives such as the Global Antibiotic Research and Development Partnership (GARDP), a partnership between WHO and DNDi (Drugs for Neglected Diseases initiative) which will have implications on the AMU/AMR in livestock and the food this produces. The aim of GARDP is to develop antibiotics for use specifically in cases where AMR is present or emerging, or where existing treatments are inadequate, focusing on patient need rather than profit for industry. This partnership has significant backing, with €56 million Euros funds pledged in 2017 (GARDP, 2017). The programme is split between general AMR work, and specific conditions such as neonatal sepsis and drug-resistant STI. As yet no links to work within livestock or animal species have been published, but there it potential for development in this area. On AMU/AMR surveillance the UK government has committed £230 million to establishing activities in LMICs in the human and animal populations, and in the environment, and this money is being utilised to mobilise other funds. The role of research within the Fleming Fund needs to be established; ILRI would be well positioned to play a role in some areas, albeit its strengths are not in the areas of the intensifying livestock systems.

On emerging initiatives, USAID has spent the last decade supporting One Health projects through the Emerging Pandemic Threats (EPT) initiative, a programme that developed after the bird flu crisis. Much of this work has been on identifying high-risk areas for novel disease emergence, carrying out monitoring and surveillance in these environments, and helping countries to prepare for disease emergence. These are development style programmes that need research to develop best practice. From EPT has come an idea of the need to develop a global virome bank: the isolation and identification of all circulating viruses at a global level (Carroll *et al.*, 2018). This is with the intention of being able to

² http://www.who.int/foodsafety/areas_work/antimicrobial-resistance/tripartite/en/

identify the pathogen threat of viruses and their ability to cause pandemics. Funding in this area is still being sought, the scale of which could well impact on funding for other research work.

In the area of animal disease impacts there have been major advances with the food borne and neglected tropical diseases, yet there is an absence of information on animal disease in general. There are difficulties in looking at impact across zoonoses and food borne diseases as they affects multiple species with different values and uses, but methods are emerging (Shaw, Rushton, Roth and Torgerson, 2017; Torgerson *et al.*, 2018). The difficulties of putting together a framework for Global Burden of Animal Diseases (GBADs) is being overcome, and has the support of the Bill and Melinda Gates Foundation, OIE, FAO and ILRI (Rushton *et al.*, 2018). GBADs will include zoonoses and food borne diseases in the initial stages, and will begin to cover AMR. ILRI, and therefore CGIAR, will be critical in making this work meaningful.

The development of antimicrobial policy interventions in food animal production at national and regional level – The South East Asia model

The development of a national action and containment plan for AMR was a requirement for all members of the World Health Assembly in-line with the 2015 global action plan on AMR (WHO, 2015). It is generally accepted that AMR issues are of great concern in the South East Asian region where the increase in meat demand, high levels of infectious diseases and poor access to human and veterinary medical advice has led to the emergence, maintenance and spread of AMR (World Bank, 2016). The increasing threat of AMR has resulted in a movement in the region to develop robust and comprehensive policies to address this concern. International standards such as the Codex Alimentarius Commission and guidance on livestock and aquaculture species produced by the OIE form the basis for many of the policy developments in LMICs (FAO and WHO, 2015; OIE, 2015). However, these may be outdated or over-ambitious for the socio-economic climate, and it may be hard to monitor progress in LMIC settings. A review of the areas in which policy has been developed relating to AMU and AMR is presented here.

Key livestock production species in South East Asia

Table 4. Key livestock species of South East Asia summarises the situation regarding the most significant livestock species in South East Asia.

