GLOBAL PUBLIC HEALTH COST OF ANTIMICROBIAL RESISTANCE RELATED TO ANTIBIOTIC USE ON FACTORY FARMS

WORLD ANIMAL PROTECTION

Cover photo: Antibiotics are extensively used in factory farming to promote fast growth or to prevent animals getting sick. Credit: KOOKLE/Shutterstock.

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EXECUTIVE SUMMARY[1]

Background

The term "factory farm" describes animal production facilities that house large numbers of animals, especially indoors, under controlled and standardized conditions to minimize costs. Factory farming is currently a major supplier of global food markets, and its role is likely to increase substantially with the growing urban population driving demand for animal products worldwide. However, factory farming is criticised for neglecting animal sentience and the effects of intensive production on the environment, human health, and society because it focuses on high-volume production and cost reduction.

Antibiotics and other antimicrobial medicines are often overused in factory farms as many animals are contained indoors in high-density conditions that increase the risk of infectious diseases. Antibiotics are used not only to treat individual animals upon clinical diagnosis of microbial infections (therapeutic administration). They are also administered with non-therapeutic purposes to:

- groups of animals without evidence of disease when they are in contact with other animals that show symptoms of infectious diseases (metaphylactic treatments);
- healthy animals that are at risk of contracting an infectious disease, e.g., because of confinement to small, crowded spaces or transport (prophylactic treatments);
- healthy animals as antibiotic growth promoters (AGP), i.e., by using sub-therapeutic doses that increase feed efficiency and stimulate weight gains thanks to interactions with bacterial micro-flora of the animals' digestive system.

In recent decades, the rapid growth of global meat production, mainly driven by the expansion of factory farming in middle and low-income countries, has led to a relevant increase in antimicrobial use (AMU) for animal production. AMU on farmed animals is now estimated to exceed the use for human health care.

The overuse of antibiotics on factory farms contributes to the spreading of antimicrobial resistance (AMR). AMR means that pathogens can become resistant to antimicrobial treatments. This loss of efficacy of drugs causes major risks for human and animal health, as well as economic losses related to deaths, longer recovery from illness, and costlier medical treatments.

In 2019, an estimated 1.27 million people worldwide died from causes "attributable to" AMR (i.e., these deaths would not have occurred if all the infections caused by resistant pathogens were instead susceptible to antibiotics), and 4.95 million died from causes "associated with" AMR (i.e., these deaths would not have occurred if all the infections caused by resistant pathogens were replaced by no infections).

Most infectious diseases are transmissible between animals and humans, and the large consumption of antibiotics in factory farms facilitates the development of resistant pathogens. People working in farms, slaughterhouses, and other activities of the food supply chain are especially at risk of being infected and becoming carriers of pathogenic bacteria non-susceptible to antibiotics.

According to the World Health Organization (WHO), without significant changes in the

[1] This research was produced by a group of researchers of the Department of Agricultural and Food Sciences, University of Bologna for World Animal Protection. The views and opinions expressed in this report do not reflect the views or positions of the Dept. of Agricultural and Food Sciences of the University of Bologna.

current trends, AMR could become the leading cause of death worldwide by 2050. In 2015, this organization, with other intergovernmental world agencies, i.e., the Food and Agriculture Organization (FAO), the World Organization of Animal Health (WOAH), and the United Nations Environmental Programme (UNEP), launched the Global Action Plan against AMR. The European Union (EU), after its ban on AGPs in 2006, has been developing specific actions on AMR since 2011.

These initiatives address AMR with a One Health approach that considers the interconnections between human, animal, and environmental health aspects and promote a more prudent AMU in animal production through the improvement of animal welfare and farm biosecurity and a significant reduction of the non-therapeutic treatments on animals. The intergovernmental actions have supported, in most countries, the approval and implementation of national action plans inspired by this holistic strategy that has led to some AMU reduction in animal production recorded over the last decade. However, the links between AMU in factory farms and the social and economic burden of AMR worldwide are still largely unexplored by the scientific literature, hence the need for a study to evaluate the public health costs.

Objectives of the study

This study had three main objectives:

1

to assess the global use of antimicrobials in livestock production and factory farms and provide information on global use of antibiotics for human health care (Chapter 1);

2

to evaluate the share of antimicrobials used on factory farms for non-therapeutic treatments (AGP, prophylactic, and metaphylactic treatments) (Chapter 2);

3

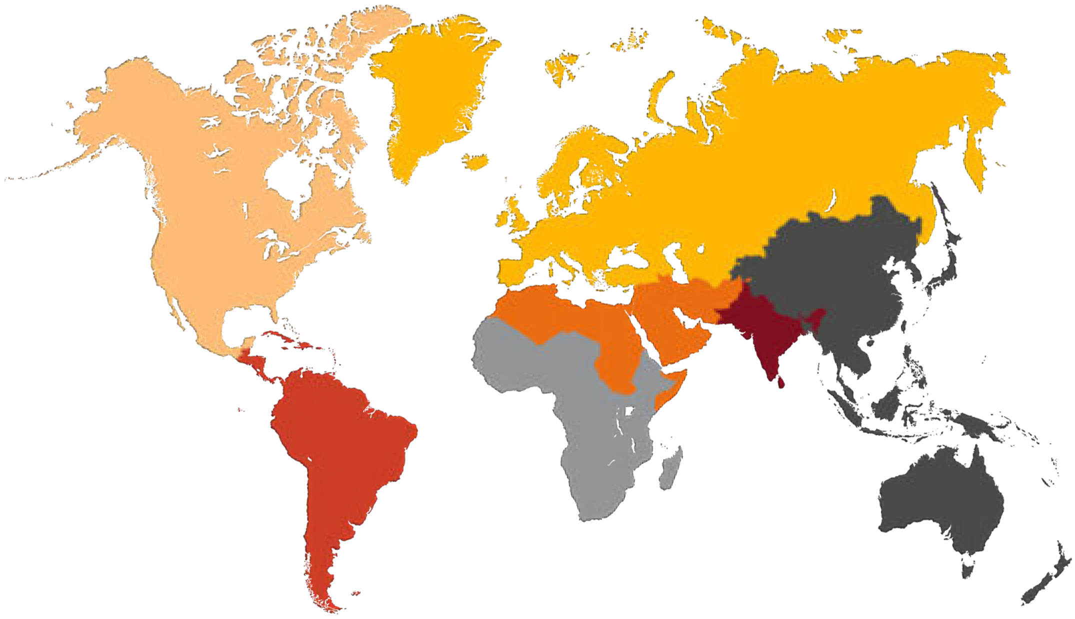
to estimate the global contribution of factory farming to the current economic burden of AMR on human health today and in future scenarios leading up to the year 2050 (Chapters 3 and 4).

