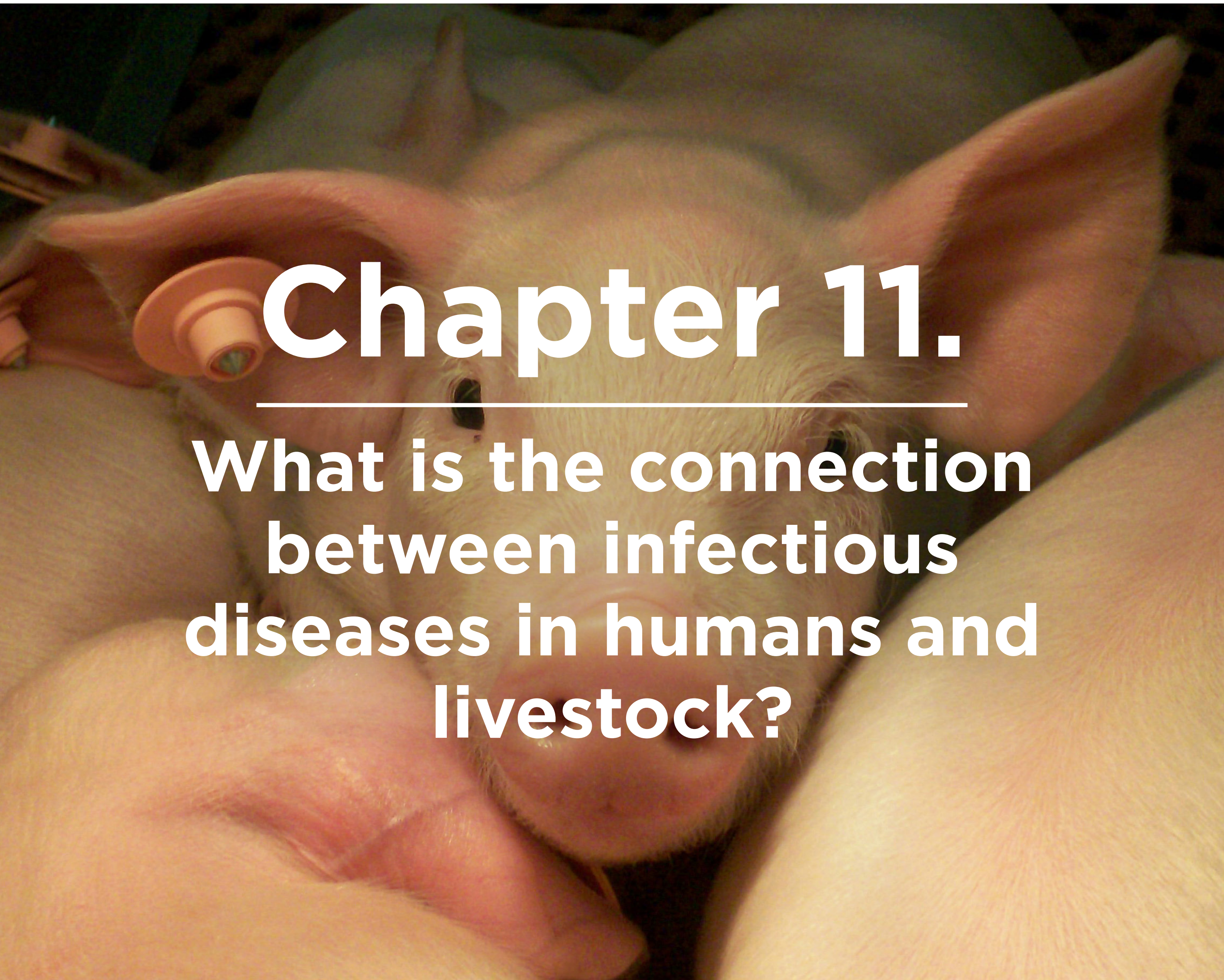
FCRN Food Climate Research Network

fondation daniel & nina carasso
sous l'égide de la Fondation de France

FCRN foodsource

A free and evolving resource to empower informed discussion on sustainable food systems



Chapter 11.

What is the connection between infectious diseases in humans and livestock?

Foodsource is supported by: Fondation Daniel & Nina Carasso — Esmée Fairbairn Foundation — The Oxford Martin programme on the Future of Food — The Oxford Martin School —Jam Today — University of Manchester Sustainable Consumption Institute — The Wellcome Trust — WRAP

Contents

Why should you read this chapter?		**3**
Key points		3
11.1	**How are animal and human diseases interconnected?**	**4**
11.1.1	What are the common factors in animal and human disease?	4
11.1.2	How are diseases transmitted between animal species, and then on to humans?	5
11.1.3	How do animal diseases become human diseases?	10
11.1.4	How do zoonotic diseases affect public health challenges?	12
11.2	**How do livestock affect the risk of zoonotic disease emergence and spread?**	**15**
11.2.1	The major point of interconnection between animals and humans	15
11.2.2	Growth in livestock numbers	16
11.2.3	Livestock-driven land use change	17
11.2.4	Growing trade in livestock and livestock products	18
11.2.5	Changes in livestock production systems	18
11.3	**Why does antibiotic resistance matter?**	**21**
11.3.1	What are antibiotics?	21
11.3.2	How do bacteria develop resistance to antibiotics?	23
11.3.3	Why is stewardship of antibiotic drugs needed?	25
11.3.4	How is antibiotic resistance a form of environmental pollution?	27
11.4	**How does livestock production affect risks from antibiotic resistance?**	**29**
11.4.1	How are antibiotics used in livestock production?	29
11.4.2	What is the extent of antibiotic use in livestock production?	32
11.4.3	How can antibiotic use in livestock production affect human health?	33
11.4.4	What evidence exists for antibiotic resistance being transmitted from livestock to humans?	36
11.4.5	What can be concluded about the health risks from antibiotic use in the livestock sector?	38
Conclusions		**40**
References		**42**
Credits		**50**

GO TO CONTENTS

Why should you read this Chapter?

Diseases that pass between animals and humans are responsible for many of the diseases affecting people worldwide, especially in developing countries. Animals (wild and domestic) also play an important role in the emergence and spread of entirely novel human diseases, with the potential for large impacts on human health, such as bird flu. Another aspect of this to which livestock contribute, is the rise and spread of resistance to antibiotic drugs.

One outcome of sustainable food systems is that they should be health promoting. It is, therefore, useful to understand the interconnection between infectious diseases in human and animals, and how these risks may be amplified or reduced by changes in farming systems.

This chapter addresses the following:

- How are infectious diseases in human and animals connected?
- How does livestock farming affect human disease risk?
- What is antibiotic resistance and why does it matter?
- How does antibiotic use in livestock affect human health risks?

Key points

- Zoonotic diseases are those where the pathogens that cause them, such as bacteria, fungi, parasites and viruses, are able to infect both humans and animals. They make up the majority of all known human infectious diseases.
- Zoonotic diseases have a large impact on global health and are responsible for over 2.5 billion cases of human illness and 2.7 million human deaths worldwide each year, with most of the burden in low-income countries and among poor livestock keepers.
- Livestock's proximity to wildlife and humans (via the food chain) makes them an important point of interconnection for zoonotic disease transmission. Changes in livestock production and consumption can affect the health risks from zoonotic diseases.
- Antimicrobials are compounds used to help kill pathogenic microbes. Antibiotics are antimicrobials, that target bacteria. Growth in antibiotic resistance threatens medicine's ability to treat common infections and safely conduct medical procedures.
- Resistance to antibiotics emerges as a direct result of their use. While a drug may kill most bacterial cells, a random genetic mutation in some may allow them to survive and proliferate. Bacteria can also exchange resistance genes with other bacteria that they encounter.
- New antibiotic drug discovery is slow and costly, and is not currently keeping up with growing levels of antibiotic resistance. Antibiotics must be conserved to avoid a rise in untreatable infections and increased risks associated with medical procedures.
- The majority of antibiotics worldwide (by weight) are used in livestock production – mostly given to pigs and poultry in intensive livestock production systems. Resistant bacteria are widely found in livestock populations. Many antibiotics used in livestock production are also those critical to human medicine.
- Pathways for resistance transmission from livestock to humans are well understood, and good evidence exists for it taking place via the food system. However, it is not a simple step for resistance to be transferred from livestock to human pathogens, and then spread further.
- Most clinical cases of antibiotic resistant infections in humans are thought to result from human use and misuse of antibiotics in hospitals and in the community. Limited and uncertain data, suggest that the current contribution from livestock is relatively limited.
- Even with small probabilities of resistance transmission to human pathogens, over time and when scaled by the growing numbers of livestock worldwide, the long-term risk posed to public health from antibiotic use in livestock is still significant.
- Given the potentially irreversible impacts and the alternative ways to reduce the burden of infection in livestock farming, delaying action to reduce antibiotic use in the livestock sector is seen by some as an unnecessary gamble on public health. Many governments, institutions and businesses are already taking action to restrict their use.

11.1 How are animal and human diseases interconnected?

11.1.1 What are the common factors in animal and human disease?

In both animals and humans, infectious diseases are caused by microorganisms known as pathogens.

Types of pathogen include:

- Fungi;
- Viruses;
- Parasites;
- Bacteria.

Many pathogens are intrinsically able or have developed the ability to infect both animals and humans, and so may be transmitted between them (Figure 1). These are collectively known as 'zoonotic' diseases and make up more than 60% of all known human infectious diseases.

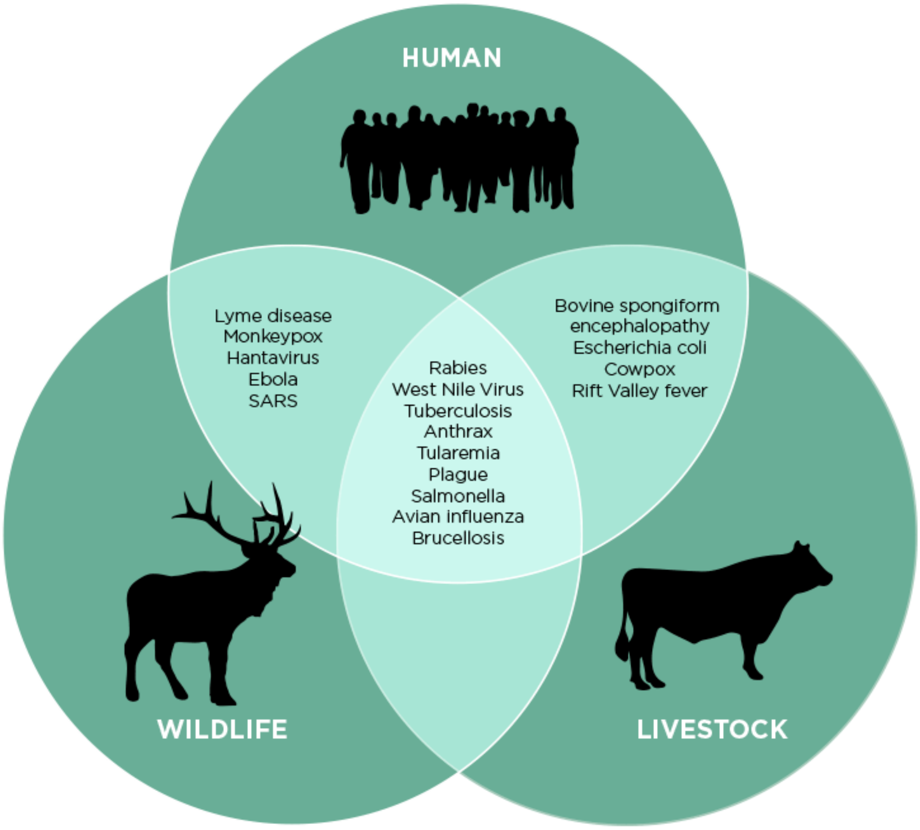


Figure 1: Examples of zoonotic diseases and their affected populations.

Source: Redrawn from United States Government Accountability Office (2011).

Through the biology and ecology of their shared pathogens, human and animal health are interconnected. In turn, humans, animals and pathogens are also influenced by wider changes in ecosystems and the natural environment in which they exist.

In recent years, a growing trend has been the adoption of more interdisciplinary and transdisciplinary approaches to managing health risks. These approaches include One Health, Planetary Health, and Ecohealth (Figure 2), which look beyond human medicine, and also incorporate the biology and health of non-human species, ecosystems functioning, and the effects of environmental change.

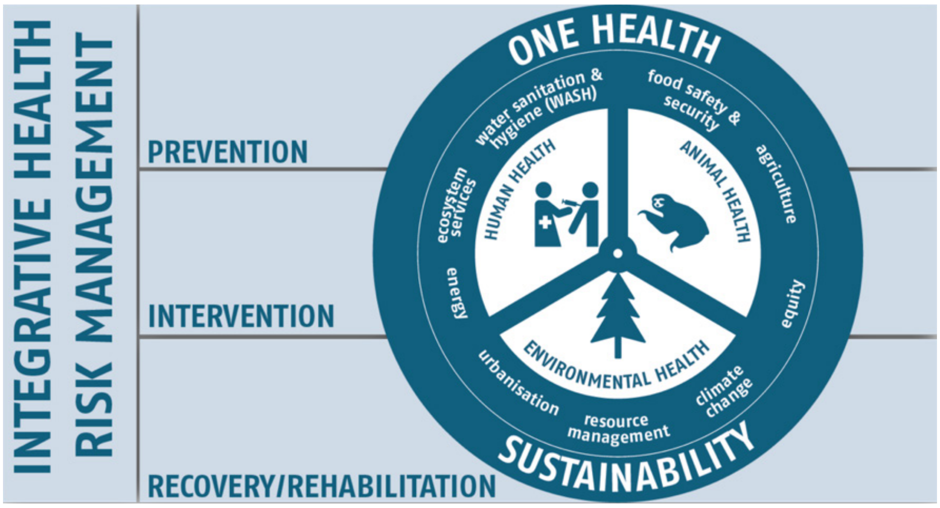


Figure 2: The one health perspective takes an integrative systems perspective on health risks, including human, animal, and environmental health within one framework.

Source: Reproduced from Davos Global Risk Forum (2017).

11.1.2 How are diseases transmitted between animal species, and then on to humans?

If pathogens are biologically able to infect more than one type of animal species (including humans), when contact is made between such animals, the potential for the pathogen to be transferred to a new host species exists. Occasions where this takes place are known as ‘spill over’ events.

Various contact routes for disease transmission are possible:

- **Direct contact** with an animal’s bodily fluids (e.g. saliva, faeces and blood), via, for example:
    - Touching an infected animal’s skin;
    - Being bitten by an infected animal.
- **Indirect contact** within areas where infected animals live and roam, including:
    - Breathing in dust particles and small droplets of saliva;

    - Consuming contaminated food products;
    - Contact with contaminated water, soil, objects or clothing.
- **Disease vectors:** organisms that transmit infectious disease between animals, and between animals and humans. These are typically insects that feed on the blood of humans and animals, and in so doing, transmit pathogens between them.

Direct contact and food consumption are the most common modes of transmission for diseases associated with food systems. Airborne transmission of viruses are also common routes for infection.

The risk of transmission to humans is higher for those with high level of occupational exposure to livestock and livestock products, such as those working with livestock, in abattoirs, and in the meat processing industry.

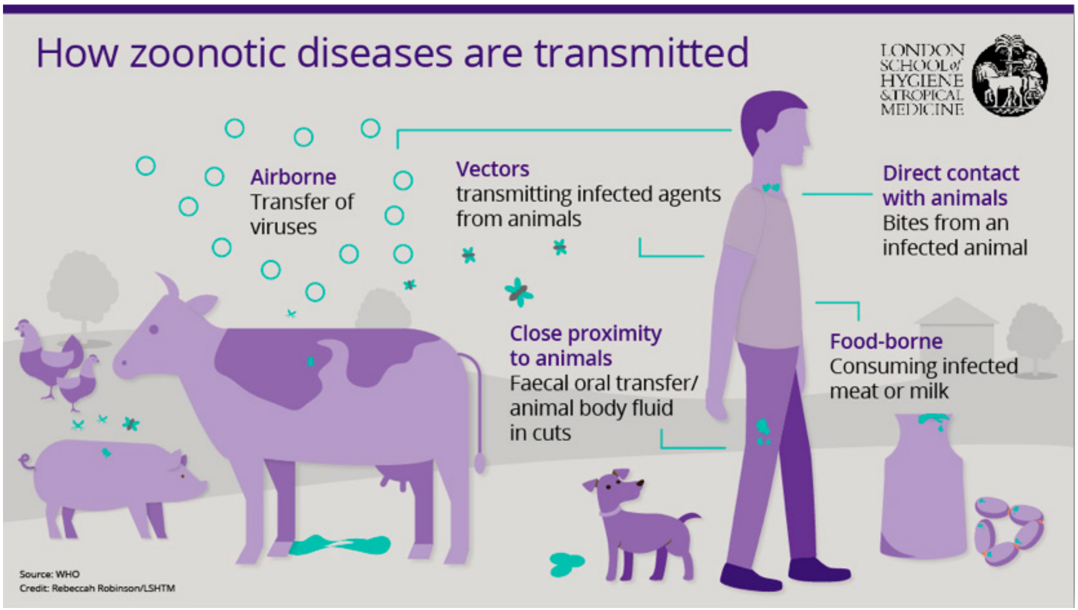


Figure 3: Some common pathways for zoonotic disease transmission.