Table 4. Key livestock species of South East Asia

Sector	South East Asia
Large ruminant species	Beef production is typically small-scale in South East Asia with the exception of Indonesia which is considered to be a medium producer globally (Waldron, Erwidodo and Nuryati, 2015). The majority of production is smallholder, with commercial feedlots more commonly fattening cattle imported from Australia (CIVAS and FAO, 2017). There has been a growing demand for milk products in the region but domestic production remains in the hands of smallholder and small-scale commercial producers (Morgan, 2008).
Small ruminant species	Goats are kept for both milk and meat and are predominantly in small-scale commercial and smallholder systems (ILRI and APHCA, 2008). Sheep are only raised in significant numbers in Indonesia in the region and 99% are raised by smallholders (Udo and Budisatria, 2011).
Poultry	Broiler production varies throughout the region from commercial integrated production through to backyard production. For example, in Thailand around 95% of the national flock are housed on large commercial farms (Ipsos Business Consulting, 2013; Tiensin, 2016). Most of the transition has occurred as a result of the highly pathogenic avian influenza (HPAI) outbreak in 2004 (Souris <i>et al.</i> , 2014). Conversely, backyard and small-scale production is practised by 8.3 million households in Vietnam in 2005 (Wang, 2009).
Pigs	There has been a move towards intensive pig production across Asia. For example, in Thailand 82% of the pigs are said to be kept on commercial pig units (Thanapongtharm <i>et al.</i> , 2016). However, smaller scale commercial production remains important in much of the region (Deka <i>et al.</i> , 2014; Dzung and TuLiem, 2014).
Aquaculture Species	Aquaculture is an important export product from the region with China, India and Vietnam being the most significant global exporters (FAO, 2014b). Brackish water (<i>penaeid shrimp</i>) aquaculture is typically undertaken in intensive and semi-intensive systems. Freshwater aquaculture species include tilapia and <i>Pangasius</i> catfish. Production systems varies from small-scale monoculture through to the intensive <i>Pangasius</i> production for export seen in Vietnam (Belton <i>et al.</i> , 2011).

Key Policy Areas

Antimicrobial production and marketing

All countries in the South East Asian region have legal frameworks for ensuring a minimum standard of quality for antimicrobial drugs manufactured for food producing animal species. However, their enforcement across the region is variable. Policies cover good manufacturing processes, quality assurance of products, and import and export. The ability to enforce policies varies, with only Thailand reporting an ability to implement legislation at the manufacturing and distribution levels (Grace, 2015). . In addition, there is reported to be an issue with counterfeit antimicrobials which are also rarely legislated against (Newton *et al.*, 2006; Goutard *et al.*, 2017).

Regulation of Antimicrobial Use

There has been a lot of progress in the development of regulation with regards to promoting responsible antimicrobial use in both human and veterinary medical settings. These responsible-use guidelines focus on improving awareness of AMR, alternative disease prevention strategies and diagnostic options for prescribers and the end-user group, most frequently farmers. Within the veterinary environment this has led most countries to ban the use of antimicrobials for growth promotion in terrestrial species. Thailand has taken this policy one step further and has also banned the use of all in-feed antimicrobials for aquaculture species (Goutard *et al.*, 2017; Zellweger *et al.*, 2017). There remain concerns over local governments having sufficient resources to enforce this prohibition.

The availability of antimicrobials

In South East Asia, as in other LMIC settings, most veterinary antimicrobials can be purchased over the counter (Grace, 2015). Regulation of non-prescription antimicrobial is either non-existent or poorly enforced (Morgan *et al.*, 2011; Grace, 2015; Sommanustweechai *et al.*, 2018). In addition, the growth of internet use has increased access to non-prescription drugs, with a wider variety being freely available in many countries (Mainous *et al.*, 2009; Van Cuong *et al.*, 2016).

There is a tendency with policy makers to take the simplistic view and to advise that non-prescription use is eliminated worldwide. This perception does not consider the complexities of the situation in many LMICs, where the non-prescription status of antimicrobials may be an important access route in resource-limited communities (Morgan *et al.*, 2011; Grace, 2015). For example, in human medicine, the CDC estimates that more people die as a result of lack of access to antimicrobials than from a resistant infection (CDC, 2015). Nevertheless, there is a move in some countries to discontinue the availability of veterinary antimicrobials over the counter; Thailand and Indonesia are looking to restrict use to prescription in-line with the Codex guidance on veterinary drug use (FAO and WHO, 2015; Goutard *et al.*, 2017).