Image: Intensive meat chicken farm, Undisclosed location. Credit: C.Lotongkum / Shutterstock.com

Study methodology and structure of the report

The study is organised into seven geographical regions according to the classification set by the Centre for Disease Dynamics, Economics and Policy (CDDEP):

1- East Asia and the Pacific
2- Europe and Central Asia
3- Latin America and the Caribbean
4- the Middle East and North Africa
5- Northern America
6- South Asia
7- Sub-Saharan Africa



In Chapter 1, based on FAO statistics on livestock and other sources, the share of factory farming in each region was estimated for the three main farmed terrestrial species (cattle, pigs, and poultry) and the six main farmed aquatic species (carp, catfish, salmon, shrimp, tilapia, and trout). We assessed the AMU in world animal production through a specific indicator called Population Correction Unit (PCU): 1 PCU equals 1 kg of live weight (or biomass) of animals at treatment. This indicator is widely used in the scientific literature to estimate AMU in farmed animals. The global PCUs correspond to the number of animals of the selected species multiplied by the respective Average Weight at Treatment (AWT). PCUs of aquatic species were assumed to correspond the total weight of world aquaculture production. By using previous estimations of global AMU, expressed in mg of antibiotic active principle (i.e., the constituent of a drug responsible for its therapeutic effect) per PCU, we calculated the global consumption of antimicrobials and the share attributable to factory farming. Using published data, we reported the total AMU in human health care by region and globally in terms of Defined Daily Doses (DDDs) per 1,000 inhabitants, an indicator referring to the relative use of treatment doses.

In Chapter 2, we assessed the share of non-therapeutic AMU on factory farms according to two distinct approaches using existing scientific information.

Chapter 3 investigated the links between the spread of antibiotic-resistant infections in the human population through the agri-food supply chain and the AMU in factory farms. A Spatial Error Model analysed this correlation by processing data from 30 countries on the resistant infections procured by the four main bacteria responsible for foodborne contaminations (*Escherichia coli*, *Staphylococcus aureus*, *Campylobacter*, and non-typhoidal *Salmonella*).

In Chapter 4, based on data already available in the scientific literature, the burden from the four selected bacteria in terms of deaths and Disability-Adjusted Life Years (DALYs) for the infections "attributable to AMR" and "associated with AMR" were calculated. The DALY is an indicator of the burden suffered by society for a given disease: one DALY corresponds to one year spent by one person in a state of complete disability. The calculation of the burden of one disease in DALYs includes, on the one side, all the time lost by the people who died because of the disease, before their life expectancy terms (Years of Life Lost, or YLL) and, on the other side, the time spent by people in a state of partial or complete disability caused by the disease, before full recovery or death (Years of Life to Disability, YLD).

Image: Envato Stock

The burden of the infections related to factory farming was estimated in terms of DALYs from the infections "associated with" AMR caused by the four selected bacteria, based on the consumption of veterinary antibiotics by factory farms previously calculated for each region and globally. We evaluated the global economic burden by converting global DALYs to current monetary values by imputing a cost per DALY equal to the global GDP per capita.

For future projections, we considered two scenarios: the first one describes a business-as-usual trend where the global AMU per PCU is constant while livestock production increases consistent with projected increases in global meat consumption and the share of factory farming in AMU varies in parallel with global urban population growth. The second scenario refers to a more prudent-AMU evolution supported by global and national policies against AMR. It foresees a decreasing AMU per unit of livestock production in the hypothesis that the reduction obtained in Europe during the last decade becomes global.

Study results

The study results are summarized at the global level and by region. The economic evaluations concern only the global level.

▪ Global analysis

Figure 1 shows the share of total farmed animals raised globally on factory farms for the selected terrestrial species, according to the estimations of this study.

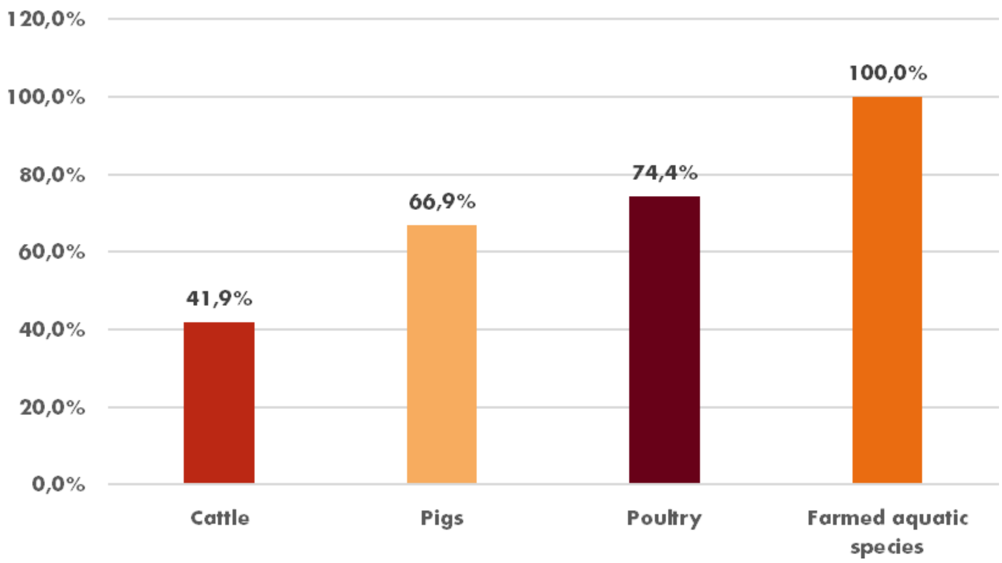


Figure 1. Share of total livestock globally raised by factory farms (yearly average 2018-2020)

For the selected farmed aquatic species, we assumed that the definition of factory farming includes total global production.