Source: Reproduced from Thornton (2017).

Table 1 gives some common examples of zoonotic diseases and their modes of transmission.

Infectious agent	Disease	Main reservoir	Usual mode of transmission to humans
Fungi	Ringworm	Wildlife, livestock and domestic animals	Direct contact with infected animals.
Virus	Ebola	Wild animals: chimpanzees, gorillas, fruit bats, monkeys, forest antelope, porcupines	Direct contact with animal Secretions/ bush meat.
	Rabies	Dogs, cats, bats, foxes	Direct contact via animal bite.
Bacteria	Campylobacter; Salmonella	Livestock: poultry, dairy products, pigs	Direct contact via ingestion of animal products.
	Bovine tuberculosis	Cattle	Direct contact via ingestion of milk.
	Lyme disease	Ticks, rodents, sheep, deer, small mammals	Indirect contact via a bite from infected tics (vector host).
	Anthrax	Livestock, wild animals, environment	Direct contact via ingestion or indirect via environment.
Parasites	Leishmaniosis	Dogs, rodents, cattle	Indirect contact via bite from infected sand-flies.

Table 1: Examples of zoonotic diseases, their infectious agents and modes of transmission.

While the type of contact is what directly enables disease transmission to take place in each case, many other factors may promote or reduce the likelihood that a contact event occurs (i.e. degree of exposure to an infection), and that if it does, this then leads to a human infection (i.e. degree of susceptibility to infection).

These include natural and human induced changes in ecosystems, changes in food and agriculture systems, and changes in human living environments and consumption practices (Figure 4).

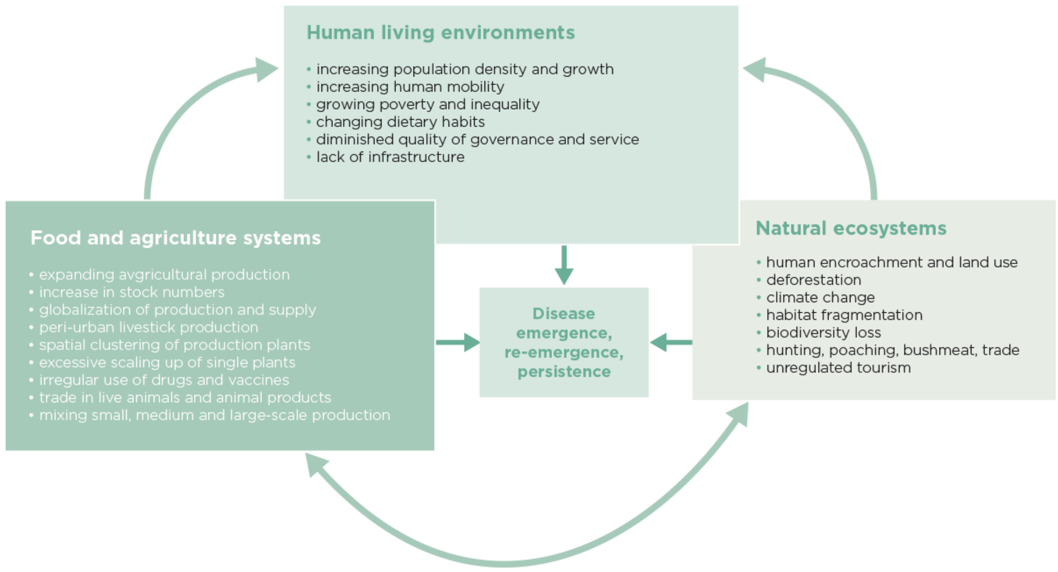


Figure 4: Overview of the disease interactions at the human-livestock-ecosystem interface that contribute to the emergence of infectious zoonotic diseases.

Source: Redrawn from World Bank (2010).

In particular, the degree of spatial overlap and interaction – and so exposure – between humans, animals (wild and domesticated) and vector species is important because it determines what steps in the chain of infection from one species to another are physically possible.

Over human history, human interaction with animals has changed considerably (Figure 5). This has been driven by the domestication of animals, expansion of agriculture into natural ecosystems (which now covers almost 40% of the earth's terrestrial surface), urbanisation, and by the industrialisation of food systems.

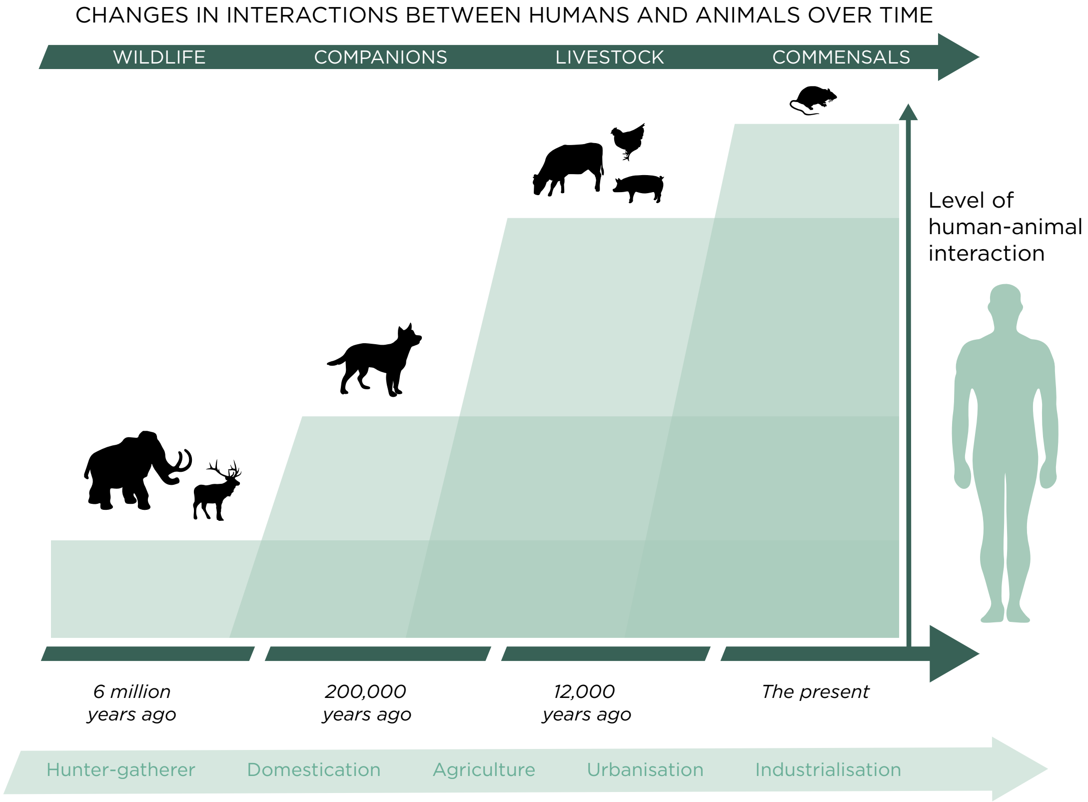


Figure 5: Schematic (non-quantitative) representation of the changes in the nature and level of human-animal interaction over time, linked to changes in the size and organisation of human societies.

Source: Redrawn based on Reperant, *et al*. (2012).

Increasing global travel of humans and of animals (via trade), means that in the absence of specific measures to control the spread of disease, localised disease sources can rapidly come into contact with new populations of animals and humans worldwide.

11.1.3 How do animal diseases become human diseases?

Animals and their pathogens often co-evolve mutually sustainable relationships, such that the host animal may experience few or no symptoms, while the rate of infection within the population of an animal species as a whole is persistent and widespread. This means that many animals can act as consistent sources (or 'reservoirs') of disease, that can then be passed on to other species that they come into contact with (Figure 6).

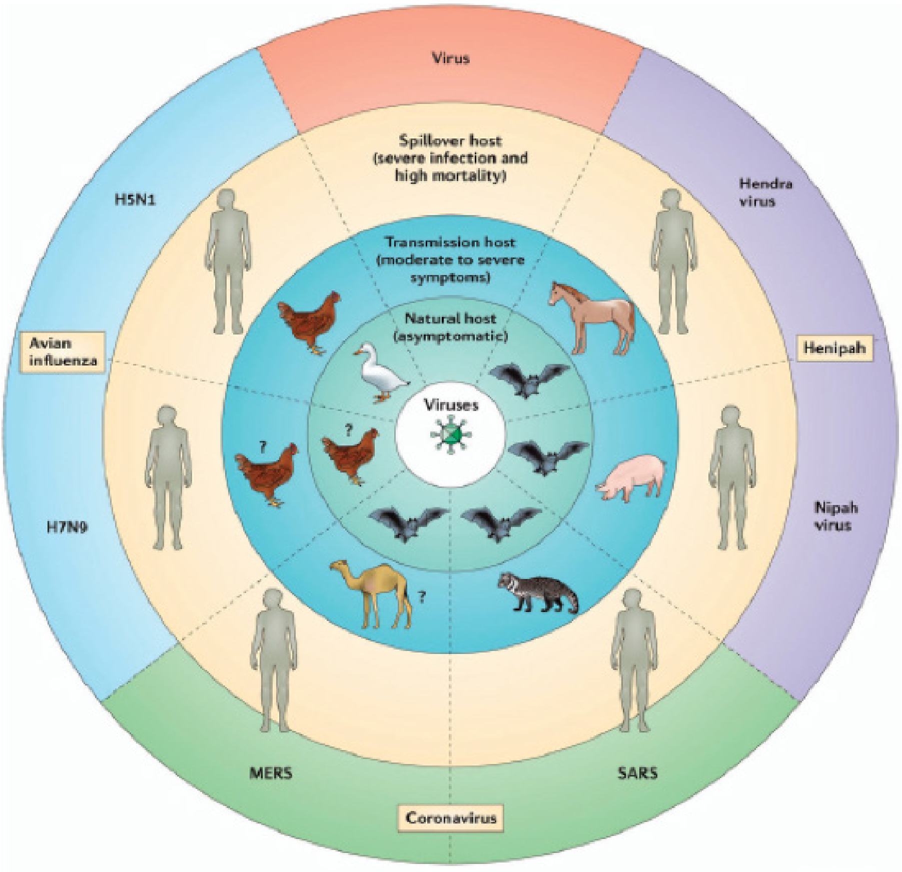


Figure 6: Example of interactions between disease reservoir species, intermediate host species, and humans. The severity of infection for viruses often increases with each step away from the original host species.

Source: Reproduced from Bean, *et al.* (2013).

Collectively, wildlife and livestock pathogens represent a vast potential source of human disease, were they all able to infect humans. Yet there is no inevitability about pathogens jumping the species barrier to infect livestock or humans, and relative to the overall amount that exist, few actually do.

Pathogens that have evolved (or have intrinsically) the ability to infect humans, do so to different degrees, and with human health impacts ranging from very minimal to terminal. The ease of a pathogen's transmission between humans and the duration over which it can survive in the human body are two factors which influence its ability to spread beyond isolated human infections (Figure 7).

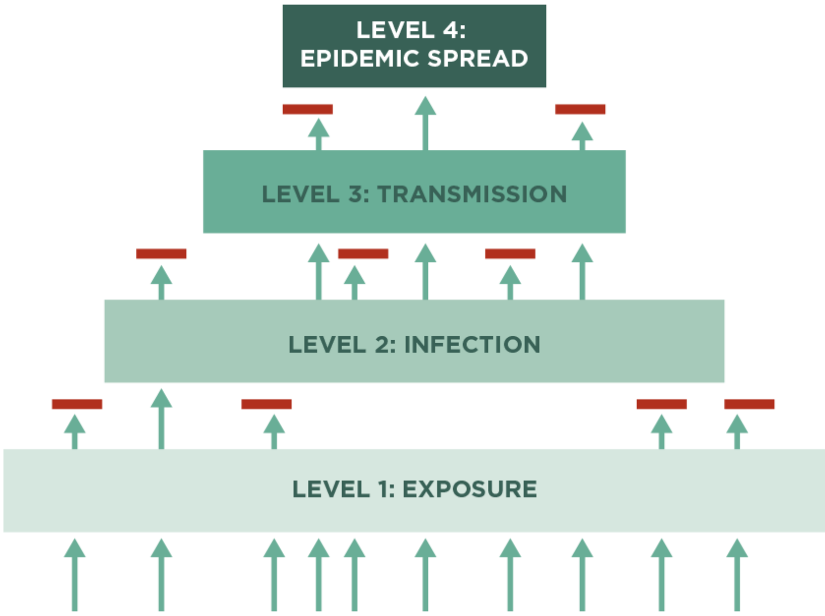


Figure 7: The pathogen pyramid. Each level represents a different degree of interaction between pathogens and humans, ranging from exposure through to epidemic spread between humans or livestock. Some pathogens are able to progress from one level to the next (arrows); others are prevented from doing so by biological or ecological barriers (bars).

Source: Redrawn from Woolhouse, *et al*. (2011).

Pathogens may at some point in time, evolve the ability to survive longer or be transmitted more effectively between humans, thereby increasing the level of threat to human health that they pose.

- Very few zoonotic pathogens (~10%) are able to be transmitted easily between humans or can persist for a long-time period in the human body before either the recovery or the death of the human host from the diseases they cause. Those that can have the potential to form pandemics, where infections spread widely and internationally (e.g. from influenza or AIDs).
- About a quarter of zoonotic pathogens are capable of some human-to-human transmission but still cannot persist in human populations for very long without repeated reintroductions from wildlife or livestock reservoirs. These may form local or regional disease outbreaks (e.g. Ebola).
- The vast majority of zoonotic pathogens are either minimally or not transmissible at all between humans, and so their prevalence in human populations depends almost entirely on individuals' exposure to infected animals or disease vectors (e.g. rabies or lime disease).

11.1.4 How do zoonotic diseases affect public health challenges?

It has been estimated that the top 56 zoonotic diseases are responsible for 2.5 billion cases of human illness and 2.7 million human deaths worldwide each year.

Emerging epidemic / pandemic zoonotic diseases

Global efforts to tackle zoonotic disease have typically been focussed on the minority of diseases capable of forming regional outbreaks or global pandemics, which in a (unlikely but possible) worst-case scenario, could result in tens of millions of deaths and cost trillions of dollars.

This is especially true for so-called 'emerging' zoonotic diseases: diseases that existing healthcare systems are either unprepared or unable to treat, because the pathogens that cause them have:

- Been newly discovered in humans;
- Appeared in a completely new geographic area;
- Acquired completely new infectious traits (e.g. suddenly become more infectious or deadly).

Their unpredictability, and the potential for quick and large-scale health impacts (particularly on wealthier population) has made them a high-profile political and public health issue worldwide, receiving large amounts of funding and research.

Most examples of emerging zoonotic diseases with pandemic potential, tend to be viruses, due to their rapid rates of evolution and ability to be transmitted and so spread quickly between hosts (Figure 8). Rates of bacterial evolution is also very fast, and for this reason, the threat to human health from emerging antibiotic resistance is also significant (Section 11.3.3).

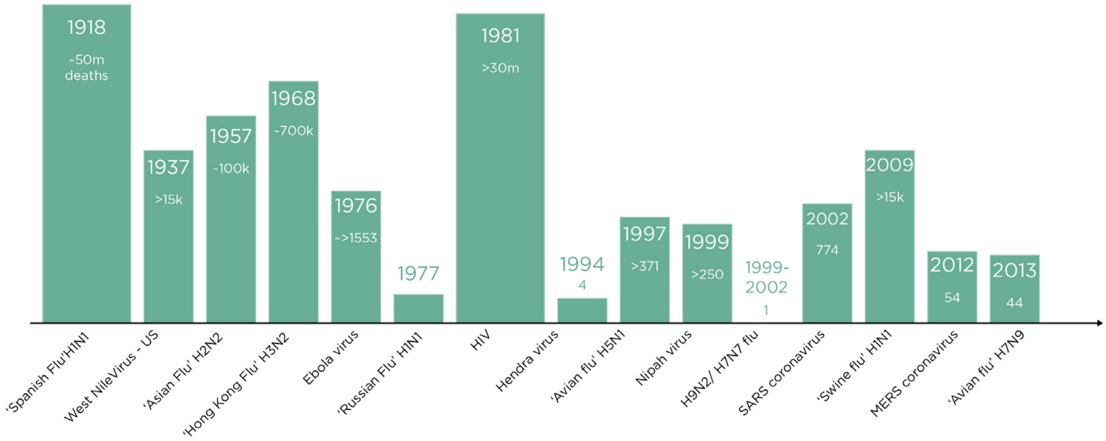


Figure 8: Emergence of zoonotic diseases and resulting deaths over the last century.

Source: Based on data from Bean, *et al*. (2013). Note: the scale is logarithmic.

While pandemic outbreaks of new diseases are rare, zoonotic diseases represent the majority of recently emerging infectious diseases recorded in humans (75%) and so are a likely source of new pandemics. Most originate from wildlife sources. However, disease outbreaks originating from livestock tend to occur in areas of dense human population and so also present a considerable risk to public health.

Notably, the number of instances where new diseases have arisen in humans ('emergence events') has increased over the 20th century; and of these events, the primary driver in almost half of cases is related to food and farming systems, through changes in land use, agricultural intensification, food industry changes, and bush meat hunting and consumption (Figure 9).