Antimicrobial use and resistance surveillance

Within South East Asia the development of a surveillance system for antimicrobial use and resistance in livestock is at an early stage. Inevitably, the development of such a surveillance system in human medicine is the priority in many LMICs. It is essential that such policies consider both food producing animals as well as aquaculture species. Ideally this would encompass both diseased and healthy animal populations for both pathogenic and commensal zoonotic bacteria (Goutard *et al.*, 2017). Thailand is at present the furthest along this journey with a national action plan for monitoring both antimicrobial use and resistance in food producing animal species with parallel methods to those employed in Europe. Similarly, Bangladesh has comparable plans to implement a use and resistance monitoring system (Thamlikitkul *et al.*, 2015; CDC Bangladesh, 2017). There has also been progress in quantifying veterinary antimicrobial use in Thailand through the private sector, with the Animal Health Products Association, the trade association for veterinary medicines, publishing veterinary sales data since 2013 (AHPA, 2017).

The role of the private sector

The private sector in South East Asia has experienced pressure to address AMR in parallel to national governments. There has been a change within many of the larger integrated production companies to move towards minimal or even no antimicrobial use. For example, Thailand is a major exporter of chicken (Preechajarn, 2016) and as such broiler production by the large integrator companies such as Charoen Pokphand Foods, Thai Food Group and Betagro must adhere to strict regulations on antimicrobial use. Farms are certified by the Thailand Government Department for Livestock Development (DLD) and must comply with Good Agricultural Practice (GAP). This requires farms to have strict biosecurity procedures and a veterinarian must oversee antimicrobial use.

Similarly, these large production companies purport to have low and responsible antimicrobial use policies for commercial pig production. For example, Charoen Pokphand Foods, the largest pig producer in Thailand, claims to have spent ‘... more than 30 years developing its swine breeding that produces great meat without using antibiotics or beta-agonist. As the pigs are not stressful and can grow healthily, there is no need to use antibiotics or hormone.’ These aforementioned examples show that antimicrobial use policies in the private sectors have been greatly influenced by the economic importance of export markets.

Government policies addressing AMR concerns have resulted in private sector responses for the domestic markets as well as export. For example, in Indonesia, Charoen Pokphand was already phasing out the non-therapeutic use of antimicrobials across its company and contractor farms in the years preceding the 2018 ban on antimicrobial growth promoters (CIVAS and FAO, 2017). In addition, there have been extensive collaborative efforts across the South East Asian region to engage with the private sector in government policy development. For example, the private sector was actively involved in the development of the action and containment plans for AMR in Thailand, Indonesia and Vietnam (Thamlikitkul *et al.*, 2015; MARD, 2017; MOH, 2017). There have also been numerous collaborative workshops which have brought together government, private sector and academic representatives across the region on the subject of antimicrobial use and resistance (Nguyen, 2018).

Lessons learned from the South East Asian Experience

The key lessons learned from the development of policy relating to AMR and AMU are presented in Table 5.

Table 5. Summary of key lessons from the South-East Asia development of antimicrobial policy adapted from (Goutard *et al.*, 2017)

Priority Area	Practical suggestions for policy development and implementation
Co-ordinated regional collaborations to focus on food and health security	<ul style="list-style-type: none"> • This should focus around the One Health tripartite partnership between FAO, OIE and WHO. • A national AMR secretariat can oversee changes in policy and practice at a country level. This would focus on food producing animals but would include expertise from across the public and animal health sectors. • A national AMR secretariat could oversee the implementation of the national AMR action and containment plan, promote best practices with regards to antimicrobial use and resistance and overcome specific country barriers to the enforcement of antimicrobial policies (Dar <i>et al.</i>, 2016). • Country-level actions should be undertaken with close communications with neighbouring countries, as well as at the wider international level
Adopting a One Health approach	<ul style="list-style-type: none"> • The complexity of AMR needs to be considered in policy with a one health approach, as success relies on a harmonised approach between sectors. • An integrated approach requires a detailed understanding of the relationship between humans, animals and the environment in each country. This includes a detailed understanding of the antimicrobial supply chain in both human and veterinary medicine as well as the food supply chain. • A one health conceptual framework for antimicrobial surveillance and control should be advocated (Queenan, Häsler and Rushton, 2016). • However, it is essential in LMICs that the socioeconomic climate is considered in policy decisions in order to reduce the chances of there being a negative effect on disadvantaged and vulnerable populations.