Considering the animal live weight in terms of AWT, the study estimated, for the selected species over the 2018-2020 period, a global yearly average of 1.19 trillion kg, or PCUs, of which 601.2 billion, or 50.3%, correspond to factory farms. Figure 2 shows the distribution by species of the global PCUs in factory farms.

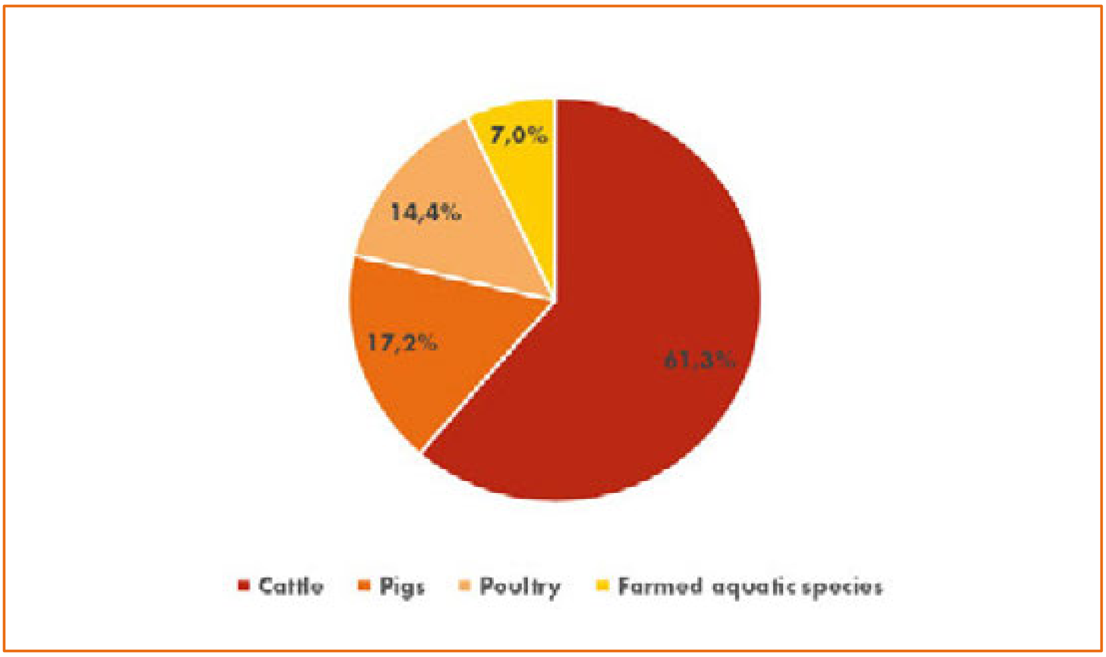


Figure 2. Distribution of the global animal live weight in factory farms by species (yearly average 2018-2020)

The global average consumption of antibiotics in livestock production was calculated as 80,541 tonnes of active principles, of which 47,156 tonnes or 58.5% in factory farms.

Figure 3 shows the percentage distribution of antibiotic consumption in factory farms by livestock species. The study assessed that more than 80% of total livestock AMU was for non-therapeutic purposes (metaphylaxis, prophylaxis, and AGPs).

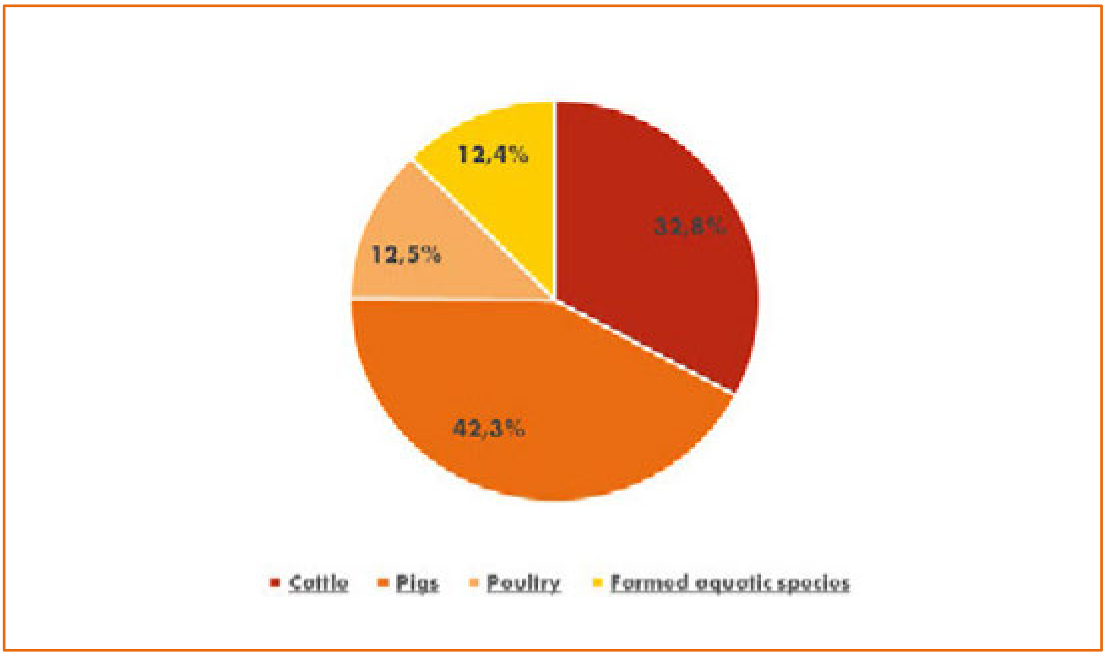


Figure 3. Distribution of the global consumption of antibiotics in factory farms by species (yearly average 2018-2020)

For comparison, according to a WHO report, in 2015, 65 countries gathering 22.5% of the world's population, consumed 14,256 tons of antibiotic active principles for human health care.