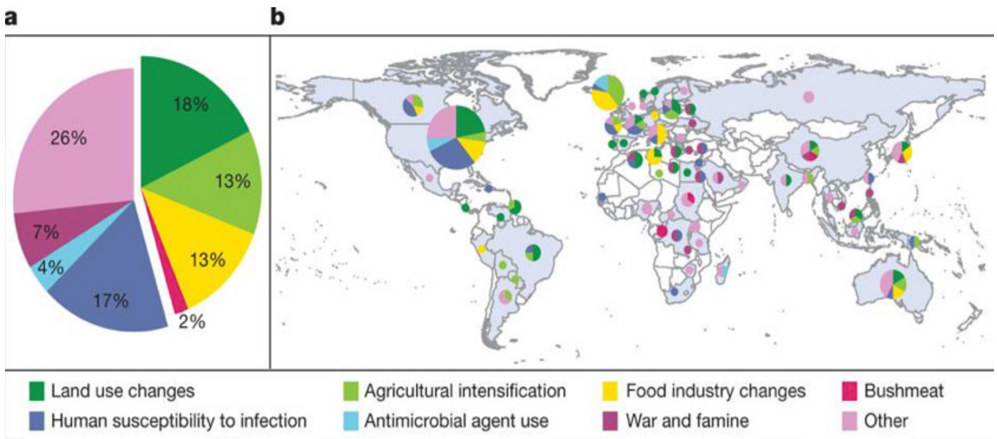


Figure 9: Drivers and locations of emergence events for zoonotic infectious diseases in humans from 1940–2005. Pie chart on the left (A) represents worldwide percentage of emerging events caused by each driver. Map on the right (B) shows, countries in which events took place and the drivers of emergence.

Source: Reproduced from Keesing, *et al*. (2010).

Already existing and endemic zoonotic diseases

Despite affecting the health of billions of people and animals, already existing zoonotic diseases that lack pandemic potential receive far less attention and research than do pandemic ones. Nevertheless, their ongoing costs to society are high: an analysis looking at just 6 major outbreaks of highly fatal diseases, estimated their costs to be at least US$80 billion.

For endemic zoonotic diseases, human cases of infection mainly arise from repeated exposure to disease-hosting animals. Because both wildlife and livestock can act as a constant source for infection and re-infection (Section 11.1.3), these diseases are generally always present in particular geographical areas where animal disease reservoirs exist, causing persistent levels of infection and sickness in local people.

By far, the greatest amount of sickness from all zoonotic diseases, worldwide, is borne by people in low-income countries (98.5% of the total burden), and particularly by poor livestock keepers who often contact endemic zoonotic diseases from their livestock (Figure 10).

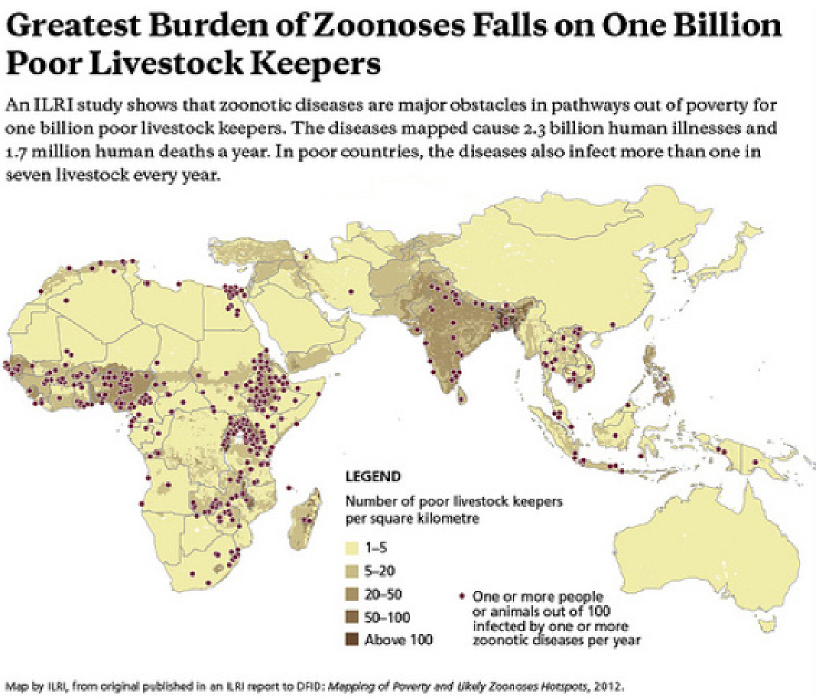


Figure 10: The disproportionate impacts of zoonotic disease on poor livestock keepers.

Source: Reproduced from Grace, *et al*. (2012).

Some reasons for this include:

- Lack of access to effective veterinary care services and national disease control policies;
- The need to live in very close contact with livestock;
- Increased susceptibility to infection from poor nutrition and sanitary conditions;
- Greater proximity and interaction with infected wildlife and disease vectors.

Zoonotic diseases have caused large economic costs in all regions, but in lower-income regions where endemic diseases are not controlled in livestock or wildlife populations, their impact on economic development and human well-being is considerable.

In such areas, poverty tends to increase both exposure and susceptibility to zoonotic diseases, and in turn, the effects of disease can compound poverty through lost income and other costs related to human and animal sickness. In this way, zoonotic diseases can trap people in a cycle of poverty and ill-health.

11.2 How do livestock affect the risk of zoonotic disease emergence and spread?

11.2.1 The major point of interconnection between animals and humans

Livestock are an important point of interconnection for many infection pathways linking humans to sources of zoonotic pathogens (Figure 11).

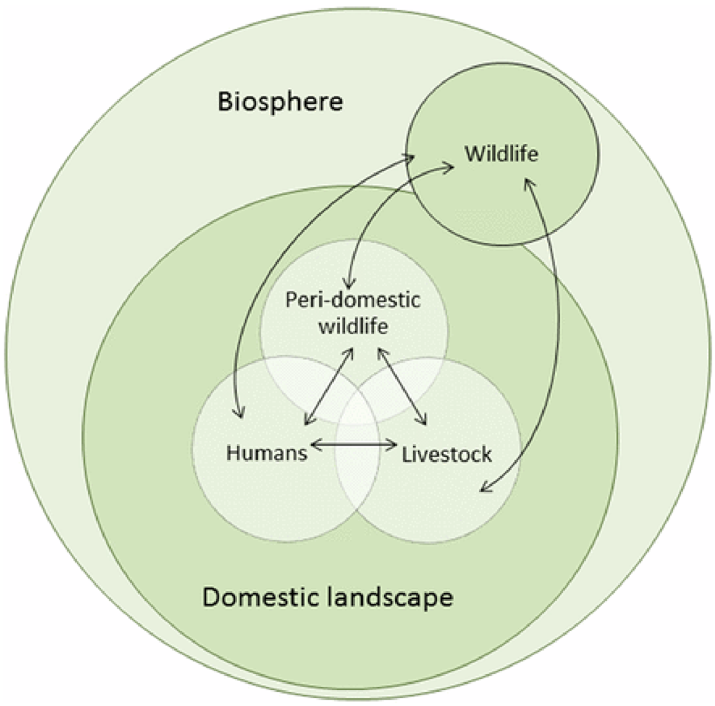


Figure 11: Illustrative flows of pathogens at the human-animal-environment interface between species. Peri-domestic wildlife signifies animals such as rats, commonly found in urban areas.

Source: Reproduced from Jones, *et al*. (2013).

GO TO CONTENTS

By sharing the landscape with wildlife and disease vectors, livestock are routinely exposed to the pathogens they carry, and may become infected. At the same time, human exposure to livestock can be considerable – especially in low-income countries where many households keep animals.

Ever since the introduction of agriculture and the domestication of animals, farms have provided a venue for human and animal pathogens to intermingle and share genetic information; and the activities of farming, butchery, preparation, and consumption of livestock products all provide pathways for zoonotic pathogens to be transmitted to humans.

The sourcing and consumption of bushmeat is another important pathway for zoonotic pathogens to infect humans directly from wildlife.

11.2.2 Growth in livestock numbers

Globally, livestock production has increased substantially. Estimates of livestock numbers are uncertain but are thought to total around 23 billion poultry and 1 billion pigs living on farms today. Some individual farms contain tens to hundreds of thousands of animals.

With a larger global livestock population comes an overall increase in the:

- Frequency of interactions between wildlife, livestock, and humans;
- Likelihood of disease emergence and transmission events occurring;
- Overall diversity of pathogens found in separate animal populations; and
- Potential for new diseases to spread among livestock and human populations.

All things being equal – i.e. without stricter measures to mitigate the risk – this trend increases the likelihood that diseases will spill over from wild animals and livestock, to affect humans (Figure 12).

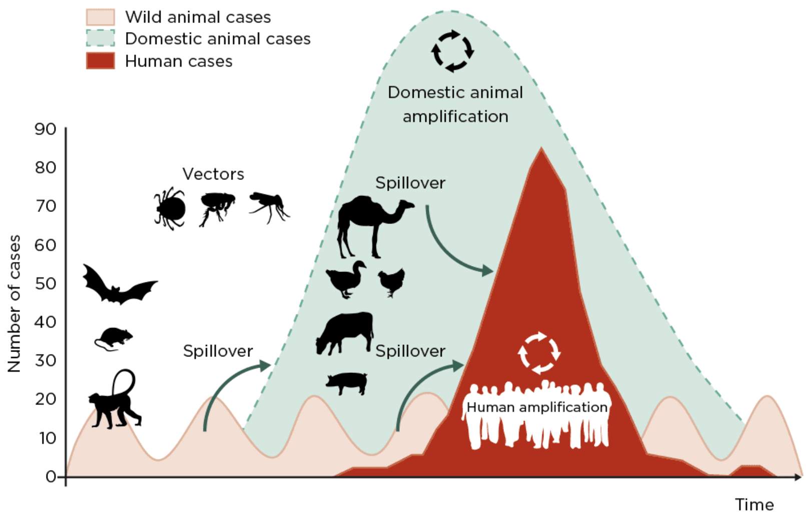
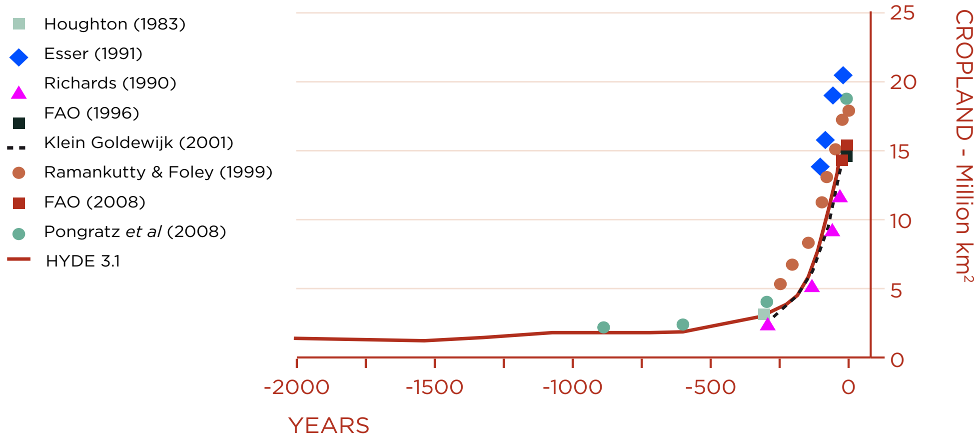


Figure 12: Transmission and amplification of zoonotic diseases. Transmission of a pathogen to people can occur directly from a wild animal or following an outbreak in livestock that amplifies the likelihood of transmissions to humans.

Source: Redrawn from Karesh, *et al.* (2012).

11.2.3 Livestock-driven land use change

Global land use for agriculture has grown dramatically over the last two hundred years, with about three-quarters of the world's agricultural land used to rear livestock (Figure 13).



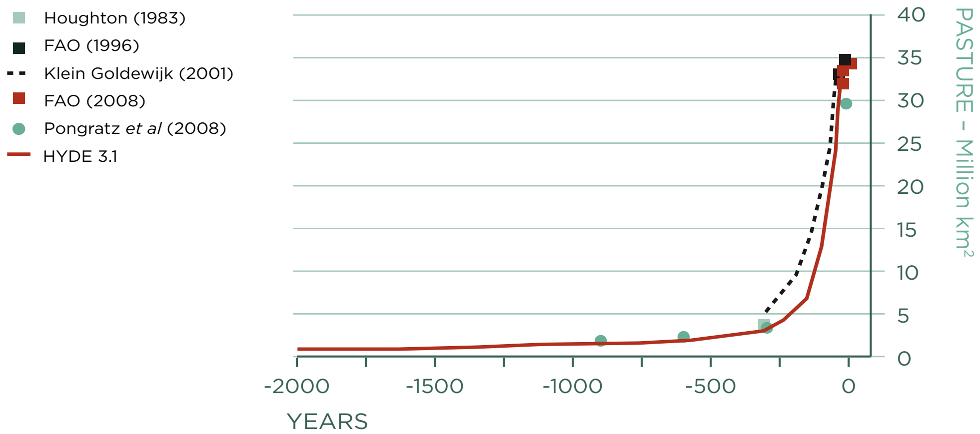


Figure 13: Growth in global land use for agriculture over the last 2000 years.

Source: Redrawn from Goldewijk, *et al.* (2011).

Expansion of agricultural land into natural ecosystems increases the likelihood of contact between wild animals, disease vectors, and livestock, and so also increases the likelihood of subsequent disease transmission to humans.

11.2.4 Growing trade in livestock and livestock products

Geographically separate populations of livestock and their pathogens, and those of the wild animals to which livestock are exposed, can be connected through trade – especially the trade in live animals that may join herds/flocks in new regions, or in the case of wild animals, that may escape and infect local species.

Modern trade and transport networks also mean that it is possible for zoonotic diseases to spread quickly, both within countries and internationally. And from countries with higher burdens of disease and poorer animal health services to those with much stronger controls.

Alongside growing animal numbers, the trade in live animals, animal feed, and animal-based products has increased substantially (Figure 14).

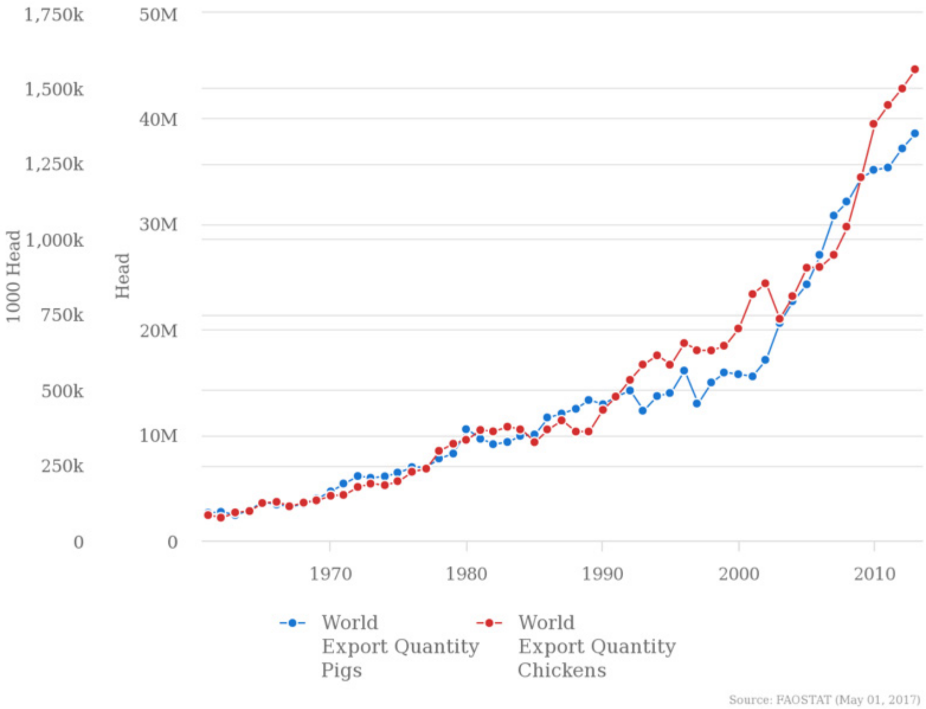


Figure 14: Live animal exports of pigs and chickens, 1961 to 2013.

Source: Data from FAOSTAT. (2017).

Without stricter measures to mitigate the risk, this trend increases the likelihood that zoonotic diseases will spread to new locations through trade. And while some preventative national and international regulations already exist, zoonotic disease outbreaks still occur regularly as a result of both legal and illegal trade. This is true both of trade in farm animals and in wild animals and their products.

11.2.5 Changes in livestock production systems

Farms are artificial ecosystems. By shaping the ecological context for pathogens, their evolution, and their opportunities for transmission, the management of livestock farming affects the risk of new diseases emerging and being transmitted to humans.

Many factors affect this risk, and different forms of livestock production come associated with different costs, benefits and trade-offs for public health that need to be actively managed (Figure 15).