<p>Increased AMR surveillance and AMU monitoring</p>	<ul style="list-style-type: none"> • There is an urgent need for reliable AMR and AMU data in LMICs in order to inform and guide policy. • AMR monitoring requires active surveillance of healthy animals as well as of disease animals. There is often a lack of capacity in government veterinary services to undertake this much needed surveillance. However, undertaking pilot studies to explore what surveillance may be practical can inform policy at a country level. • AMU surveillance systems should take a standardized approach to monitoring and surveillance. This would allow comparison between countries and species sectors. For example, the ESVAC scheme in Europe has established a harmonised approach for monitoring antimicrobial consumption (EMA, 2017). The ESVAC approach has been used by the pharmaceutical sector in Thailand to monitor veterinary antimicrobial sales data (AHPA, 2017).
<p>The context of policies in animal production systems</p>	<ul style="list-style-type: none"> • The WHO global action plan includes an international agreement to ban antimicrobial growth promoters in livestock (WHO, 2015). • There is a need for the development of measures to control disease burden (e.g. Biosecurity, management improvements) in order to ensure farms remain productive and profitable with a ban (Founou, Founou and Essack, 2016; World Bank, 2016). • There is also a need for enhanced surveillance for animal diseases to ensure that health is not adversely affected by an antimicrobial growth promoter ban. There may be a risk of farmers seeking antimicrobials from unofficial and black-market sources if health and productivity are adversely affected. • There may be poor enforcement of some antimicrobial use legislation for livestock reared for the domestic market in comparison to the export market. There is a need to ensure that policies are enforced uniformly across livestock species and farms. • Any legislation or policy affecting animal production should introduced only with sufficient consideration to effects on farmers and consumers of livestock products (Dar <i>et al.</i>, 2016). • Any policy proposals should be considered alongside the political, economic and social climate of the individual country(Kirkpatrick and Parker, 2004).
<p>Understanding the drivers of antimicrobial use and resistance pathways</p>	<ul style="list-style-type: none"> • Codex and OIE offer some guidance on the risk of AMR transmission however this is limited. • There are limited data on the risk factors for the emergence of resistance and transmission pathways of resistant pathogens or resistance genomes (e.g. through food, environments and contact). • WHO, FAO and OIE have a role in providing more risk analysis models to assess the potential transmission of AMR in animals, humans and the environment. This should include advice on risk management options, communication with key stakeholders and the perception of risk by end users. • There must be continual education of farmers and veterinarians with regards to the latest evidence with regards to AMR risk.
<p>Private sector engagement</p>	<ul style="list-style-type: none"> • Due to the growing importance of private production companies it is essential that the private sector is consulted on policy decisions and involved in ongoing AMR and use strategies.

- It is important to engage with private sector production for domestic consumption alongside those for the export market to avoid a divide in food safety with higher policy enforcement for export products than domestic.

Summary

An illustration of the direction of policy development in the domains of AMR and zoonotic disease risk reduction has been presented. In cases where control of AMU has been most enthusiastically embraced by producers, strong incentives in terms of market access are present. In the absence of such incentives, the public sector has a role to play in legislating, but should engage with the private sector during that process. Progress has been made in many countries toward legislative control of non-therapeutic AMU, but significant challenges exist where enforcement capacity is weak, and the market is open to non-prescription and internet sales, or counterfeit products.

With reference to zoonoses, the global trend has been to focus on three areas: foodborne diseases, neglected diseases, and emerging viral diseases. Of relevance to the field of AMR and therefore of particular interest are the foodborne and neglected diseases. For CGIAR, the key issues are the evaluation of current efforts directed at change and whether they are well co-ordinated, and the need for institutional responses to mitigate zoonotic diseases and AMR. There are also gaps in our understanding of what will replace the antimicrobials we want farmers not to use, and what this could mean in risk to the farm businesses, and the food systems our urbanised populations rely on. Research is needed in these areas.

CONCLUSIONS AND RECOMMENDATIONS

Introduction

Having presented a synopsis of the risks presented by the rapid intensification of livestock systems, the use of antimicrobials and the presence of zoonotic pathogens, as well as the initiatives being undertaken to address them, this section aims to summarise key areas where CGIAR would be able to further the research and policy agendas. Specifically, note is taken of the need for a revolution in data collection and sharing including a broadening of existing geographical foci for research, which is currently centred in East Africa and South East Asia. Similarly, cross-disciplinary collaboration is a necessity for understanding the economic and geographic contexts in which AMR and zoonoses exist, and the link between these conditions and human health outcomes to assess intervention effectiveness.