Based on existing data, the average human AMU at the global level grew at an annual rate of 1.7% between 2000 and 2020, from 5,769 to 8,290 DDDs per year per 1,000 individuals. The difference in average consumption over the period between the region with the world's highest levels of human AMU (North America) and the one with the lowest consumption (Latin America) is 2.4 times.

The Spatial Error correlation analysis indicated that an AMU increase of 1 tonne of active principles in factory farms causes an increase in antibiotic-resistant human infections from E. coli, S. aureus, Campylobacter, and Non-T. Salmonella of 0.021% ($p = 0.005$).

The study estimated that, in 2019, resistant infections from the four examined bacteria globally caused 403,000 deaths attributable to AMR (i.e., compared to a scenario where all drug-resistant infections are replaced by drug-susceptible infections) and 1.604 million deaths associated with AMR (i.e., compared to a scenario where all drug-resistant infections are replaced by no infections). The global burden of these infections amounted to 13.65 million DALYs attributable to AMR and 56.84 million DALYs associated with AMR. The estimated global incidence per 1 million people resulted in 49.4 deaths and 1,730.3 DALYs attributable to AMR, and 197 deaths and 6,884.6 DALYs associated with AMR. The contribution of factory farming to this burden was in 975,000 deaths and 33.5 million DALYs associated with AMR. Based on the global GDP per capita, we calculated that the economic value of global productivity losses from the population affected by resistant infections related to livestock production was at 648.37 billion US$. Factory farms' contribution amounted to 382.54 billion US$, corresponding to 0.43% of the global GDP (Figure 4).

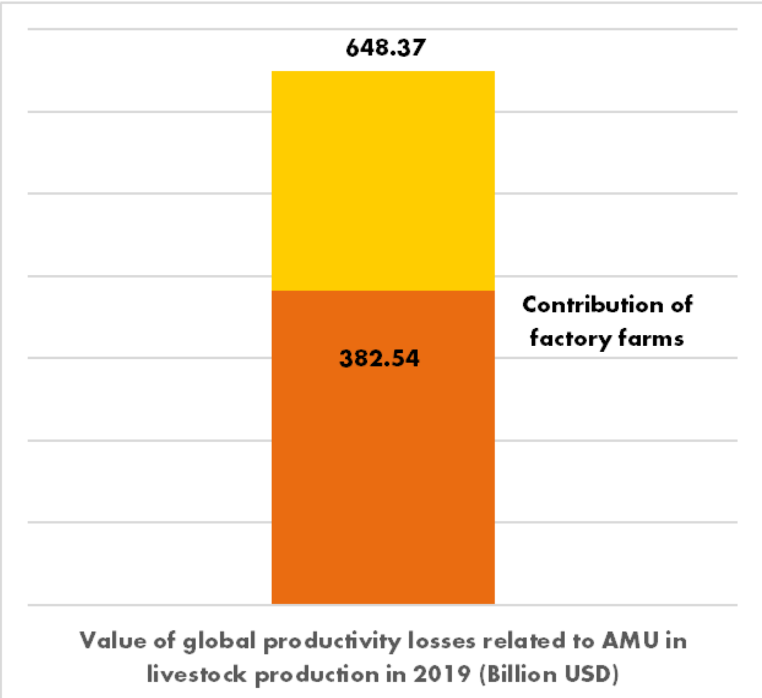


Figure 4 - Global economic burden from AMR related to AMU in livestock production and contribution of factory farming (year 2019)

Our projections indicate that, in the business-as-usual scenario (Scenario One), where the amount of antibiotic administered per kg of animal live weight remains constant over the 2019-2050 period (at the level of 2019), the global burden of the AMR related to AMU in animal production will rise to 113.72 million DALYs in 2050.

In the more-prudent-AMU scenario (Scenario Two), where the implementation of global and country strategies against AMR succeeds in reducing the AMU per unit of animal liveweight globally with the same diminishing annual rate achieved by Europe in the last decade, the burden will drop to 18.76 million DALYs in 2050 (Figure 5).