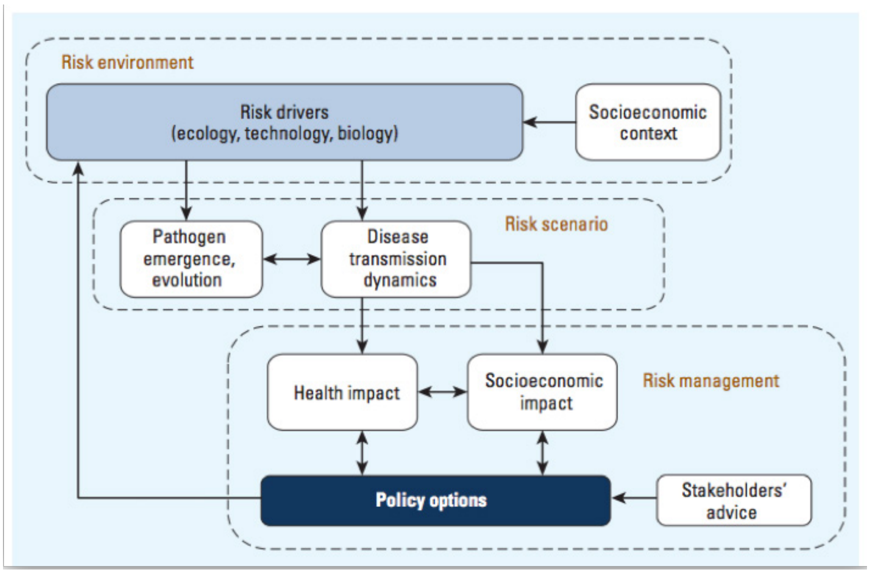


Figure 15: A conceptual framework for zoonotic disease risk in livestock industries.

Source: Reproduced from Liverani, *et al.* (2013).

A shift away from domestic or 'backyard' forms of livestock production in lower-income countries is likely to reduce levels of sickness from those zoonotic diseases that are almost exclusively transmitted via ongoing direct contact between people and infected animals (i.e. endemic diseases).

This type of shift has already been observed in countries such as China. However, it has also been associated with an increase in more commercial and intensive models of livestock production that bring a whole new set of health risks.

Intensive livestock systems

In simplistic terms, 'intensive' livestock production systems are characterised by their greatly increased scale and speed of production, alongside significant investments in the use of technology. The goal of this being to optimise levels of output (i.e. meat, milk, eggs) in relation to inputs such as human labour, land, animal feed, and other resources, and ultimately, to reduce the overall costs of producing a unit of food.

By making animal products more affordable for more people, intensive livestock production systems have enabled significantly increased overall consumption of animal products. Data on numbers of livestock in different systems is sparse and uncertain. However, it has been estimated that, globally, this type of production system is responsible for about:

- 76% of all pork;
- 79% of all poultry; and
- 61% of eggs.

On the one hand, greater availability and ability to access even small amounts of nutrient-dense animal products can help to alleviate problems associated with malnutrition among those in extreme poverty. However, a by-product of more intensive production methods is an increased risk of infectious disease resulting from:

- Large and densely populated livestock populations that enable pathogens to be quickly transmitted and spread to large numbers of animals;
- Greater susceptibility to infection due to the animals' genetic similarity and optimisation for faster growth, as well as weakened animal immune systems as a response to stress;
- More frequent movements of people, vehicles, and livestock between farms that may spread disease to new locations;
- Increased levels of airborne particles and large concentrations of animal waste, each containing pathogens that may lead to environmental contamination;
- The exchange of genetic information between both animal and human pathogens, co-existing within livestock populations, to create entirely new forms of infectious disease;
- Increased use of antibiotics and the development of antibiotic resistance (Section 11.4.1).

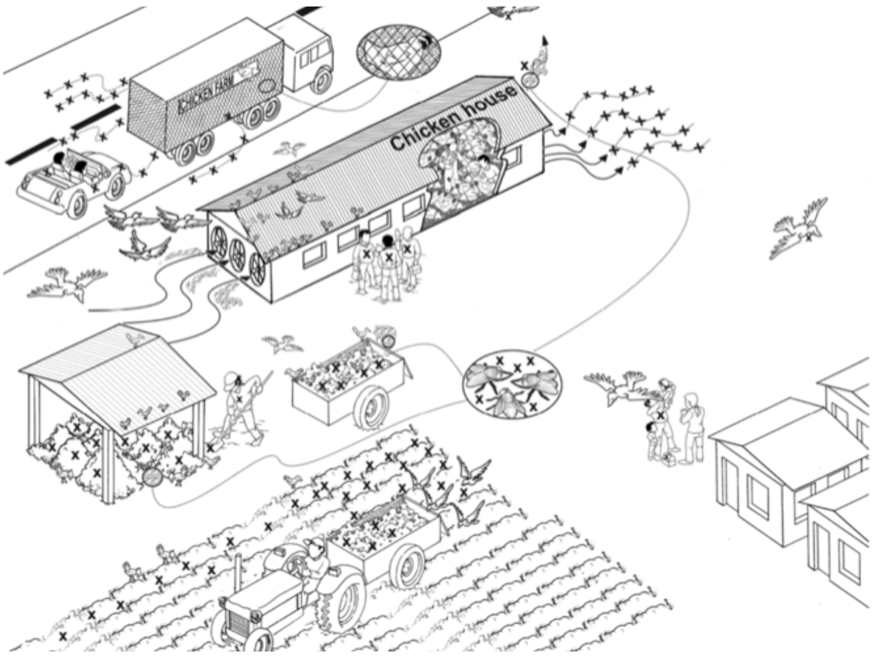


Figure 16: A schematic representation of potential pathways for exposure to and transfer of pathogens within the environs of an intensive chicken farm.

Source: Reproduced from Graham, *et al*. (2008).

Due to these elevated risks, it is necessary to monitor and maintain a high degree of control over livestock's physical environment and biological functioning (i.e. 'biosecurity'; Figure 17 below), in order to:

- Prevent new pathogens from being introduced to and infecting a livestock herd/ flock;

GO TO CONTENTS

- Identify and contain the spread of new pathogens within a farm; and
- Stop dangerous pathogens from being released and spreading off-farm.

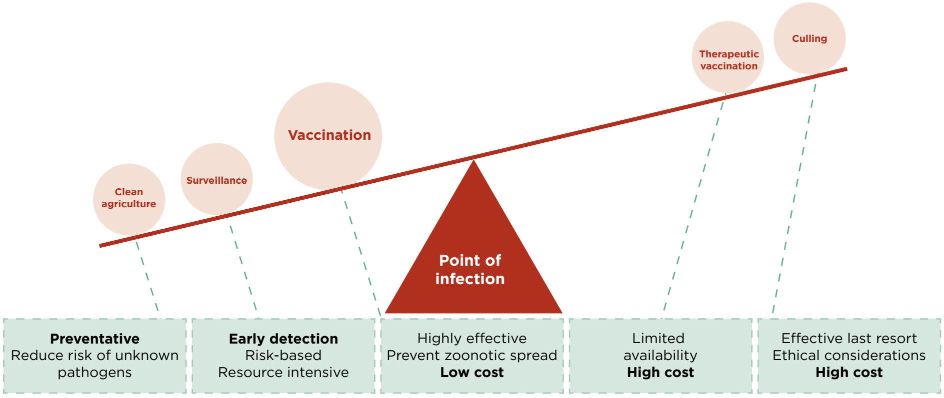


Figure 17: A hierarchy of risk mitigation measures to maintain the biosecurity of livestock systems using vaccination measures.

Source: Redrawn from Layton, *et al.* (2017).

Unfortunately, strong biosecurity practices and food safety measures are not universally adopted, especially in low-income countries where most of the world's livestock production actually takes place. Neither are they always effective at preventing or containing outbreaks of disease, even where implemented.

Intensive livestock production systems also present significant health risks because of the routine use of high levels of antibiotics (Section 11.4.2).

11.3 Why does antibiotic resistance matter?

11.3.1 What are antibiotics?

Bacteria exist in all environments, including on and within the bodies of animals (i.e. their microbiome). Most cause no harm to health and are even beneficial. However, some are actively harmful (pathogens) and can cause a wide range of diseases (Figure 18).

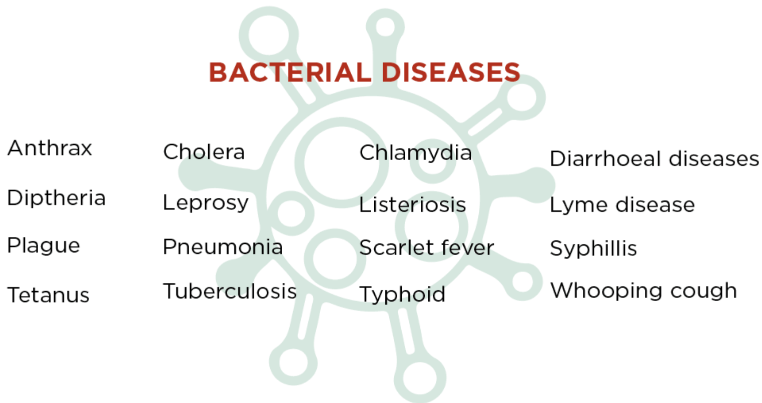


Figure 18: Some diseases caused by bacterial infections.

Antibiotics are the group of medicines and chemicals used to treat these pathogenic bacteria and the diseases that they cause. They form a sub-group of a wider class of substances known as antimicrobials that are used to target a wide range of pathogenic microbes such as parasites, fungi, and viruses, in addition to bacteria.

Before antibiotics, many infectious diseases were untreatable and some frequently resulted in death – a situation that still exists for many people living in poverty in low-income countries. The power to reliably treat infection is a foundation of modern medicine, critical for reducing the risks for patients facing major surgeries and those with compromised immune systems (Figure 19).

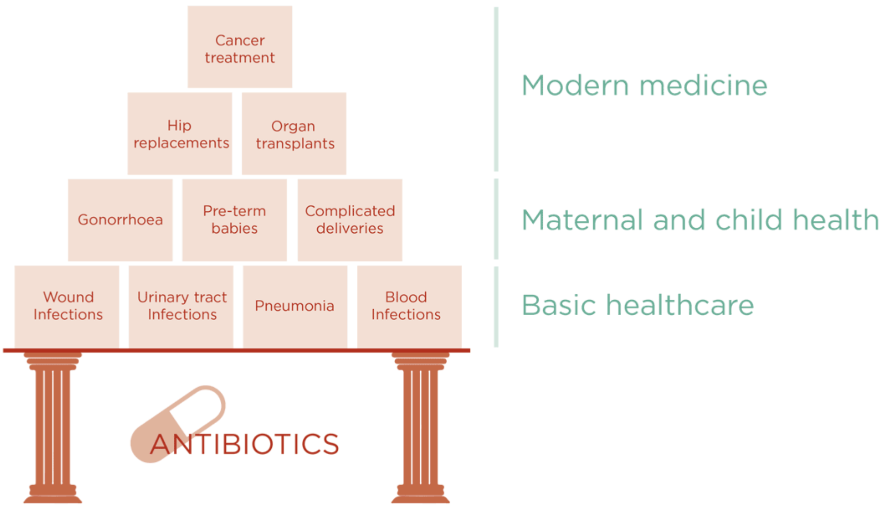


Figure 19: Diseases caused by bacterial infections.

Source: Reproduced from Jørgensen. *et al.* (2017).

All antibiotics help the body's natural immune system to fight bacterial infections but do so in different ways. Today, there are well over 100 antibiotic drugs available that fall within a very limited number of 'classes', which are grouped according to the similar ways in which they target bacteria (Figure 20).

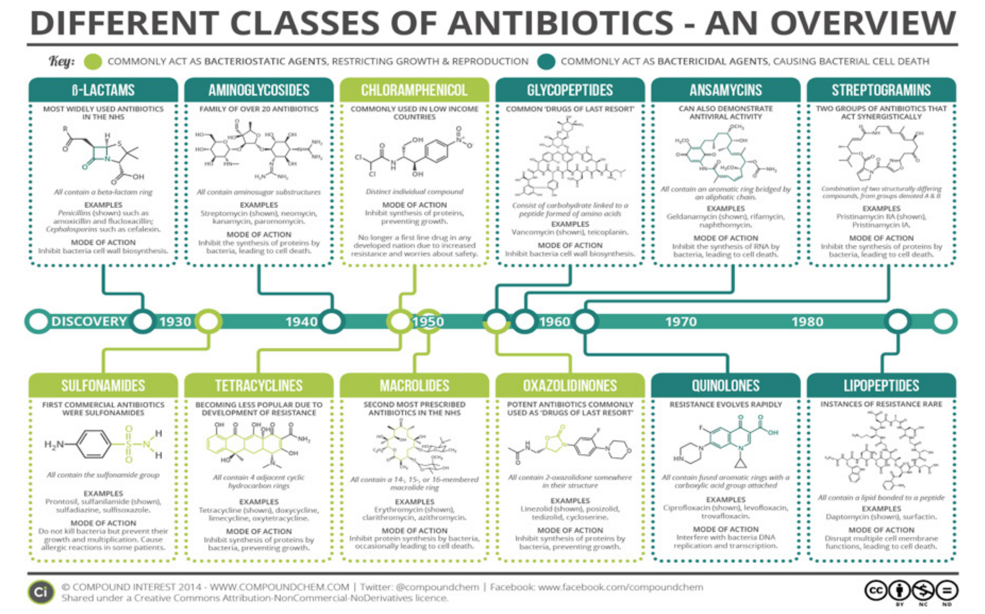


Figure 20: An overview of the different classes of antibiotics.

Source: Reproduced from Compound Interest (2014).

Some 'broad spectrum' antibiotics are effective at killing a wide range of different bacteria, whereas 'narrow spectrum' antibiotics target only specific types of bacteria. Side-effects from antibiotics also range hugely, and in some cases, can themselves cause very severe health impacts – often making them drugs of last resort, used only when everything else fails.

11.3.2 How do bacteria develop resistance to antibiotics?

'Antibiotic resistance' refers to a situation where a specific type of antibiotic drug is not effective at treating an infection caused by a specific bacterial species or strain.

Bacteria species: the huge genetic diversity of bacteria, make the species concept much less precise than for larger organisms. Broadly, it denotes a generic group of bacteria which all share a certain amount of genetic similarity (akin to that between humans and all primates) and so have similar functional characteristics.

Bacterial strain: in contrast to a species, a strain denotes a specific population of bacteria that share a very close genetic similarity. Strains are subtypes of a bacterial species existing in a specific context, which can have unique characteristics that differ from other bacteria of the same species.

This may happen for two reasons:

- **Intrinsic resistance:** antibiotic resistance is a natural outcome of the bacteria's unique biology. In nature, antibiotic compounds are produced by many microorganisms to kill one another and discovering these compounds has formed the basis for most current antibiotic drugs. As a result, resistance to antibiotics has evolved and is found widely in natural settings, with some bacterial species having an intrinsic resistance to some types of antibiotic compounds.
- **Acquired resistance:** a specific population of bacterial cells that previously were sensitive to an antibiotic compound, may evolve by acquiring new genetic solutions and so biological capabilities, that enable it to disable the drug's ability to do them harm.

For public health, acquired resistance is of major concern because it can progressively erode the efficacy of existing antibiotic drugs. The introduction of new genetic traits conferring resistance to a drug, may occur in two distinct ways:

- **Random mutation:** bacterial strains are composed of huge numbers of cells that replicate very quickly. Random mutations can result in genetic variation between bacterial cells in a strain, some of which may confer resistance to a drug.
- **Horizontal gene transfer:** different strains and species of bacteria that come into contact with one another are able to exchange genetic traits between them, including those conferring resistance to one or more types of antibiotic drug.

Once some bacterial cells have acquired resistance, these will have a greater likelihood of surviving when exposed to the drug, while other cells will selectively be killed-off. Most remaining cells will thus have resistance genes, multiply rapidly, and so become predominant in the overall population (Figure 21).

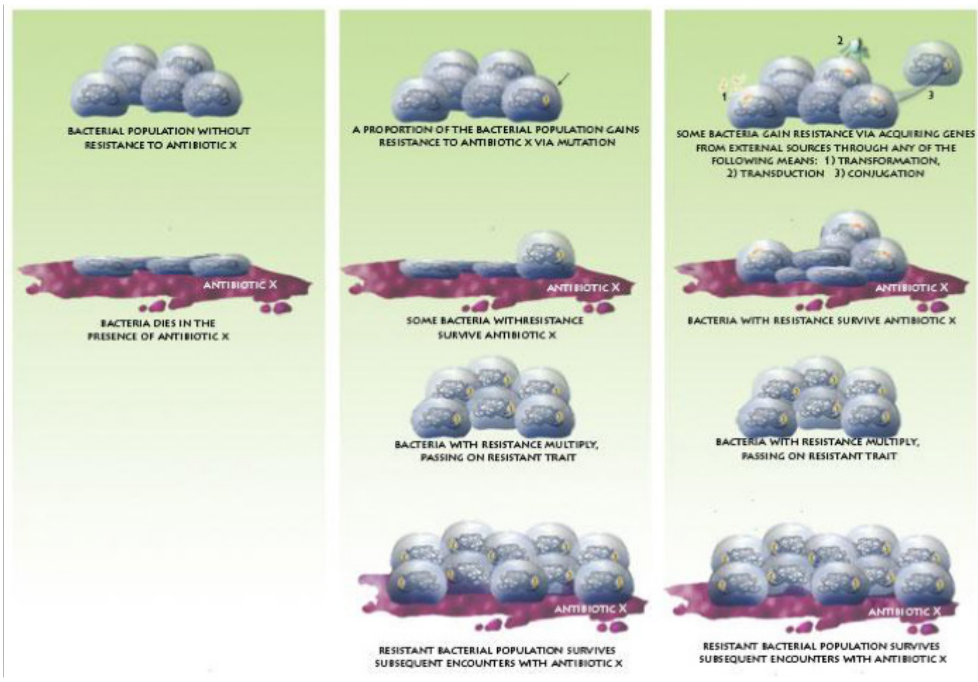


Figure 21: How antibiotic resistance occurs via a process of selection pressure.