Current gaps in the knowledge of livestock production related issues on zoonoses and AMR

The **trends of zoonotic and food borne diseases** are relatively poorly understood, particularly within intensifying livestock systems. For example the **epidemiology** of influenza viruses in the intensive pig and poultry sectors that have major pandemic risk implications are **still being explored** and have **yet to fully take into account economic drivers and human behavioural dimensions**. This major shift of risk with the adoption of intensive pig and poultry systems is a gap, not just in LMICs, but globally, and has been shown to have major negative impacts on food supply, employment and business success, such as in Egypt and SE Asia during the 2000s HPAI outbreaks, in Chile during the salmon infectious anaemia outbreak, and USA with highly pathogenic influenza in the chicken layer sector. An aspect of these outbreaks has been the **lack of resilience of the intensive livestock systems** to zoonotic disease incursions, and the relative **low ability of the societal structures to absorb and manage risks**. A major issue has to be how the response to the presence or risk of disease is managed to ensure that consumers, the market and society as a whole do not overreact to a threat, thereby generating greater impact than is necessary to mitigate the losses to production or human health.

In a much broader context, the **intensifying livestock systems** adopt different species, breeds, feeding and management systems, leading to different types of livestock products being made available. Simultaneously, grazing and scavenge based systems shift toward grain-fed and housed systems. The combined effect of these changes generates **alters levels of risk for different pathogens for different people**. For example, the risk of cysticercosis in pigs would be anticipated to be reduced with the intensification of pork production systems, yet there could be an increase in food borne disease risks such as that caused by *Salmonella typhimurium*. In both, cases consumers would be affected. In the former case, people working with the pigs are part of the issue and in the latter case the levels of disease risk can be managed through consumer's management of cooking processes. The critical issue is capturing how risks change with intensification and how these can be best mitigated in terms of surveillance, prevention and control measures that adopt a combined public and private sector approach.

Similarly in cattle systems that are becoming more intensive there will be a move to housing and stall feeding, which could well change the patterns of diseases such as brucellosis and tuberculosis. These diseases can be managed with pasteurisation of milk, yet there is a significant risk of exposure to the people who manage the animals on a day to day basis, the animal health staff who treat the sick animals, and the people who slaughter these animals. The need to have a recognition of these changes and that some populations will be at greater risk than others merits further work supporting existing efforts of the CGIAR.

There also maybe a case that food borne disease burdens will change with livestock food systems that are based on grain-fed systems with a high proportion of meat coming for pig and poultry and a proportion of protein from chicken egg systems. There needs to be careful monitoring of **non-typhoidal salmonella** issues to ensure that precious gains in

improved food security and nutrition through better access to livestock products are not lost through poor food safety issues. Similarly, issues on **campylobacter** in poultry, humans and the environment are relatively poorly understood and are not well reported in LMICs (Carron *et al.*, 2018).

The intensifying livestock systems and their associated value chains involve change, and in general such changes lead to different levels of risk for pathogens that affect human health in terms of zoonoses and food borne diseases. Where livestock are being raised with significant levels of antimicrobials this implies that there will also be **risks of AMR transmission across the food system**, either through **direct contact with people** working in the livestock food systems, through the **food** itself especially where there is poor food hygiene and also through the environment contaminated with waste from the production and processing units. Data collection and capture of antimicrobial use in LMICs are being updated and improved through international and national mechanisms in order to establish potential risks to human health and to identify areas for targeting interventions to address the risks of AMR emergence, albeit this tends to be reduced to a very simple statement of “reduced antimicrobial use”. Despite the lack of data currently available on AMU outside of the OECD group of countries, the current best estimates suggest global antimicrobial consumption will increase in food producing animals by 50% between 2015 and 2030 (Van Boeckel *et al.*, 2015). Firstly, improvements to data collection outside of the OECD would allow this projection to be refined; secondly, and perhaps more significantly, restrictions and practical interventions aimed at reducing AMU are already being put in place which, without adequate data collection protocols running in parallel, cannot be properly assessed for efficacy or cost-effectiveness. Data on antimicrobial use in food producing animals can be collected at a national, regional or individual farm level. These data can be sought from a variety of sources, such as farm-level or antimicrobial suppliers. With regards to antimicrobial suppliers this may include national-level data such as drug distributors, national feed sellers or pharmaceutical companies, or may be more local-level such as individual veterinarians, feed stores, or drug retailers (Singer, Reid-Smith and Sicho, 2006; Redding *et al.*, 2014). LMICs create a unique challenge to data collection when sales records and on-farm medicine use records are often not retained and where available data may be in a number of different formats, are not centralised and are not available as an electronic record (Redding *et al.*, 2014).