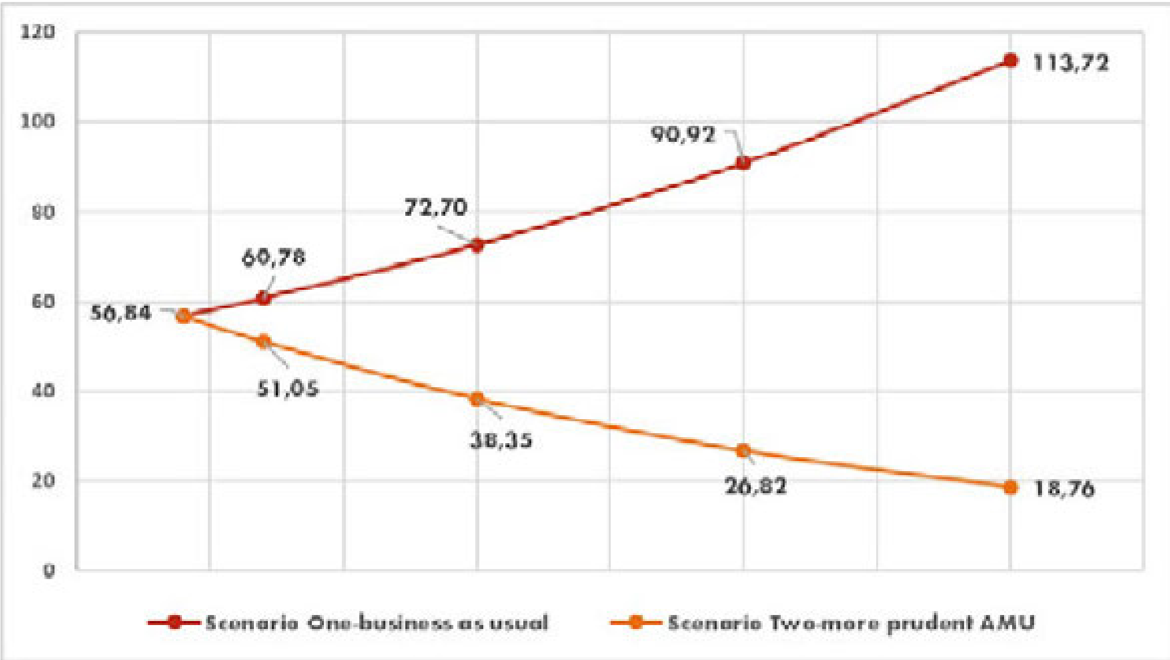


Figure 5 - Projections of the global burden from AMR related to AMU in livestock production: million DALYs associated with AMR (2019-2050)

Both scenarios foresee a growth of global animal production at an annual rate of 2.26% over the period. Figure 6 shows the projected evolution of the share of factory farming in the global AMU for animal production.

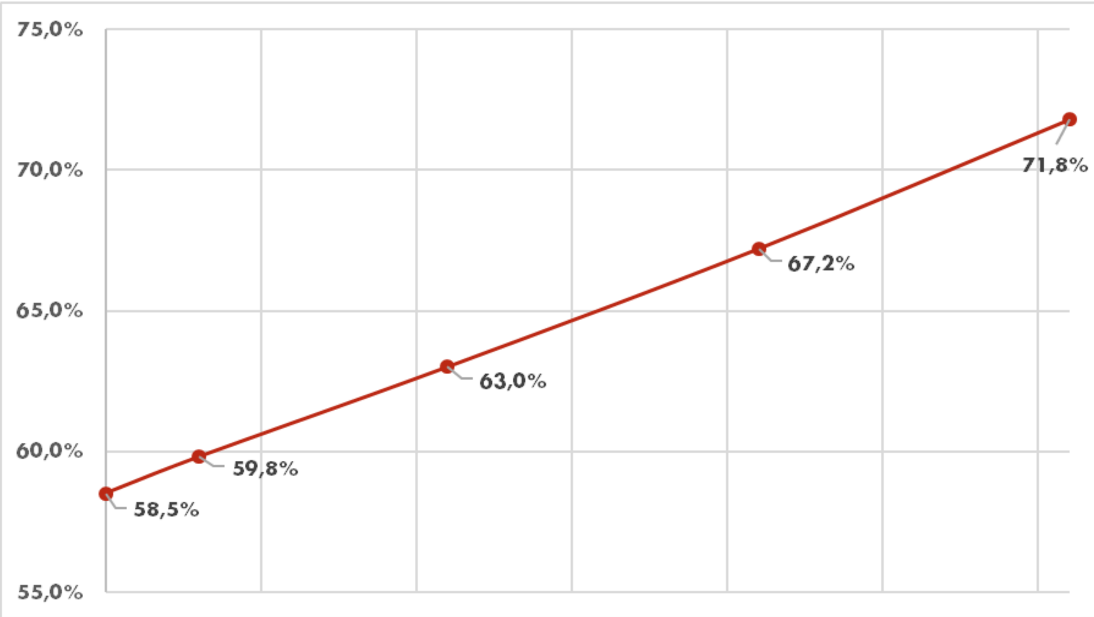


Figure 6 - Estimation of the share of factory farming in global AMU, percentage values (2019-2050)

The projected estimations of the economic value of the health burden consider an annual growth in the global average GDP per capita of 1.9%. Under the business-as-usual scenario (Scenario One), we estimated the contribution of factory farming to the economic burden of AMR related to AMU in livestock production to rise to more than 1 trillion US$ in 2040 and 1.67 trillion US$ in 2050, corresponding to 0.84% of the global GDP at that time. The cumulative cost to human societies between 2019 and 2050 will amount to 28.14 trillion US$. In the more-prudent-AMU scenario (Scenario Two), following the reduction of the global burden of AMR related to reduced veterinary AMU, the value of factory farms' contribution declines to 275.4 billion US$ in 2050, corresponding to 0.14% of the global GDP (Figure 7). Compared to the business-as-usual scenario, the more-prudent-AMU scenario generates 17.69 trillion US$ of cumulative savings for society over the analysed period.

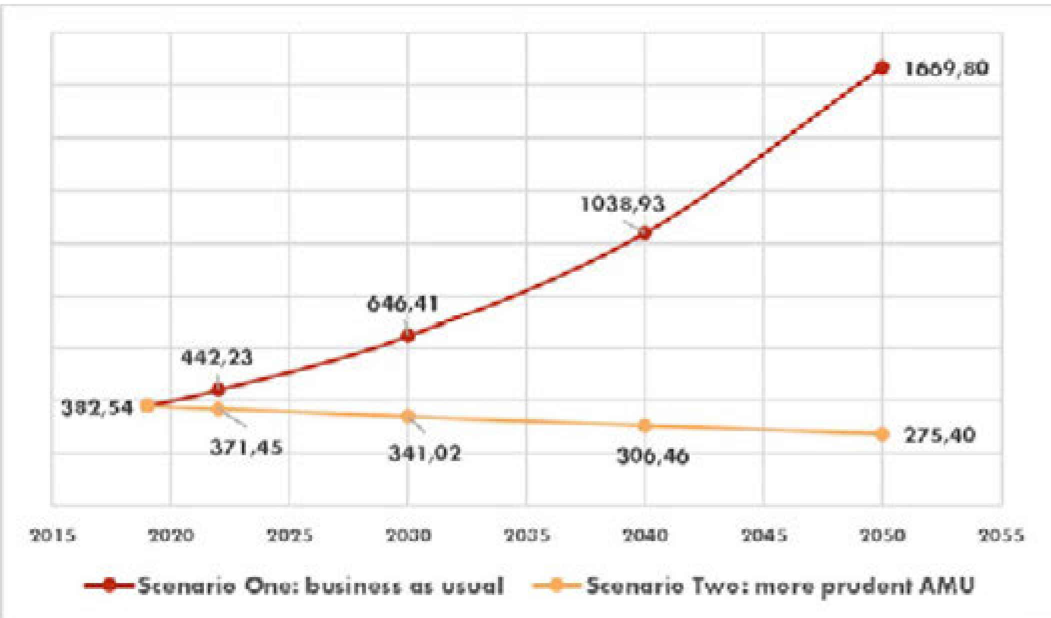


Figure 7 - Contribution of factory farming to the total economic burden from AMR related to livestock production: billion US$ (2019-2050)