Source: Reproduced from MSU (2017).

Because of this, the use of antibiotic drugs will always create the driving conditions for resistance to emerge (known as selection pressure), and evidence shows that this can happen quickly (Figure 22). Once resistance has emerged, it can persist long after the use of antibiotics has stopped, and in some contexts, may never fully disappear.

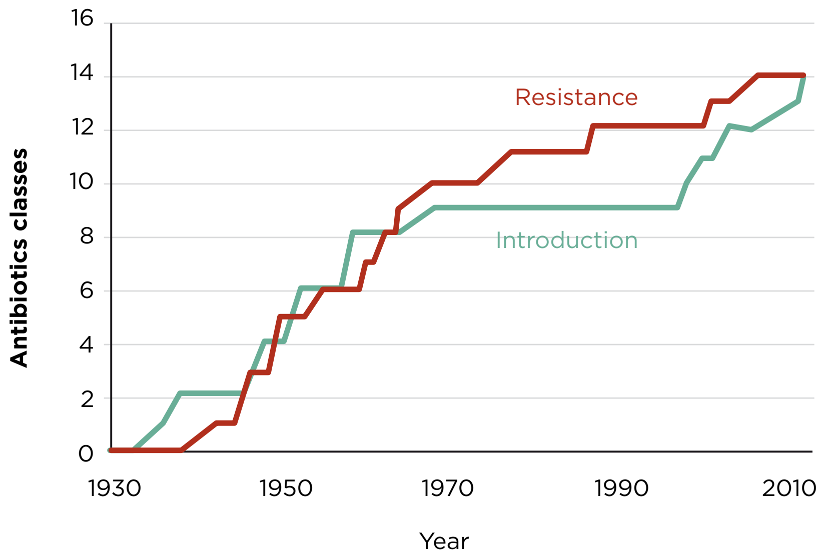


Figure 22: Resistance has evolved to all major classes of antibiotics on the market.

Source: Reproduced from Jørgensen. *et al.* (2017).

Pathogens other than bacteria (e.g. parasites, fungi, and viruses) can also evolve in response to antimicrobial drugs, and so the problem of resistance is, in fact, a much broader issue that goes beyond just antibiotics and bacteria.

11.3.3 Why is stewardship of antibiotic drugs needed?

Antibiotics (like vaccinations) are unusual medical tools because each instance of their use has social and ethical implications that reach far beyond the individual human or animal that they are being used to treat.

While individuals may benefit from using an antibiotic drug today, the contribution this makes towards the emergence of resistance in the local or global community can deny that same opportunity for effective treatment of disease to others, and to future generations.

Effective antibiotic drugs currently in existence, must, therefore, be seen as being finite, non-renewable resources – or as an eroding foundation upon which, modern medicine is dependent. The degree to which new technologies and methods are able to deliver effective and cheap substitutes for currently effective drugs is widely debated, and highly uncertain.

If the supply of newly developed drugs were always able to substitute, perfectly, for older antibiotics that have begun to fail, there would not be a problem. But currently, this is not the case (Figure 23):

- Rates of observed antibiotic resistance are increasing – often to multiple drugs at once;
- The rate of new drug discovery and number of companies working on it has substantially declined in recent decades;
- Access to new drugs is also inequitable, as high costs of development make them unaffordable for those with low-income;
- Drugs of last resort – often with severe side-effects – are increasingly being used. And even to these, resistance is emerging.

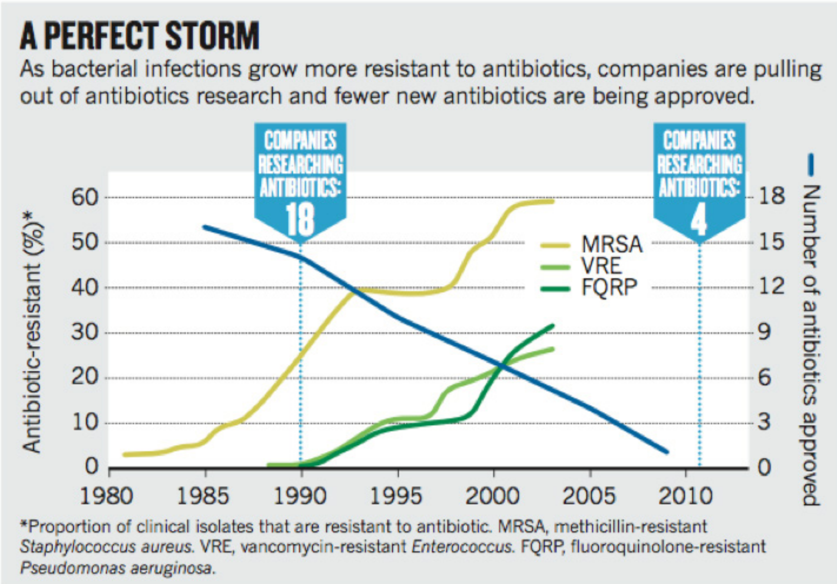


Figure 23: Relationship between antibiotic resistance, research and approval of new antibiotics between 1980 and 2010.

Source: Reproduced from Cooper and Shales (2011).

Data and statistics on the total impact of antibiotic-resistant infections worldwide are not comprehensive or reliable but are thought to be large. In places where health data exists like the European Union, estimates indicate substantial impacts: 25,000 deaths from antibiotic drug-resistant infections and EUR 1.5 billion in economic costs.

For antibiotic infections to remain treatable, the rate at which resistance develops and spreads must be slowed, and new drugs also need to be developed. However, conserving antibiotic resources presents huge challenges.

Antibiotics are easily available for human and animal use in almost all countries worldwide, with very few, if any, restrictions on their use in many regions. While this may benefit a particular individual at any one time, the collective contribution this makes towards increasing antibiotic resistance is ultimately harmful to everyone.

Out of this situation has come the concept of antibiotic stewardship that is now widely supported, summarised by Prescott (2014) as follows:

> *"The concept is evolving but basically describes the multifaceted approach required to optimize the use of antibiotics while minimizing the development of resistance and of other adverse effects. The term stewardship resonates with the acceptance of responsibility for the long-term management of something of enormous value".*

Priorities for antibiotic stewardship include:

- Avoidance of any unnecessary uses of antibiotics and so the development of resistance;
- Selection of the most effective drug(s), doses, and treatment duration for a given situation;
- Ensuring that recommended treatments are carried out accurately and fully;
- Containing and mitigating the spread of any antibiotic resistance that does arise.

11.3.4 How is antibiotic resistance a form of environmental pollution?

Antibiotic resistance may arise in humans or animals following treatment and may be driven to evolve in bacteria living in the wider environment by the release of antibiotic drugs that are left-over in human or animal effluent, or via the environmental release of antibiotic drugs from industrial processes.

Once this has taken place, there are many pathways – direct and indirect – by which antibiotic resistance can be transmitted, with its spread potentially accelerated by modern transport networks, wildlife movements, agricultural practices, and flows of water (Section 11.1.2; Figure 24).

It follows that the emergence of antibiotic resistance in one place, can at lease potentially, lead to antibiotic resistant bacteria or the genes carrying resistance being spread to anywhere else.

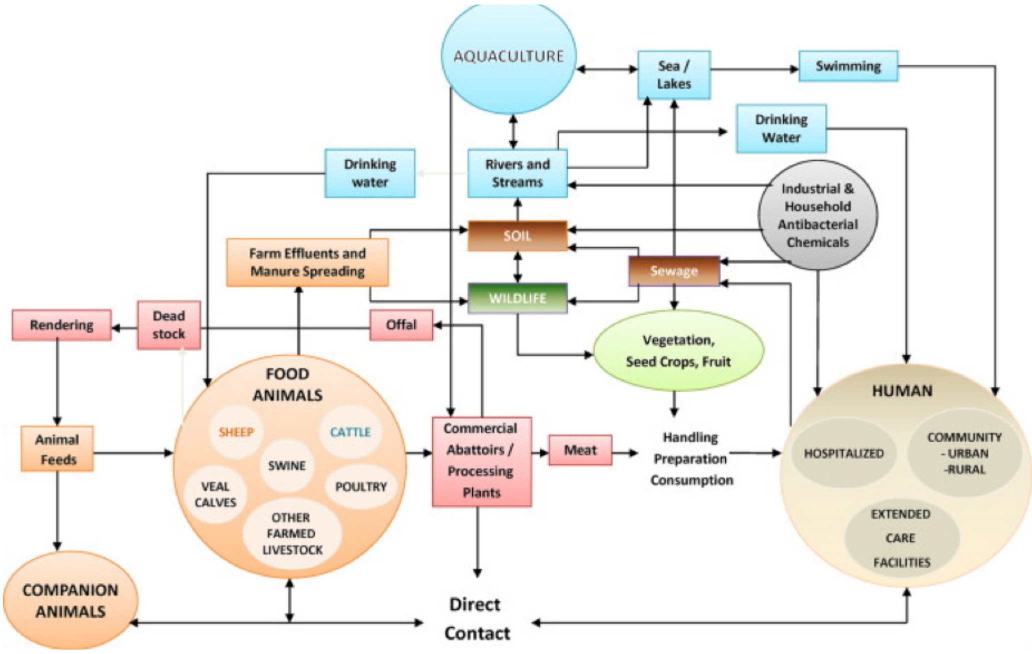


Figure 24: Diagrammatic representation of movement of resistance genes in bacteria through different routes.

Source: Reproduced from Prescott (2014).

Bacteria's ability to share resistance genes between one another, has particularly important implications. In hospitals, for example, because multiple patients, diseases, and drugs coexist within a confined area, the sharing of resistance genes between different strains of pathogenic bacteria can result in 'superbugs' that are multi-drug resistant and so untreatable.

Pathogenic bacteria may also acquire resistance through their encounters with more benign bacteria commonly found living in or on human or animal bodies, or from bacteria encountered in the wider environment (Figure 25).

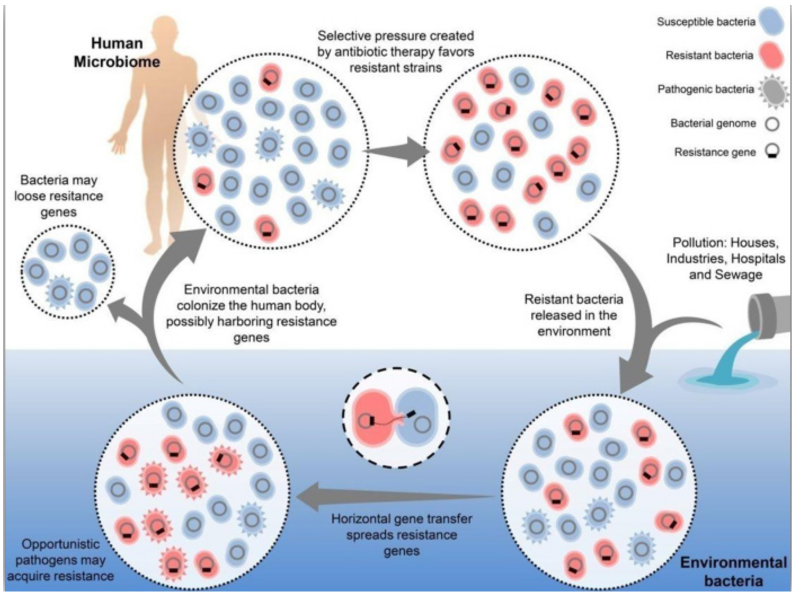


Figure 25: Schematic representation of the interactions between pollution, resistant bacteria and aquatic environments.

Source: Reproduced from Hernandes Coutinho, *et al*. (2013).

Antibiotic resistance in environmental bacteria is driven by the release of antibiotic resistant bacteria and large volumes of antibiotics (at low doses) into the natural environment, via human and animal waste streams.

As the overall reservoir of resistance genes in the natural environment accumulates – a concept known as the environmental resistome – so too does the overall risk of antibiotic resistance being transferred to human pathogenic bacteria.

11.4 How does livestock production affect risks from antibiotic resistance?

11.4.1 How are antibiotics used in livestock production?

As is the case with humans, antibiotics are often over-used or misused in the livestock sector. However, a key distinction when it comes to livestock production, is that antibiotics are deliberately given to healthy animals, and so are used for non-medical purposes (Figure 26).

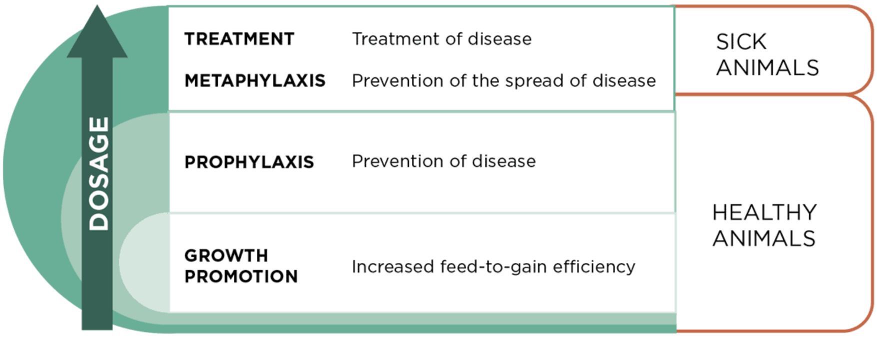


Figure 26: Uses of antibiotics in livestock.

Source: Redrawn from O'Neil (2016).

Treatment of disease

Veterinary use of antibiotics to treat disease after it has arisen, and in order to maintain animal welfare, is a necessary part of all forms of livestock production (including aquaculture) and provides tremendous benefits.

Following diagnosis, treatment involves high doses of antibiotics over short periods of time, given to individual animals so as to completely kill off bacterial pathogens.

Prevention of disease spreading (metaphylactic use)

Where one animal in a herd / flock is found to have a bacterial infection, antibiotics are commonly administered to all animals to stop its spread. This is known as metaphylactic use of antibiotics. High doses are given for relatively short periods in order to completely kill off bacterial pathogens in the entire herd / flock.

Growth promotion

A widespread practice in intensive livestock production is to provide healthy animals with constant low doses of antibiotics as a means to raise the conversion efficiency of animal feed into animal growth, and so increase overall profitability.

How antibiotics act to increase growth is not well understood but may result from reduced low-level infections. This hypothesis is supported by observations of little additional benefits from their use in terms of growth enhancements, where production has been optimised in other respects such as for hygiene, nutrition, and biosecurity.

Preventative use (prophylactic use)

Continuous provision of antibiotics to healthy animals at doses below those used to treat disease is another common practice in intensive livestock production, that is used to prevent infection. As with growth promoters, they are delivered continuously via the animals' feed and water.

Trade-offs: production intensity, antibiotic use, and producer costs

A key cost for livestock producers is managing disease. This is particularly problematic for more intensive production methods (including aquaculture), which tend to increase animals' susceptibility to infection (Section 11.2.5).

To reduce productivity losses from bacterial infections there are three major options:

1. Use antibiotics to prevent infections (growth promotion / prophylactic use);
2. Prevent infections through better hygiene, biosecurity, and animal welfare;
3. Use antibiotics to treat infections that arise (treatment / metaphylactic).

Non-therapeutic (i.e. growth promotion) and sub-therapeutic (i.e. preventative) uses of antibiotics are not always necessary, even for more intensive models of production. This is demonstrated by the example of some European Union countries where their use for growth promotion has been phased out for over a decade (30 years in Sweden), and where antibiotic use is less than half the global average per kg of animal.

Denmark, for example, cut antibiotic use in both swine and poultry (per animal), while increasing overall levels of pork production, and with only minimal changes to the cost of producing a pig (~1%) (Figure 27).

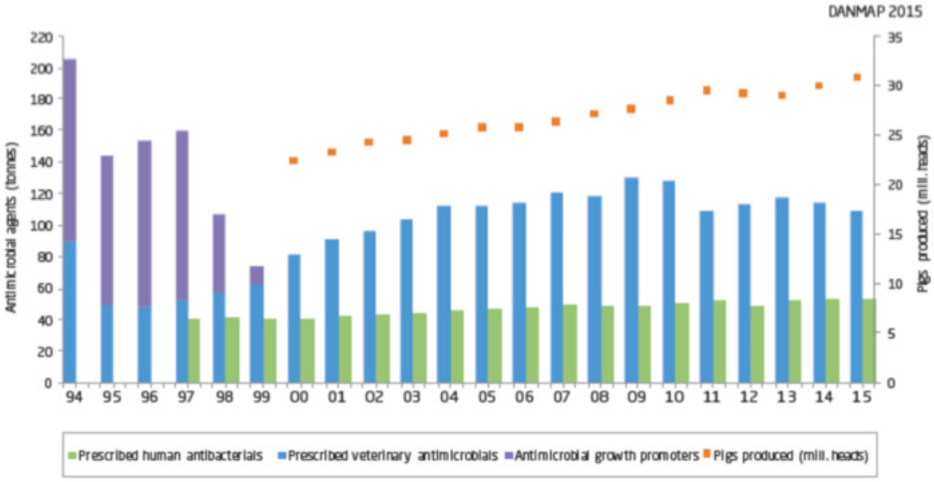


Figure 27: Antibiotic consumption and millions of pigs produced in Denmark, 1994-2015. Notably as antibiotic use for growth promotion decreased other uses increased, but still dropped overall.