Table 6. Existing data and data gaps in need of addressing for the development of productive AMR and zoonosis risk mitigation policy setting.

	Existing data	Data gaps identified
Pharmaceutical supply chain	Privately owned data by pharmaceutical companies. Nine large pharmaceutical companies have a platform called CEESA (European Animal Health Study Centre) collecting data from 45 countries, however these data are unlikely to include LMICs. There is little or no data sharing at present.	Antimicrobial supply levels, including active ingredients are not known. Distribution networks or import and export of antimicrobial compounds are unknown. Antimicrobial sales incentives are also unknown and likely to vary considerably (Morgan <i>et al.</i> , 2011).
Animal population and associated production systems	FAOSTAT and WAHIS (World Animal Health Information System by the OIE) have estimates of international populations. ESVAC system for denominator data. There are country-level government data collected but often lacking for LMICs.	There are discrepancies between data sources. Data are often out of date. Data do not often define life-stage or production type for livestock/aquaculture species.

	<p>The private sector may collect data.</p> <p>Private sector and country-level data may not be available.</p>	<p>No standardised metric for reporting slaughter data (e.g. kilograms of livestock product)</p>
Quantity of antimicrobials used	<p>Sales and import data in HICs and some LMICs.</p> <p>Data capture at farm-level has been initiated mainly in some OECD countries (OIE survey).</p> <p>ESVAC collects and collates national data for 30 European countries.</p> <p>Some information on when antimicrobial use is most likely during the life of animals and fish.</p> <p>Commercial animal feed frequently contain antimicrobials for growth promotion but quantities are not known (Sneeringer <i>et al.</i>, 2015).</p>	<p>Farm level use, species and production system use unknown, main points in production cycle uncertain. Including for in-feed antimicrobials.</p> <p>Critical periods of infection and vulnerability of animals and fish in LMICs need to be documented.</p> <p>Specific indications for antimicrobial use in key livestock/aquaculture species.</p> <p>Alternative methods of managing these vulnerable periods need to be explored.</p>
Farmer, veterinarian and animal health workers' antimicrobial use perceptions and practices	<p>Limited academic studies have explored antimicrobial use practices in LMICs (Eltayb <i>et al.</i>, 2012; Om and McLaws, 2016; Caudell <i>et al.</i>, 2017).</p>	<p>Knowledge of concerns over antimicrobial use, resistance and residues.</p> <p>Understanding of the drivers behind antimicrobial use and any financial incentives.</p> <p>Knowledge of veterinarians and animal health workers on types of different antimicrobials.</p>
Monitoring of AMR in livestock/aquaculture species	<p>Mainly limited academic studies in LMICs but some surveillance emerging in OECD countries.</p> <p>No standardised sampling or antimicrobial susceptibility testing procedures.</p> <p>No standardised antimicrobial panel and methodology for defining resistance.</p> <p>WHO and EU have published guidelines on which antimicrobial pathogens should be monitored e.g. EU recommend non-</p>	<p>A gold standard global methodology for AMR testing for key pathogens in the most common livestock and aquaculture species.</p> <p>These data need to be integrated with livestock population and antimicrobial use data.</p> <p>Social and economic analysis of AMR impacts is needed to support policy decision-making and linkage of AMR to interventions around antimicrobial use.</p>