Regional results

- ## East Asia and the Pacific

Over the 2018-2020 period, East Asia and the Pacific countries had a share of 36% of the global production in the poultry sector, 55% of the pig sector, and 12% of cattle. China produced 56% of the chosen aquatic food species alone (carp, catfish, tilapia, trout, salmon, and shrimp). In the region, factory farms produced 79% of the poultry, 69% of the pigs, and 42% of the cattle. Of the 41,323 tonnes of antibiotics used by factory farms worldwide for terrestrial species, 15,530 tonnes (38%) were used in this region. In the aquatic sector, 3,748 tonnes of antibiotics were consumed (65% of the global aquaculture AMU). 90% of the antibiotics administered to farmed animals in this region are estimated to be used for non-therapeutic purposes. The recorded prevalence of resistant infections (from the total of *E. coli* and *S. aureus* infections) in the region was respectively 30% and 12% over the 2000-2018 period. East Asia and the Pacific suffered 21% of global deaths and 16% of global DALYs associated with AMR from AMU in animal production in 2019 (*E. coli*, *S. aureus*, and *Non-T. Salmonella*).

Image: Pigs are amongst the most intensively farmed animals on the planet. To meet demand, they are reared in intensive, barren factory farms and mother pigs are confined to steel cages; Undisclosed location in China – Credit: World Animal Protection

Image: Factory farm at undisclosed location in UK. Credit: World Animal Protection / Tracks Investigations

- Europe and Central Asia

Over the 2018-2020 period, Europe and Central Asia had a share of 14% of poultry, 22% of pigs, and 13% of cattle in the global production of those species. One of the major world producers of aquatics is Norway, which has a 3% share of the global market. Factory farms produced 85% of the region's poultry, 74% of pigs, and 65% of cattle. Factory farms in Europe and Central Asia consumed 9,027 tonnes or 22% of the antibiotics used globally for terrestrial species, of which 86% were used for non-therapeutic purposes. The recorded prevalence of resistant infections (from the total of *E. coli* and *S. aureus* infections) in the region was respectively 28% and 11% over the 2000-2018 period. Europe and Central Asia suffered 15% of global deaths and 8% of global DALYs associated with AMR from AMU in animal production in 2019 (*E. coli*, *S. aureus*, and *Non-T. Salmonella*).

- Latin America and the Caribbean

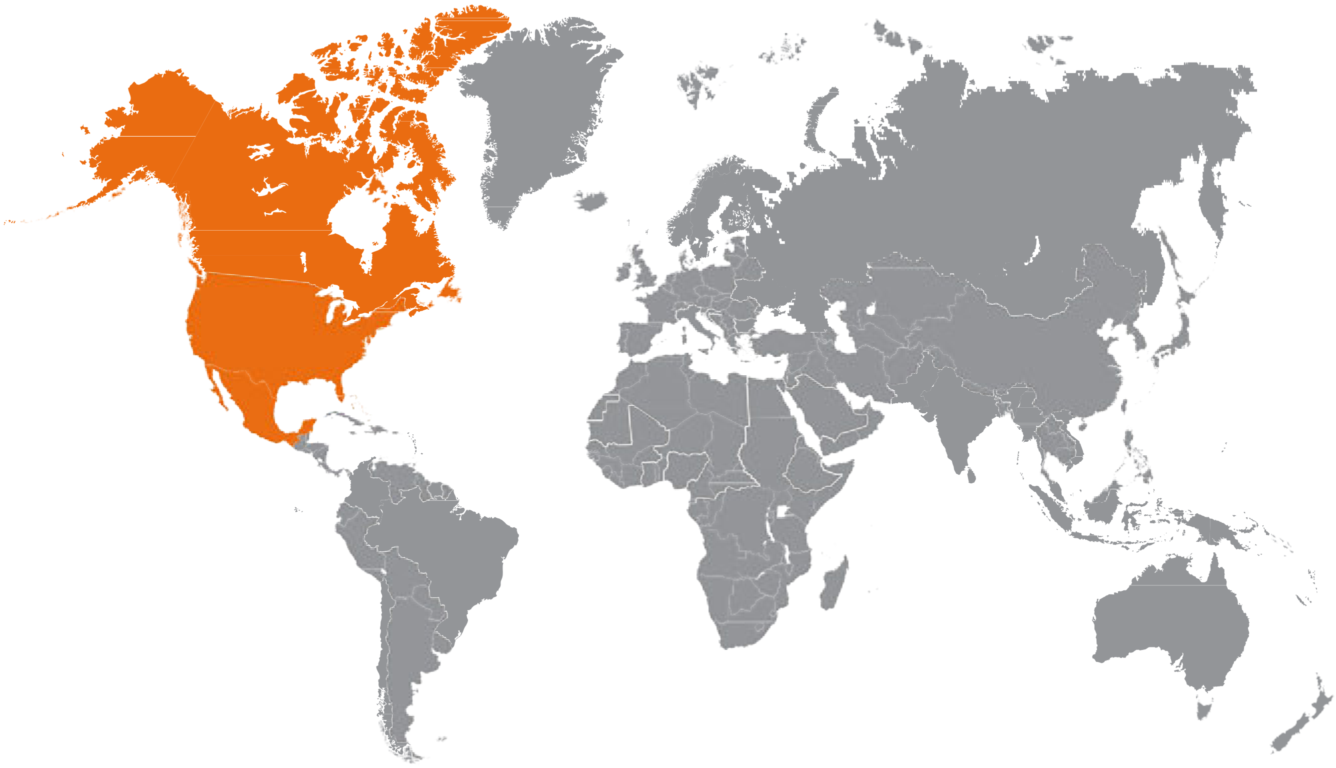
Between 2018 and 2020, the output of poultry, pigs, and cattle production in Latin America and the Caribbean equalled 15%, 8%, and 25%, respectively, of vglobal production. 3% of global aquaculture production comes from Chile and Ecuador. In Latin America and the Caribbean, 64% of poultry, 17% of pigs, and 34% of cattle are produced on factory farms, consuming 4,383 tons of antibiotics (12% of the global AMU for factory farms). 90% of those antibiotics were used for non-therapeutic purposes. The recorded prevalence of resistant infections (from the total of *E. coli* and *S. aureus* infections) in the region was respectively 24% and 11% over the 2000-2018 period. Latin America and the Caribbean suffered 8% of global deaths and 6% of global DALYs associated with AMR from AMU in animal production in 2019 (*E. coli*, *S. aureus*, and *Non-T. Salmonella*).