Source: Reproduced from Price, *et al*. (2017).

However, organic pork production in Denmark still uses ten times fewer antibiotics – illustrating the role that production systems as a whole play in controlling the burden of disease in livestock and the corresponding level of antibiotics needed.

Yet even in leading EU countries, managing disease in intensive production systems while also reducing antibiotics has encountered difficulties, resulting in greater antibiotic use for prophylactic, metaphylactic and treatment purposes, until farming and regulatory systems adapt sufficiently (Figure 28).

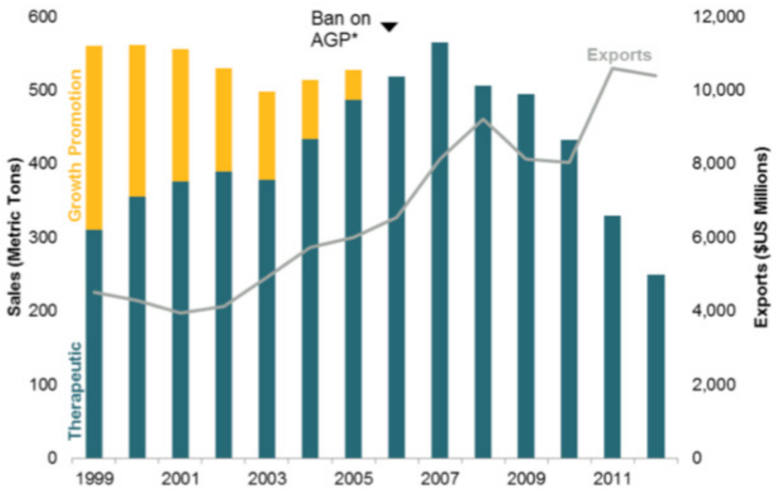


Figure 28: Sales in active ingredients of Antimicrobials for food producing animals and exports of meat productions in The Netherlands.

Source: Reproduced from Elliot (2015).

Replicating, elsewhere, the approach taken by leading EU countries presents serious challenges. The investments, technology, monitoring systems, and improvements to farm management needed to raise levels of hygiene, biosecurity, and animal welfare are not necessarily cheap or easy – especially for smaller scale producers.

For this reason – and in the absence of legislation and government support – many food producers worldwide choose the cheapest and easiest means at hand to manage the risk to their businesses from bacterial infection: antibiotics.

An additional related problem, is that without as sufficient incentive to reduce antibiotic use, there is also little commercial incentive to produce effective alternatives to antibiotics (e.g. vaccines), thus perpetuating reliance upon antibiotics as a means of disease control.

11.4.2 What is the extent of antibiotic use in livestock production?

Comprehensive data on the use of antibiotics in livestock are very limited. Even in high-income countries, monitoring of antibiotic use in agriculture has been weak – often consisting of only national level sales data for antibiotics and not differentiated by species or production system.

Nevertheless, the use of antibiotics in livestock production is known to be common worldwide – especially in regions where intensive livestock production is more prevalent (Figure 29).

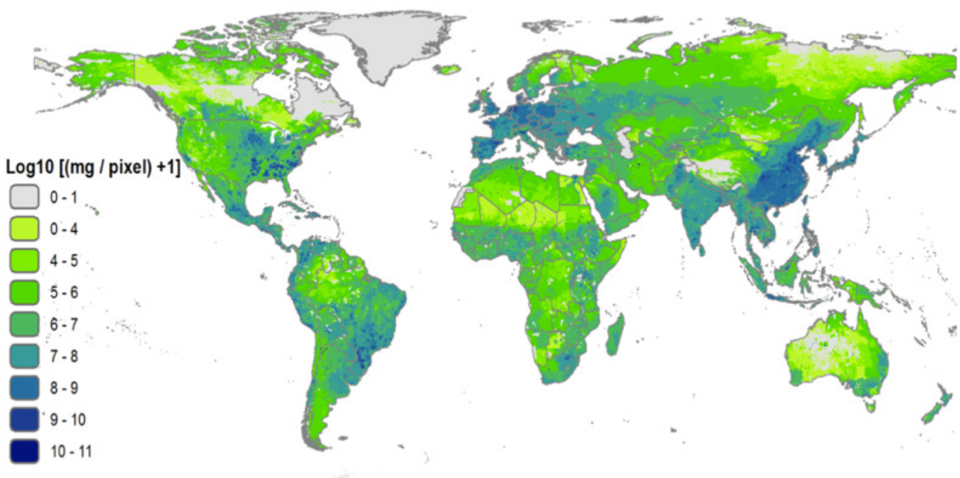


Figure 29: Global antimicrobial use in food animals.

Source: Reproduced from Van Boeckel *et al*. (2015).

Modelling studies suggest that global consumption of antibiotics by the livestock sector accounts for at least two-thirds of all antibiotics produced worldwide, and in locations where data exists, such as Europe and the United States, their total use in animals tends to exceed that found in humans (when measured by weight).

Among livestock, most antibiotics are used in intensively farmed species such as pig and poultry production, and less so in extensively farmed species such as cattle and sheep.

As much as 30 to 90% of antibiotics consumed by animals are released in urine and manure, and so may come to pollute the environment through their spreading on land and release into waterways.

Data on antibiotic use in aquaculture is even poorer. Specific studies show that their use in aquaculture systems as compared to other livestock systems, ranges from very high to very low, although the overall amount is unclear. Antibiotics are also frequently given to companion animals (i.e. pets).

Trends indicate that global use of antibiotics in the livestock sector is projected to grow by 67% in 2030 mostly taking place in low income countries (Figure 30). Most of this is because of the growth in overall animal numbers (Section 11.2.2), in turn, driven by increasing demand for animal-source foods. About a third attributable to the shift towards more intensive production systems.

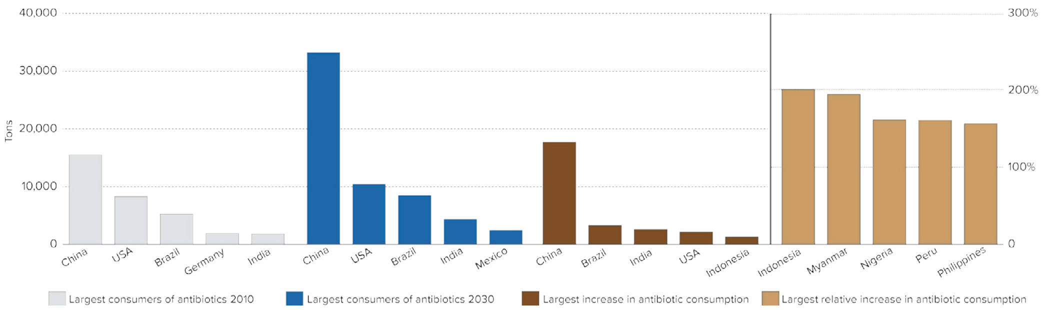


Figure 30: Estimated antibiotic consumption in high-consuming countries 2010 and 2030 projections.

Source: Reproduced from Van Boeckel *et al.* (2015).

11.4.3 How can antibiotic use in livestock production affect human health?

Reservoirs of resistance

Once resistance has emerged, livestock farms become reservoirs of antibiotic resistant bacteria and resistance genes, which can potentially spread to the wider environment and to humans.

The pathways by which this may occur (Section 11.1.2; Figure 31) can be divided into three major routes:

1. Direct contact with animals and their waste, colonised by antibiotic resistant bacteria;
2. Foodborne contact via handling and consumption of infected animal products;
3. Environmental contact with antibiotic resistant bacteria.

GO TO CONTENTS

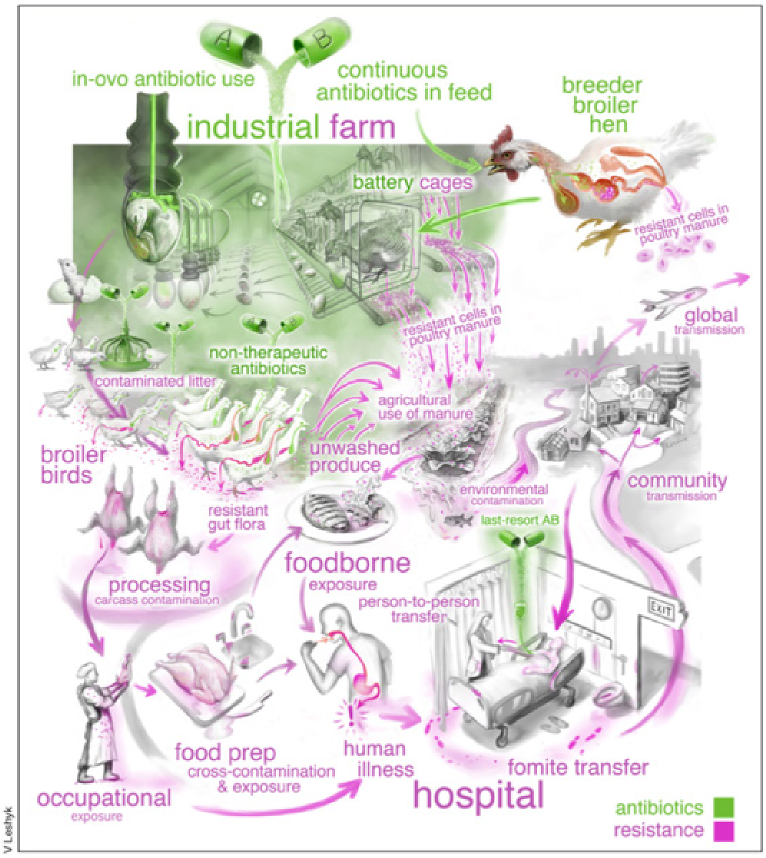


Figure 31: Multiple pathways link antibiotic use (green) and antibiotic resistance (pink) in the food-animal and human health sectors.

Source: Reproduced from Koch *et al.* (2017). Image created by the artist Victor O. Leshyk.

Volumes of antibiotics used

The emergence of antibiotic resistance is correlated with their total use: with each person or animal treated with antibiotics, the risk for emergence, enrichment and spread of antibiotic resistance goes up (Section 11.3.2).

As a consequenc of this, the very large volumes of antibiotics used in the livestock sector worldwide, constitute a major driver of antibiotic resistance – and so also a potential risk to public health.

The majority of antibiotic use in livestock production is probably used for intensive production. However, evidence suggests that small scale livestock production can also transmit resistance to humans.

Dosage and duration of use

How antibiotics are administered also makes a big difference.

The continuous use of antibiotics in low doses– as widely practiced in intensive production systems for preventative or growth promoting purposes – creates a long-term evolutionary pressure that selectively favours bacterial cells with resistance traits, while not killing them outright.

This method of use also increases the total stretch of time over which resistance could evolve, allowing for a step-by-step path to greater levels of resistance.

GO TO CONTENTS

Types of antibiotic used

Many antibiotics administered to animals are also those that are used to treat humans and are often are classified as ‘critically important’ to human medicine (Figure 32).

Antibiotics of last resort – meaning they are the only drugs able to treat some infections – have also been routinely included in animal feed as growth promotors in some places. Older antibiotics or those not used in humans can still have a detrimental effect, because resistance developed to these drugs can still help bacteria to resist the effects of more newly developed drugs used to treat humans.

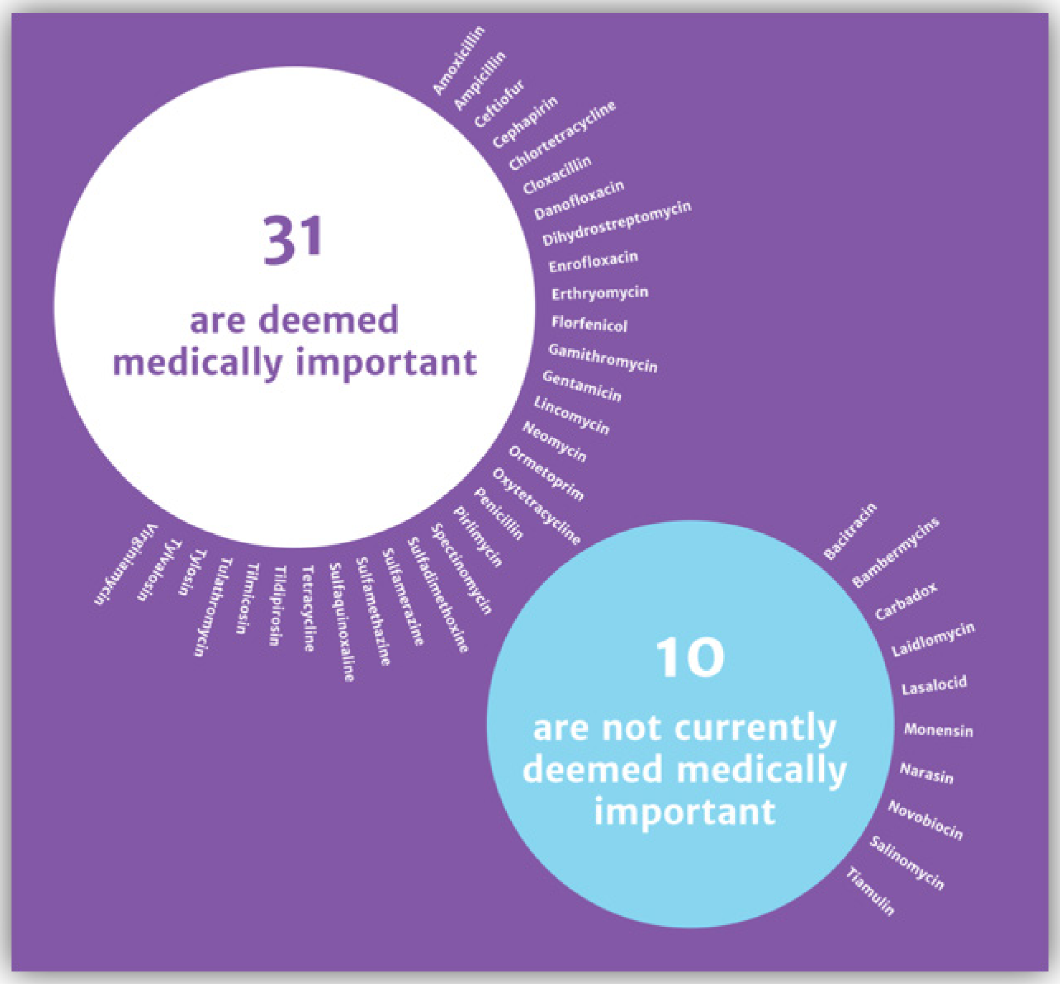


Figure 32: Of the 41 antibiotics that are approved for use in food producing animals by the FDA, 31 are characterised as being medically important for human use.

Source: Reproduced from O’Neil (2016).

Animal health

Beyond humans, the use of antibiotics is also critical for veterinary medicine. The development of resistance in livestock production threatens not only human health but also the health and welfare of animals, and the people that depend on them.

11.4.4 What evidence exists for antibiotic resistance being transmitted from livestock to humans?

The potential pathways linking antibiotic use and resistance in the livestock sector to antibiotic-resistant pathogens in humans, are well understood. But proving each step in the chain of infection can be very difficult to achieve (Figure 33).

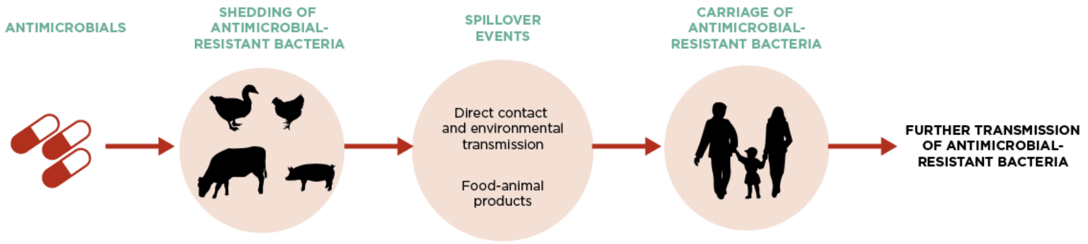


Figure 33: Conceptual illustration of AMR spill over from food animals to humans.

Source: Redrawn from Graham *et al.* (2017).

Antibiotic resistance genes that are observed in human bacterial infections, may previously have been passed between several different species of bacteria, and may have been altered during this journey – making it extremely challenging to trace their original source.

Nevertheless, although the size of the risk is hard to quantify, growing direct and indirect evidence shows a link between antibiotic use in animals and antibiotic resistance found in humans.

A comprehensive review has found that reduced antibiotic use in livestock is linked to reduced presence of antibiotic resistant bacteria in livestock, and some evidence suggesting reduced rates in human populations – particularly those with direct exposure to livestock.

On this basis, the World Health Organisation has recommended an overall reduction in use of all classes of medically important antimicrobials in food-producing animals, and their complete restriction in food-producing animals for purposed of growth promotion and diseases prevention, and before a diagnosis has been made.

As early as the 1990's evidence for the presence of a risk was deemed sufficient for some countries to ban the use of antibiotics for growth promotion, with a total European Union ban taking place in 2006. The underpinning research for the legislation showed that:

- Low-dose, nontherapeutic use of antibiotics selects for resistance to those antibiotics;
- Resistance genes disseminate via the food chain into the intestinal flora of humans.