	<p>typhoidal <i>Salmonella</i> (NTS), <i>Campylobacter jejuni</i>, commensal <i>Escherichia coli</i>, ESBL- or AmpC- or carbapenemase- producing <i>E. coli</i>. (ECDC, 2006).</p> <p>Genotypic technologies such as whole genome sequencing are currently being used in outbreak investigations to elucidate gene flow between species and to identify sources of AMR genes and organisms.</p>	<p>There is a need for a global system to monitor AMR at slaughter.</p> <p>There is a need for a global standardised sampling strategy, antimicrobial panel and methodology for defining resistance.</p> <p>There is a need for a global standard list of pathogens for monitoring for AMR in LMICs as the WHO/EU guidelines do not consider key pathogens for aquaculture e.g. <i>Aeromonas</i> spp. <i>Pseudomonas</i> spp., <i>Vibrio</i> spp., <i>Flavobacterium</i> spp..</p> <p>There is a need for ongoing work to better utilise advanced technologies such as whole genome sequencing for identification and surveillance of AMR.</p> <p>The Canadian integrated program for AMR surveillance has been recommended as an exemplar program for Asia (Nguyen-Viet <i>et al.</i>, 2017) 5</p>
Antimicrobial residues	<p>There is monitoring of residues for export to OECD countries.</p> <p>There are some published information by FDA and EU on the environmental impacts of antimicrobials.</p>	<p>There is very little known on residues in food in LMICs.</p> <p>The potential public health consequences from antimicrobials in the environment is mainly unknown.</p>
Environmental effects of AMR	<p>There is limited information on the environmental effects of effluent containing resistance genes. Most is in small-scale academic studies.</p>	<p>Further research on the environmental aspects from AMR in effluent and wastewater.</p> <p>Standardised testing that is comparable between countries (Kahlmeter, 2014).</p> <p>Audit of legislation on effluent management, and its enforcement.</p>
Modelling for AMR for zoonotic pathogens	<p>Small scale mechanistic models of dynamics such as within-host treatment (Spicknall <i>et al.</i>, 2013) and dissemination within farm environment E.g. (Græsbøll <i>et al.</i>, 2014) Conceptual models or statistical association models.</p>	<p>More models need to be developed that aim to represent the dynamics of antimicrobial use, through to AMR risk to humans.</p> <p>Social and economic models needed that predict impacts of changes in antimicrobial use on pharmaceutical sector, farm sector and food supply;</p>

		Resilience models needed to examine food supply e.g. (Toutain <i>et al.</i> , 2016)
Antimicrobial use and resistance policy	<p>Existing regulatory frameworks -<i>Codex Alimentarius</i>; OIE codes; OIE PVS tool and Public/Private initiatives (VICH).</p> <p>Active antimicrobial use policy development in OECD countries, including setting of reduction targets.</p> <p>1- Large food and retail companies are increasingly demanding information from suppliers on antimicrobial use.</p> <p>LMICs with export markets tend towards higher standards, including tighter controls on AMU and product testing for AM residues</p>	<p>Regulatory frameworks need updating and are not always applied in LMICs.</p> <p>Absence of analysis of policy conflicts, particularly regarding potentially negative impacts of changes of antimicrobial use on food supply and management of AMR in the food system.</p> <p>Corporate responsibility charters on antimicrobials should be encouraged;</p> <p>Domestic markets in LMIC tend to have a lower level of control of antimicrobial use than export-led production in the same country – this ‘two tier’ approach needs to be addressed.</p>
One-health surveillance & mitigation strategies	<p>There is increasing understanding of the ‘one health’ paradigm and acknowledgement of the need for integrated interventions and surveillance. A conceptual framework for economic analysis of ‘one health’ surveillance has been developed and utilized for <i>campylobacter</i> and West Nile virus surveillance (Babo Martins, Rushton and Stärk, 2016, 2017; Paternoster <i>et al.</i>, 2017)</p>	<p>Operational research needed to better understand the practical challenges involved with inter-sectoral working (Bardosh <i>et al.</i>, 2017). Real-life examples needed of the cost-effectiveness of ‘one-health’ interventions including quantification of zoonotic disease burden (Shaw, Rushton, Roth and Torgerson, 2017; Torgerson <i>et al.</i>, 2018)</p>