Image: Beef cattle at Ipiranga do Norte in Brazil. Credit: Noelly Castro / World Animal Protection

Image: Cattle in Africa. Credit: World Animal Protection.

- The Middle East and North Africa

Over the 2018-2020 period, the Middle East and North Africa had a share of 7% of poultry, 0.1% of pigs, and 2% of cattle in the global production of those species. 4% of the world's production of the chosen aquatics came from Egypt and Iran. In the Middle East and North Africa, factory farms produced 57% of poultry, 6% of pigs, and 34% of cattle. 90% of the 565 tons of antibiotics used on factory farms were for non-therapeutic purposes. The recorded prevalence of resistant infections (from total *E. coli* and *S. aureus* infections) in the region was respectively 36% and 39% over the 2000-2018 period. The Middle East and North Africa suffered 6% of global deaths and 6% of global DALYs associated with AMR from AMU in animal production in 2019 (*E. coli*, *S. aureus*, and *Non-T. Salmonella*).



North America

Over the 2018-2020 period, North America had a share of 17% of poultry, 10% of pigs, and 7% of cattle in the global production of those species. The United States (US) controls less than 1% of the world market of selected aquatic species. Factory farms in North America produce around 100% of poultry, 98% of pigs, and 70% of cattle and consumed 6,287 tonnes of antibiotics (15% of the global AMU for factory farms). 94% of antibiotics were utilized for non-therapeutic reasons. The recorded prevalence of resistant infections (from total *E. coli* and *S. aureus* infections) in the region was respectively 16% and 16% over the 2000-2018 period. North America suffered 6% of global deaths and 3% of global DALYs associated with AMR from AMU in animal production in 2019 (*E. coli*, *S. aureus*, and *Non-T. Salmonella*).

Image: Indoor dairy farm, Wisconsin, USA. Credit: Alvis Upitis / Getty Images

Image: Intensive egg farm in South India, where over 300,000 laying hens are crammed into battery cages. Credit: Amy Jones / Moving Animals

- South Asia

Over the 2018-2020 period, South Asia had a share of 7% of poultry, 1% of pigs, and 18% of cattle in the global production of those species. 13% of the aquatics were produced in Vietnam, India, and Bangladesh combined. Factory farms produced 30% of the poultry, 8% of the pigs, and 34% of the cattle in the region by using 2,486 tons of antibiotics, or 6% of the global AMU for factory farms. Non-therapeutic AMU was 90% of the total regional AMU. The recorded prevalence of resistant infections (from total *E. coli* and *S. aureus* infections) in the region was respectively 46% and 41% over the 2000-2018 period. South Asia suffered 25% of global deaths and 29% of global DALYs associated with AMR from AMU in animal production in 2019 (*E. coli*, *S. aureus*, and *Non-T. Salmonella*).

- Sub-Saharan Africa

Over the 2018-2020 period, Sub-Saharan Africa had a share of 4% of poultry, 3% of pigs, and 22% of cattle in the global production of those species. Factory farms produced 29% of poultry, 21% of pigs, and 34% of cattle in the region's overall production by using 3,044 tons of antibiotics (7% of the global factory farms' AMU), of which 46% were used for non-therapeutic purposes. The recorded prevalence of resistant infections (from total *E. coli* and *S. aureus* infections) in the region was respectively 37% and 11% over the 2000-2018 period. Sub-Saharan Africa suffered 19% of global deaths and 32% of global DALYs associated with AMR from AMU in animal production in 2019 (*E. coli*, *S. aureus*, and *Non-T. Salmonella*).

Image: Broiler (meat) chickens in an indoor, system in Africa. Credit: World Animal Protection / Georgina Goodwin

Conclusions

Global intergovernmental organizations emphasize the need to avoid the overuse of antibiotics in humans and farmed animals to safeguard their efficacy, which is critical for human and animal health. This study found that more than 80% of global AMU on farmed animals is not for therapeutic treatments but for prophylaxis or metaphylaxis or to promote animal weight growth. The WHO classifies these uses as non-therapeutic. Moreover, they are often associated with conditions of low animal welfare. For example, prophylactic treatments reduce the risk of infections when animals are confined in small, crowded spaces.

The WHO Global Action Plan against AMR recommends national governments to implement plans against AMR covering multiple actions for the livestock sector, including: the increase of stakeholders' awareness, monitoring of AMU on farms and AMR across the agro-food supply chain, improvement of farm animal health management, especially for animal welfare and biosecurity, stricter AMU regulations limiting non-therapeutic uses, and the reinforcement of governance by harmonizing the initiatives of all public and private actors involved. The EU and its Member States have probably taken the most advanced policy initiatives in this direction. Between 2011 and 2020, the European One Health Actions against AMR led to reducing sales of veterinary antibiotics per unit of animal liveweight in Europe by 43.2%. Further progress is expected in the coming years with the gradual enforcement of the new European legislation on veterinary medicines and medicated feeds and the AMU reduction targets set by the European Common Agricultural Policy.