Many studies show correlations between antibiotics use in livestock production and levels of resistant bacteria observed in food and in humans. Figure 34, for example, shows the rapid decline in levels of antibiotic resistant bacteria found in retail chicken and in humans, following the withdrawal of an antibiotic drug from chicken production.

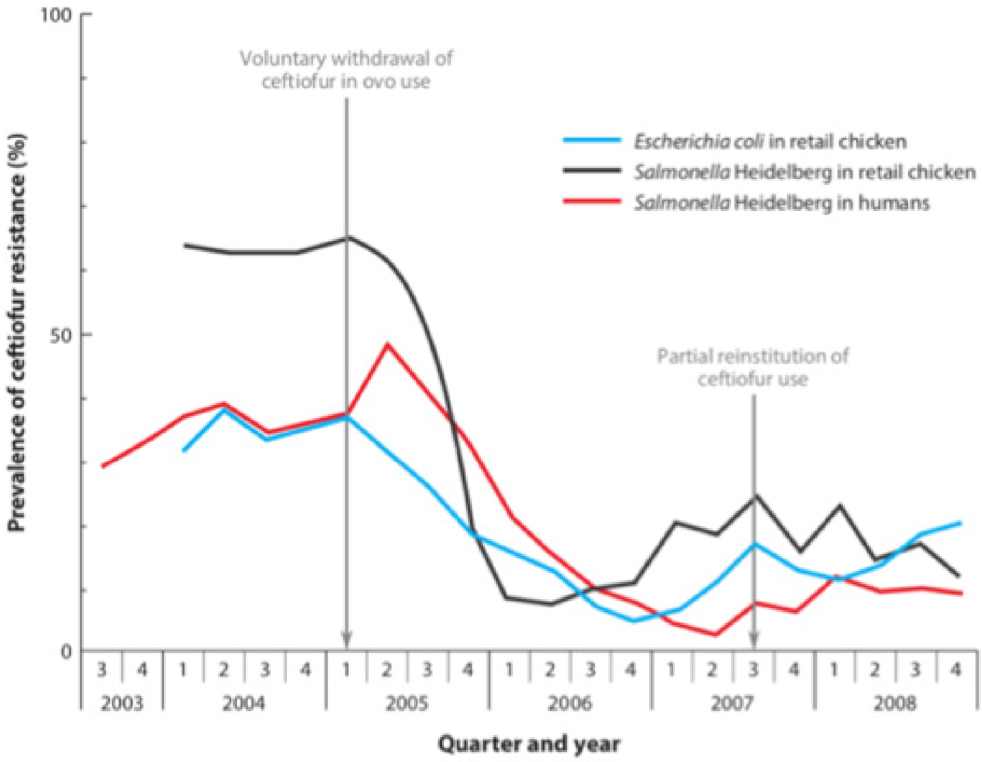


Figure 34: Prevalence of ceftiofur resistance (moving average of the current quarter and the previous 2 quarters) among retail chicken Escherichia coli, and retail chicken and human clinical Salmonella enterica serovar Heidelberg isolates during 2003–2008 in Québec, Canada.

Source: Reproduced from Dutil *et al.* (2010).

In addition to the foodborne pathway, transmission of resistance via direct exposure to animals and their immediate environments (e.g. farms), has been extensively documented among those in occupations such as farm workers, veterinarians, and butchers – and in their families and local communities.

The disposal of manure or effluent, farm waste, and the release of particulate matter in the air, can pollute the wider environment by dispersing antibiotics, antibiotic resistant bacteria, and so also resistance genes – albeit at much diluted levels (Figure 35).

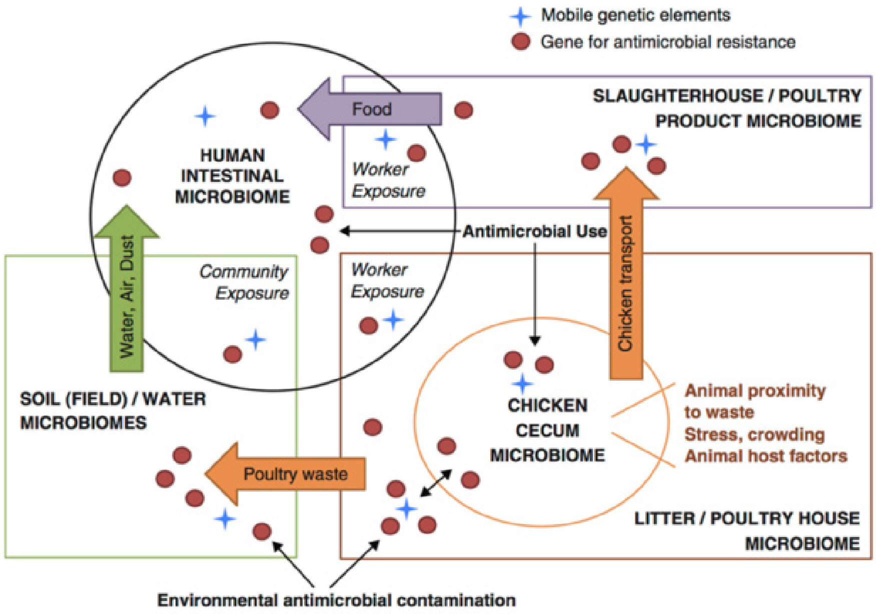


Figure 35: Conceptual framework for understanding the flow of resistance genes across microbiomes within food animals, the environment, and human populations.

Source: Reproduced from Davis *et al.* (2011).

While a link between antibiotic use in agriculture and the spread of antibiotic resistance to soils and waterways has been demonstrated, antibiotic resistant infections in humans arising via this pathway have not been proven. Given the complexities in tracing such a route, the risk it presents may in practice be unknowable, which is not to say that there is no risk.

11.4.5 What can be concluded about the health risks from antibiotic use in the livestock sector?

Antibiotics are widely used in the livestock sector with a corresponding rise in antibiotic resistance found in livestock populations. The available evidence is also compelling for the transmission of antibiotic resistance from livestock to humans taking place via foodborne and occupational exposure to resistant bacteria.

However, antibiotic resistant bacteria transmitted to humans from livestock are not necessarily specialist human pathogens, and the transfer of resistance genes to human pathogens, while possible, isn't entirely straightforward. Evidence for sustained onward transmission between humans of pathogenic bacteria that have acquired their resistance from bacteria previously infecting livestock is limited.

Very little data exists with which to estimate the overall proportion of antibiotic resistant infections in humans that are attributable to livestock, and to some extent it may be unknowable. This lack of understanding means that it is not currently feasible to accurately quantify the benefits to human health from reduced use of antibiotics in animals.

GO TO CONTENTS

This is problematic in terms of managing risks to human health and weighing up appropriate responses. In particular, because reducing antibiotic use in agriculture has proved difficult to date, and will inevitably have repercussions for animal health, welfare, and productivity, in the absence of major changes to the organisation of livestock production systems. Such changes would, in turn, have significant implications for farmers, food prices and ultimately consumers.

As a point of comparison, human use and misuse of antibiotics – although lower overall in terms of total volume – is thought to pose an overall greater risk to human health, by driving the emergence of resistance in bacteria already well adapted to human hosts, and in contexts where they can more easily be spread between humans (i.e. hospitals) (Figure 36).

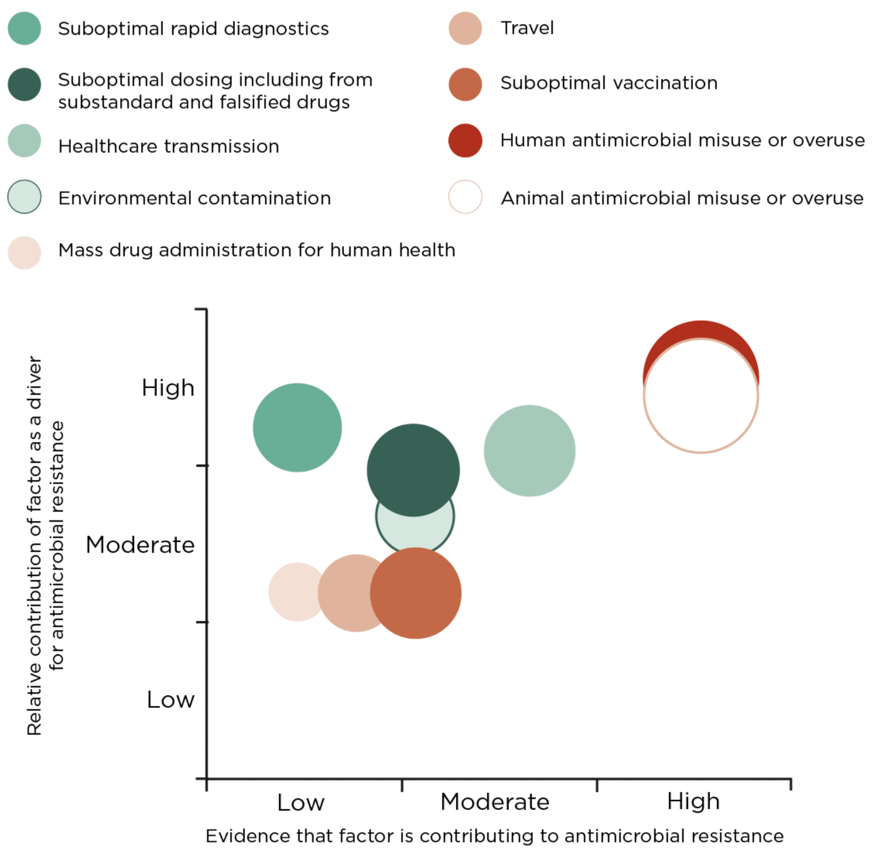


Figure 36: The role of modifiable drivers of antimicrobial resistance: a conceptual framework. Subjective assessment of relative contributions by authors of review.

Source: Redrawn from Holmes *et al.* (2015).

But lower probability events with high impacts – such as the emergence of resistance in human specialised pathogens originating from bacteria linked to livestock – can still pose signification health risks. Especially when considering the huge scale of animals and antibiotics involved in livestock production, and the demonstrable transmission pathways that exist.

GO TO CONTENTS

Moreover, antibiotic use in the livestock sector is expected to grow, especially in poorly regulated regions, increasing the risk of the emergence and transmission of resistance further.

For many, delaying action due to uncertainty about the precise level of risk, is seen as an unnecessary gamble on public health, considering the potentially irreversible impacts. And for this reason, many governments, institutions and food businesses have committed to taking precautionary action by reducing unnecessary uses of antibiotics in agriculture, and the food system more generally – as well as in human healthcare.

For example:

- UN declaration on antimicrobial resistance;
- WHO global action plan on antibiotics.

11.5 Conclusions

- Animals (wild and domesticated) are a major source of human disease.
- Diseases shared with animals have large potential (and current) health impacts.
- Trends in livestock production and consumption affect the risk of disease transferring from animals to humans.
- The vast majority of sickness is caused by endemic zoonotic diseases which predominantly affect poor people (especially poor livestock keepers) in low-income countries. However, animals' role in new pandemic diseases receives more attention, in part, because they pose a risk to more affluent countries.
- Antibiotic resistance emerging in bacteria is the inevitable result of their use in order to kill bacteria.
- Growth in antibiotic resistance threatens the medical community's ability to treat common infections and safely conduct other medical procedures.
- Antibiotic drug discovery is too slow and costly. Antibiotic resources must be conserved to avoid untreatable infections. Appropriate incentives are also needed to increase the rate of antibiotic drug discovery and lower the costs of new drugs.
- Most clinical cases of antibiotic resistant infections in humans are thought to result from human use and misuse of antibiotics in hospitals and in the community.
- The majority of antibiotics worldwide are used in livestock production – mostly in intensive livestock production systems.
- While possible, it is not a simple biological step for antibiotic resistant bacteria to adapt and become human pathogens or to transfer of resistance genes to human pathogens that are able to spread between human hosts. This is why overuse in humans poses a higher risk to health.

Conclusions continued.

- Pathways for resistance transmission from livestock to humans are well understood, and good evidence exists for it taking place via food and occupational contact with livestock.
- Current data – which are very limited and uncertain - suggest that the overall share of antibiotic resistant human infections originating from a livestock source is small.
- Low probability events with high potential impacts can still present significant risks: such as the transfer of resistance to a highly infectious and harmful human bacterial pathogen.
- Many antibiotics used in livestock production are also those critical to human medicine, or drugs of last resort – increasing the likelihood of untreatable infections resulting from the transmission of resistance.
- The use of antibiotics in livestock production is expected to increase substantially, due to increases in livestock numbers and a shift towards more intensive production methods – with most increases taking place in low- and middle-income regions.
- Antibiotic use in livestock can be greatly reduced by investment in farm hygiene, infection control, animal welfare, and improved monitoring systems for antibiotic resistance. Regulation and government support has been essential to achieving this in EU countries.
- Many governments, businesses, and institutions are now advocating to eliminate unnecessary use of antibiotics in livestock, to preserve antibiotic efficacy for both human and animal medicine.

References

11.1

Bean, A. G., Baker, M. L., Stewart, C. R., Cowled, C., Deffrasnes, C., Wang, L. F., & Lowenthal, J. W. (2013). Studying immunity to zoonotic diseases in the natural host—keeping it real. *Nature Reviews Immunology*, 13(12), 851

Choffnes, E. R., Mack, A., Institute of Medicine (U.S.)., Institute of Medicine (U.S.)., & Emerging Viral Diseases: The One Health Connection (Workshop). (2015). Emerging viral diseases: The one health connection : workshop summary

Cleaveland, S., Laurenson, M. K., & Taylor, L. H. (2001). Diseases of humans and their domestic mammals: pathogen characteristics, host range and the risk of emergence. *Philosophical Transactions of the Royal Society B: Biological Sciences*, 356(1411), 991-999

Davos Gloval Risk Forum (2017). One Health - An Integrative Health Risk Management Perspective. Retrieved October 27, 2017,

Foley, J. A., Ramankutty, N., Brauman, K. A., Cassidy, E. S., Gerber, J. S., Johnston, M., ... & Balzer, C. (2011). Solutions for a cultivated planet. *Nature*, 478(7369), 337

Grace, D., Lindahl, J., Wanyoike, F., Bett, B., Randolph, T., & Rich, K. M. (2017). Poor livestock keepers: ecosystem–poverty–health interactions. *Phil. Trans. R. Soc. B*, 372(1725), 20160166

Grace, D., Mutua, F., Ochungo, P., Kruska, R., Jones, K., Brierley, L., ... & Thao, N. B. (2012). Mapping of poverty and likely zoonoses hotspots. Zoonoses Project 4. Report to the UK Department for International Development. International Livestock Research Institute, Nairobi, Kenya

Haagsma, J. A., Tariq, L., Heederik, D. J., & Havelaar, A. H. (2011). Infectious disease risks associated with occupational exposure: a systematic review of the literature. *Occup Environ Med*, oemed-2011

Jones, B. A., Grace, D., Kock, R., Alonso, S., Rushton, J., Said, M. Y., ... & Pfeiffer, D. U. (2013). Zoonosis emergence linked to agricultural intensification and environmental change. *Proceedings of the National Academy of Sciences*, 110(21), 8399-8404

Jones, K. K. E., Patel, N. G. N., Levy, M. A., Storeygard, A., Balk, D., Gittleman, J. L., & Daszak, P. (2008). Global trends in emerging infectious diseases. *Nature*, 451(7181), 990–3

Keesing, F., Belden, L. K., Daszak, P., Dobson, A., Harvell, C. D., Holt, R. D., ... & Myers, S. S. (2010). Impacts of biodiversity on the emergence and transmission of infectious diseases. *Nature*, 468(7324), 647

Klous, G., Huss, A., Heederik, D. J., & Coutinho, R. A. (2016). Human–livestock contacts and their relationship to transmission of zoonotic pathogens, a systematic review of literature. *One Health*, 2, 65-76

Lowenthal, J. W., Baker, M. L., Stewart, C. R., Cowled, C., Deffrasnes, C., & Wang a, L.-F. (2015). Studying zoonotic diseases in the natural host. In *Emerging viral diseases: the one health connection: workshop summary*. Washington, D.C.: National Academies Press. https://doi.org/10.17226/18975

Mableson, H. E., Okello, A., Picozzi, K., & Welburn, S. C. (2014). Neglected zoonotic diseases—the long and winding road to advocacy. *PLoS neglected tropical diseases,* 8(6), e2800

Maudlin, I., Eisler, M. C., & Welburn, S. C. (2009). Neglected and endemic zoonoses. *Philosophical Transactions of the Royal Society B: Biological Sciences*, 364(1530), 2777-2787

McDermott, J., Grace, D., & Zinsstag, J. (2013). Economics of brucellosis impact and control in low-income countries. *Rev Sci Tech,* 32(1), 249-61

Murray, K. A., Allen, T., Loh, E., Machalaba, C., & Daszak, P. (2016). Emerging viral zoonoses from wildlife associated with animal-based food systems: risks and opportunities. In *Food Safety Risks from Wildlife* (pp. 31-57). Springer, Cham

Plowright, R. K., Parrish, C. R., McCallum, H., Hudson, P. J., Ko, A. I., Graham, A. L., & Lloyd-Smith, J. O. (2017). Pathways to zoonotic spillover. *Nature Reviews Microbiology,* 15(8), 502

Reperant, L. A., Cornaglia, G., & Osterhaus, A. D. (2012). The importance of understanding the human–animal interface. In *One Health: The Human-Animal-Environment Interfaces in Emerging Infectious Diseases* (pp. 49-81). Springer, Berlin, Heidelberg

Smith, J. W., Le, G. F., & World Bank. (2012). *People, pathogens, and our planet: Volume 2*. Washington, DC: World Bank

Taylor, L. H., Latham, S. M., & Mark, E. J. (2001). Risk factors for human disease emergence. *Philosophical Transactions of the Royal Society B: Biological Sciences,* 356(1411), 983-989

Thornton, J. (2017). *Where humans and animals collide: Emerging infections and newfound resistance*. Retrieved October 27, 2017, from LINK

United States Government Accountability Office. (2011). *Report to Congressional Requesters. BIOSURVEILLANCE. Nonfederal Capabilities Should Be Considered in Creating a National Biosurveillance Strategy*. Washington, [D.C.]