Overall there is a general lack of information being generated on what the trade-offs are between antimicrobial use, AMR and food production and overall a general lack of economic assessment that would lead to useful policy advice (Rushton, 2015). Data on the costs of interventions and the selection of appropriate outcome metrics are lacking. Structured analyses of cost-effectiveness and cost-benefit for interventions would help provide focus in this regard (Babo Martins and Rushton, 2014), and combined with the use of marginal abatement cost curves, generate evidence for intervention prioritisation ((Macleod and Moran, 2017). On the zoonoses side, further work is required on how the economic burden of disease is assessed for zoonoses ((Shaw, Rushton, Roth and Torgerson, 2017; Torgerson *et al.*, 2018).

Across the livestock food systems in general there is a need for more information on the role of people and their actions in the introduction, maintenance and spread of zoonoses and food borne diseases, with an emphasis on which groups of people in society are at greatest risk. A part of this risk analysis has to incorporate these people’s ability to manage risk and be resilient to the changes that intensification implies.

Role of research and the comparative advantage of the CGIAR to manage the identified gaps

From an external perspective the CGIAR would be seen to have a competitive advantage in LMICs in supporting and providing research on livestock and animal health. Within this set of countries their focus has tended to be on the poor and poverty-ridden families associated with agriculture, and on pastoral farming, and there is a tendency for the research work to be geographically focussed. Traditionally the work would be livestock keepers with small-scale cattle systems, with some attention to small ruminants. More recently there has been work with pigs and poultry, and on the wider impacts of disease along food chains, which follow an emerging research trend from the late 1990s and 2000s. The disease focus has tended to be related to vector management and investigations at the interface between human activity, climate and livestock production, leading to negative outcomes on human health. This gradual shift has been in recognition of the increasing importance of intensive livestock systems and their associated value chains, both in generating livestock products for the growing urban populations and in providing income and employment for a range of people, including the poor in rural and urban settings. Within this has been a greater emphasis on food borne pathogens across the food chain, along with an awareness of how zoonotic pathogens can be monitored with well-functioning surveillance systems.

The suggested gaps and opportunities for technical related research would be as follows:

- Zoonoses and food borne diseases
 - The ILRI work on livestock food chains could contribute strongly to an improved understanding of the general importance of these diseases and their epidemiology, and to the development of cost-effective mitigation measures
 - Such work should move in the direction of understanding the dynamics of the food systems and how these change, bringing together skills from the basic biological sciences, economics and social sciences.
 - Natural partnerships across the CGIAR would be through livestock focused research groups in ILRI along with the policy groups in IFPRI
- AMU/AMR in livestock
 - The ILRI focused surveillance work (ZOO LINK) would be a good basis for guiding the new investments in surveillance on AMU and AMR in livestock that are being led by the Fleming Fund, OIE and FAO.

On a more general scale there are areas that action could be taken to make ongoing work more global and help to close gaps:

- Pig and poultry sectors
 - Further engagement with the private sector companies who manage feeding, housing and health of animals
 - Sharing of state of the art surveillance and diagnostics with these companies
 - In exchange, privately-held data on animal health and disease is needed in order to estimate disease losses and expenditure, feeding into the information being generated through the Global Burden of Animal Disease programme.
- Small ruminant sector
 - Continuing engagement of this sector in terms of risks on brucellosis and Q fever through the work on PPR management and elimination

- Cattle and buffalo
 - The dairy sector have large amounts of privately held data that could be a source of information on animal, herd and sector performance that could be linked to zoonotic diseases and AMU/AMR

On a regional level, the CGIAR's research on zoonoses, food borne diseases and AMU/AMR in livestock needs careful partnerships in Latin America to ensure major intensifying livestock systems have access to the information generated. At an institutional level, collaboration between CGIAR colleagues and the zoonotic and AMR tripartite (OIE/WHO/FAO) should continue, along with engagement with regional organizations such as ASEAN, AU-IBAR, MERCOSUR, IICA and the development banks at global and regional level (The World Bank, InterAmerican Development Bank, Asian Development Bank, African Development Bank, European Bank of Reconstruction, IFAD). These partnerships all need to focus on regulations and standard setting initiatives that optimize food availability and quality with the minimization of zoonotic, food borne and AMR externalities.

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