Webster, J. P., Gower, C. M., Knowles, S. C., Molyneux, D. H., & Fenton, A. (2016). One health–an ecological and evolutionary framework for tackling Neglected Zoonotic Diseases. *Evolutionary Applications*, 9(2), 313-333

Wolfe, N. D., Dunavan, C. P., & Diamond, J. (2007). Origins of major human infectious diseases. *Nature*, 447(7142), 279

Woolhouse, M., Scott, F., Hudson, Z., Howey, R., & Chase-Topping, M. (2012). Human viruses: discovery and emergence. *Phil. Trans. R. Soc. B*, 367(1604), 2864-2871

Woolhouse, M. E., & Gowtage-Sequeria, S. (2005). Host range and emerging and reemerging pathogens. *Emerging Infectious Diseases*, 11(12), 1842

World Bank. (2010). People, pathogens and our planet, Volume 1: Towards a One Health approach for controlling zoonotic diseases

11.2

Foley, J. A., Ramankutty, N., Brauman, K. A., Cassidy, E. S., Gerber, J. S., Johnston, M., ... & Balzer, C. (2011). Solutions for a cultivated planet. *Nature*, 478(7369), 337

Food and Agriculture Organisation of the United Nations. (2017). FAOSTAT. Retrieved October 27, 2017.

Fèvre, E. M., Bronsvoort, B. M. D. C., Hamilton, K. A., & Cleaveland, S. (2006). Animal movements and the spread of infectious diseases. *Trends in Microbiology,* 14(3), 125-131

Graham, J. P., Leibler, J. H., Price, L. B., Otte, J. M., Pfeiffer, D. U., Tiensin, T., & Silbergeld, E. K. (2008). The animal-human interface and infectious disease in industrial food animal production: rethinking biosecurity and biocontainment. *Public Health Reports*, 123(3), 282-299

Gummow, B. (2010). Challenges posed by new and re-emerging infectious diseases in livestock production, wildlife and humans. *Livestock Science*, 130(1), 41-46

Jones, B. A., Grace, D., Kock, R., Alonso, S., Rushton, J., Said, M. Y., ... & Pfeiffer, D. U. (2013). Zoonosis emergence linked to agricultural intensification and environmental change. *Proceedings of the National Academy of Sciences*, 110(21), 8399-8404

Karesh, W. B., & Noble, E. (2009). The bushmeat trade: increased opportunities for transmission of zoonotic disease. *Mount Sinai Journal of Medicine: A Journal of Translational and Personalized Medicine*, 76(5), 429-434

Karesh, W. B., Dobson, A., Lloyd-Smith, J. O., Lubroth, J., Dixon, M. A., Bennett, M., ... & Machalaba, C. C. (2012). Ecology of zoonoses: natural and unnatural histories. *The Lancet*, 380(9857), 1936-1945

Kimball, Ann Marie. (2017). *Risky Trade: Infectious Disease in the Era of Global Trade.* Routledge

Klein Goldewijk, K., Beusen, A., Van Drecht, G., & De Vos, M. (2011). The HYDE 3.1 spatially explicit database of human-induced global land-use change over the past 12,000 years. *Global Ecology and Biogeography*, 20(1), 73-86

Layton, D. S., Choudhary, A., & Bean, A. G. (2017). Breaking the chain of zoonoses through biosecurity in livestock. *Vaccine*, 35(44), 5967-5973

Liverani, M., Waage, J., Barnett, T., Pfeiffer, D. U., Rushton, J., Rudge, J. W., ... & White, L. J. (2013). Understanding and managing zoonotic risk in the new livestock industries. *Environmental Health Perspectives*, 121(8), 873

Perry, B. D., Grace, D., & Sones, K. (2013). Current drivers and future directions of global livestock disease dynamics. *Proceedings of the National Academy of Sciences*, 110(52), 20871-20877

Reperant, L. A., Cornaglia, G., & Osterhaus, A. D. (2012). The importance of understanding the human–animal interface. In *One Health: The Human-Animal-Environment Interfaces in Emerging Infectious Diseases* (pp. 49-81). Springer, Berlin, Heidelberg

Rivera–Ferre, M. G., López–i–Gelats, F., Howden, M., Smith, P., Morton, J. F., & Herrero, M. (2016). Re–framing the climate change debate in the livestock sector: mitigation and adaptation options. *Wiley Interdisciplinary Reviews: Climate Change*, 7(6), 869-892

Smith, J., Sones, K., Grace, D., MacMillan, S., Tarawali, S., & Herrero, M. (2013). Beyond milk, meat, and eggs: Role of livestock in food and nutrition security. *Animal Frontiers,* 3(1), 6-13

11.3

Compound Interest. (2014). *Different classes of antibiotics - an overview* [Figure]. Retrieved February 23, 2018

Cooper, M. A., & Shlaes, D. (2011). Fix the antibiotics pipeline. *Nature*, 472(7341), 32

Coutinho, F. H., Pinto, L. H., Vieira, R. P., Martins, O. B., Salloto, G. R. B., de Oliveira Santoro, D., ... & Cardoso, A. M. (2013). Antibiotic resistance in aquatic environments of Rio de Janeiro, Brazil. In *Perspectives in Water Pollution*. InTech

Doron, S., & Davidson, L. E. (2011, November). Antimicrobial stewardship. In *Mayo Clinic Proceedings* (Vol. 86, No. 11, pp. 1113-1123). Elsevier

ECDC, & EMEA. (2009). *Technical Report: The bacterial challenge: time to react.* Stockholm. Retrieved February 23, 2018

Jørgensen, P. S., Wernli, D., Folke, C., & Carroll, S. P. (2017). Changing antibiotic resistance: sustainability transformation to a pro-microbial planet. *Current Opinion in Environmental Sustainability*, 25, 66-76

Laxminarayan, R., Duse, A., Wattal, C., Zaidi, A. K., Wertheim, H. F., Sumpradit, N., ... & Greko, C. (2013). Antibiotic resistance—the need for global solutions. *The Lancet Infectious Diseases*, 13(12), 1057-1098

Levy, S. B., & Marshall, B. (2004). Antibacterial resistance worldwide: causes, challenges and responses. *Nature Medicine*, 10(12s), S122

Michigan State University. (2011). *Aquired resistance* [Figure]. Retrieved February 23, 2018

Normark, B. H., & Normark, S. (2002). Evolution and spread of antibiotic resistance. *Journal of Internal Medicine*, 252(2), 91-106

O'Neill, J. (2016). *The review on antimicrobial resistance. Tackling drug-resistant infections globally: final report and recommendations*

Prescott, J. F. (2014). The resistance tsunami, antimicrobial stewardship, and the golden age of microbiology. *Veterinary Microbiology*, 171(3-4), 273-278

Singer, A. C., Shaw, H., Rhodes, V., & Hart, A. (2016). Review of antimicrobial resistance in the environment and its relevance to environmental regulators. *Frontiers in Microbiology*, 7, 1728

Staley, J. T. (1997). Biodiversity: are microbial species threatened?. *Current Opinion in Biotechnology*, 8(3), 340-345

Teillant, A., Gandra, S., Barter, D., Morgan, D. J., & Laxminarayan, R. (2015). Potential burden of antibiotic resistance on surgery and cancer chemotherapy antibiotic prophylaxis in the USA: a literature review and modelling study. *The Lancet Infectious Diseases*, 15(12), 1429-1437

Woolhouse, M., Waugh, C., Perry, M. R., & Nair, H. (2016). Global disease burden due to antibiotic resistance–state of the evidence. *Journal of Global Health*, 6(1)

Wright, G. D. (2010). Antibiotic resistance in the environment: a link to the clinic?. *Current Opinion in Microbiology*, 13(5), 589-594

You, Y., & Silbergeld, E. K. (2014). Learning from agriculture: understanding low-dose antimicrobials as drivers of resistome expansion. *Frontiers in Microbiology*, 5, 284

11.4

Andersson, D. I., & Hughes, D. (2014). Microbiological effects of sublethal levels of antibiotics. *Nature Reviews Microbiology*, 12(7), 465

Cabello, F. C. (2006). Heavy use of prophylactic antibiotics in aquaculture: a growing problem for human and animal health and for the environment. *Environmental Microbiology,* 8(7), 1137-1144

Center for Disease Dynamics Economics & Policy. (2015). The State of the world's antibiotics 2015. Centre for Disease Dynamics, Economics & Policy, CDDEP: Washington, D.C, 1-84. https://doi.org/10.1016/S1473-3099(13)70318-9

Chang, Q., Wang, W., Regev‐Yochay, G., Lipsitch, M., & Hanage, W. P. (2015). Antibiotics in agriculture and the risk to human health: how worried should we be?. *Evolutionary Applications*, 8(3), 240–247

Cogliani, C., Goossens, H., & Greko, C. (2011). Restricting antimicrobial use in food animals: lessons from Europe. *Microbe*, 6(6), 274

Davis, M. F., Price, L. B., Liu, C. M. H., & Silbergeld, E. K. (2011). An ecological perspective on US industrial poultry production: the role of anthropogenic ecosystems on the emergence of drug-resistant bacteria from agricultural environments. *Current Opinion in Microbiology*, 14(3), 244-250

Defoirdt, T., Sorgeloos, P., & Bossier, P. (2011). Alternatives to antibiotics for the control of bacterial disease in aquaculture. *Current Opinion in Microbiology*, 14(3), 251-258

Dutil, L., Irwin, R., Finley, R., Ng, L. K., Avery, B., Boerlin, P., ... & Demczuk, W. (2010). Ceftiofur resistance in *Salmonella enterica* serovar Heidelberg from chicken meat and humans, Canada. *Emerging Infectious Diseases*, 16(1), 48

Elliott, K. (2015). *Antibiotics on the Farm: Agriculture's Role in Drug Resistance.* Washington, D.C. Retrieved February 24, 2018, from LINK

FAO, OIE, & WHO. (2006). *Antimicrobial use in aquaculture and antimicrobial resistance*. Retrieved February 24, 2018, from LINK

Graham, J. P., Eisenberg, J. N., Trueba, G., Zhang, L., & Johnson, T. J. (2017). Small-Scale Food Animal Production and Antimicrobial Resistance: Mountain, Molehill, or Something in-between?. *Environmental Health Perspectives*, 104501, 1

Guardabassi, L., Schwarz, S., & Lloyd, D. H. (2004). Pet animals as reservoirs of antimicrobial-resistant bacteria. *Journal of Antimicrobial Chemotherapy*, 54(2), 321-332

Holmes, A. H., Moore, L. S., Sundsfjord, A., Steinbakk, M., Regmi, S., Karkey, A., ... & Piddock, L. J. (2016). Understanding the mechanisms and drivers of antimicrobial resistance. *The Lancet*, 387(10014), 176-187

Khardori, N. (2016). *Food microbiology: In human health and disease*

Koch, B. J., Hungate, B. A., & Price, L. B. (2017). Food‐animal production and the spread of antibiotic resistance: the role of ecology. *Frontiers in Ecology and the Environment*

Levy, S. B., & Marshall, B. (2004). Antibacterial resistance worldwide: causes, challenges and responses. *Nature Medicine,* 10(12s), S122

Lloyd, D. H. (2007). Reservoirs of antimicrobial resistance in pet animals. *Clinical Infectious Diseases*, 45 (Supplement_2), S148-S152

O'Neill, J. (2015). Antimicrobials in Agriculture and the Environment: Reducing Unnecessary Use and Waste. *The Review on Antimicrobial Resistance*

O'Neill, J. (2016). Tackling drug-resistant infections globally: final report and recommendations the review on antimicrobial resistance. *The Review on Antimicrobial Resistance*. HM Government and Wellcome Trust. https://doi.org/10.1016/j.jpha.2015.11.005

Österberg, J., Wingstrand, A., Jensen, A. N., Kerouanton, A., Cibin, V., Barco, L., ... & Bengtsson, B. (2016). Antibiotic resistance in *Escherichia coli* from pigs in organic and conventional farming in four European countries. *PloS one,* 11(6), e0157049

Prescott, J. F. (2014). The resistance tsunami, antimicrobial stewardship, and the golden age of microbiology. *Veterinary Microbiology*, 171(3-4), 273-278

Price, L. B., Newland, J., Bole, A., Bortolaia, V., Larsen, J., Loneragan, G. H., ... & Wagenaar, J. (2017). *Combating antibiotic resistance-A Policy Roadmap to Reduce Use of Medically Important Antibiotics in Livestock*

Schrijver, R., Stijntjes, M., Rodríguez-Baño, J., Tacconelli, E., Rajendran, N. B., & Voss, A. (2017). A review of antimicrobial resistance surveillance programmes in livestock and meat thereof in Europe with a focus on antimicrobial resistance patterns in humans. *Clinical Microbiology and Infection*

Singer, A. C., Shaw, H., Rhodes, V., & Hart, A. (2016). Review of antimicrobial resistance in the environment and its relevance to environmental regulators. *Frontiers in Microbiology*, 7, 1728

Smith, D. L., Dushoff, J., & Morris Jr, J. G. (2005). Agricultural antibiotics and human health. *PLoS Medicine*, 2(8), e232

Surette, M. D., & Wright, G. D. (2017). Lessons from the Environmental Antibiotic Resistome. *Annual Review of Microbiology*, 71, 309-329

Sustain. (2015). At least 10 times less antibiotics used in organic pigs. Retrieved October 31, 2017, from LINK

Tang, K. L., Caffrey, N. P., Nóbrega, D. B., Cork, S. C., Ronksley, P. E., Barkema, H. W., ... & Ghali, W. A. (2017). Restricting the use of antibiotics in food-producing animals and its associations with antibiotic resistance in food-producing animals and human beings: a systematic review and meta-analysis. *The Lancet Planetary Health*, 1(8), e316-e327

Teillant, A. (2015). Costs and benefits of antimicrobial use in livestock. *AMR Control,* 2015, 116-122

Teillant, A., Brower, C. H., & Laxminarayan, R. (2015). Economics of antibiotic growth promoters in livestock. *Annu. Rev. Resour. Econ.*, 7(1), 349-374

Van Boeckel, T. P., Brower, C., Gilbert, M., Grenfell, B. T., Levin, S. A., Robinson, T. P., ... & Laxminarayan, R. (2015). Global trends in antimicrobial use in food animals. *Proceedings of the National Academy of Sciences*, 112(18), 5649-5654

Van Boeckel, T. P., Glennon, E. E., Chen, D., Gilbert, M., Robinson, T. P., Grenfell, B. T., ... & Laxminarayan, R. (2017). Reducing antimicrobial use in food animals. *Science*, 357(6358), 1350-1352

Venter, H., Henningsen, M. L., & Begg, S. L. (2017). Antimicrobial resistance in healthcare, agriculture and the environment: the biochemistry behind the headlines. *Essays in Biochemistry*, 61(1), 1-10

WHO. (2017) Guidelines on use of medically important antimicrobials in food-producing animals

Williams-Nguyen, J., Sallach, J. B., Bartelt-Hunt, S., Boxall, A. B., Durso, L. M., McLain, J. E., ... & Zilles, J. L. (2016). Antibiotics and antibiotic resistance in agroecosystems: state of the science. *Journal of Environmental Quality*, 45(2), 394-406

Woolhouse, M., Ward, M., van Bunnik, B., & Farrar, J. (2015). Antimicrobial resistance in humans, livestock and the wider environment. *Phil. Trans. R. Soc. B*, 370(1670), 20140083

Credits

Suggested citation

Lee-Gammage, S., Atherton, E., Head, J., Stewart, S. (2018). What is the connection between infectious diseases in humans and livestock? (Foodsource: chapters). Food Climate Research Network, University of Oxford.

Written by

Samuel Lee-Gammage, Food Climate Research Network, University of Oxford.

Contributing authors

Elizabeth Atherton, Medact.
Josephine Head, Medact.
Sarah Stewart, Medact.

Edited by

Tara Garnett, Food Climate Research Network, University of Oxford.

Reviewed by

Delia Grace, International Livestock Research Institute.
Andrew Singer, Centre for Ecology and Hydrology.

Reviewing does not constitute an endorsement. Final editorial decisions, including any remaining inaccuracies and errors, are the sole responsibility of the Food Climate Research Network.

Funded by

The production of this chapter was enabled by funding from the following sources:

The Daniel and Nina Carasso Foundation
The Esmée Fairbairn Foundation