Beyond the limitations due to scarcity of information and data, the estimates made for this study indicate that human society globally in 2019 suffered a potential burden associated with AMR from AMU in farmed animals of 1.6 million deaths and 56.84 million DALYs. The contribution of factory farming was quantified in 975,000 deaths and 33.5 million DALYs. The estimated economic damage for productivity losses for human deaths and disability due to disease corresponds to 0.73% of the global GDP and to 0.43% for the contribution of factory farming.

In a business-as-usual scenario, where farms maintain the current levels of AMU, the rising trends in animal product consumption stimulated by global population growth, urbanization, and increasing per capita income could double the human burden of AMR from antibiotic use in farms by 2050, according to the estimations of this study. The economic value of the burden from AMU in factory farms alone would increase more than 4-fold, approaching 1.7 trillion US$, or 0.84% of the projected global GDP for that year.

However, the study results also indicate that, if the progress achieved in the European farms in terms of more prudent AMU and AMU reduction becomes global in the coming decades, in 2050, the global burden from AMR related to AMU in livestock production could drop by 67.0% compared to the year 2019, despite the expected growing trends in demography, urbanization, income, and food consumption. In this global more-prudent-AMU scenario, the projected economic burden related to AMU in factory farms in 2050 will decrease by 28.0%

from the 2019 value. Compared to a business-as-usual situation, in 2050, the value of the social savings for avoided productivity losses would be near 1.4 trillion US$, corresponding to 0.70% of the global GDP.

The more prudent-AMU scenario is not easy to achieve globally. But the European experience indicates that, on the one hand, it is feasible, and, on the other hand, the measures recommended by the Global Action Plan can be effective. It is crucial to adopt knowledgeable and site-specific measures, particularly for the prevention and control of infections, access to treatments, and development of novel antibiotics and all the other alternatives to current antibiotics: e.g., vaccines, immune modulators, bacteriophages, endolysins, hydrolases, infeed enzymes, prebiotics, probiotics, peptides, organic acids, and phytochemicals. The prevention of disease through proper husbandry, improved biosecurity and animal welfare, genetics, and feeding, as opposed to prophylactic treatments, and a global ban on AGP are fundamental measures for lowering AMU in factory farming.

Governments should cooperate to establish harmonized regulations and metrics to monitor, trace, and optimize AMU in farms. Food supply chain transparency regarding the use of antibiotics in food-producing animals should enable better-informed consumer choices. A concerted effort among producers, consumers, healthcare providers, and business organizations is necessary to promote more prudent use of antibiotics and counter AMR and its associated social costs.

Image: Envato Stock

GLOBAL PUBLIC HEALTH COST OF ANTIMICROBIAL RESISTANCE RELATED TO ANTIBIOTIC USE ON FACTORY FARMS

ACRONYMS

AGP	Antibiotic Growth Promoter
AMR	Antimicrobial Resistance
AMU	Antibiotics Use
ASOA	Alliance to Save Our Antibiotics
AVMA	American Veterinary Medical Association
AWT	Average Weights at Treatment
CDC	Center for Disease Control
CDDEP	Center for Disease Dynamics, Economics and Policy
CIA	Critically Important Antibiotics
CIDRAP	Center for Infectious Disease Research and Policy
DALY	Disability-Adjusted Life Year
DDD	Defined Daily Dose
ECDC	European Centre for Disease Prevention and Control
EFSA	European Food Safety Authority
EMA	European Medicines Agency
ERS	Economic Research Service
ESVAC	European Surveillance of Veterinary Antimicrobial Consumption
EU	The European Union
EUFIC	European Food Information Council
EUROSTAT	European Statistics
FAO	Food and Agriculture Organization of the United Nation
FAWC	Farm Animal Welfare Compendium
GDP	Gross Domestic Product
HIQA	Health Information and Quality Authority
IHME	Institute for Health Metrics and Evaluation
OECD	Organization for Economic Co-operation and Development
PCU	Population Correction Unit
PPP	Purchased Power Parity
SEM	Spatial Error Model
SLM	Spatial Lag Model
UK	The United Kingdom
UN	The United Nations
UNEP	The United Nations Environment Programme
USA	The United States of America
USDA	The United States Department of Agriculture
USEPA	The United States Environmental Protection Agency
USFDA	The United States Food and Drug Administration
WAP	World Animal Protection
WHO	World Health Organization
WOAH	World Organization for Animal Health
YLD	Years Lost due to Disability
YLL	Years of Life Lost

INTRODUCTION AND RESEARCH QUESTIONS

The use of antibiotics and other antimicrobial compounds to treat human and animal diseases caused by pathogenic microorganisms implies that, over time, the targeted pathogens can develop the capability to resist the action of these drugs. This phenomenon, called antimicrobial resistance (AMR), makes infections more difficult to treat and increases the risk of disease spread, serious illness and death, with higher costs for society and public health systems.

Today, at the global level, antimicrobial use (AMU) in animal farming widely overcomes the use for human health care. Several studies that have addressed this issue attributed from 60% to around 75% of global antibiotic consumption to animal husbandry (Okocha et al., 2018; Tiseo et al., 2020; Wegener, 2003).

In farms, antibiotics are used, and often overused, not only to treat individual animals for therapeutic purposes but also for group treatments carried out to prevent the spread of a disease before the pathogen presence is detected within the farm (prophylactic treatments) or after the pathogen detection (metaphylactic treatments) without knowing if the treated animals are healthy or already infected (Landers et al., 2012; WHO, 2017a). Furthermore, in many countries, including some world's major livestock producers like Brazil, India, and the USA, antibiotics are still commonly used as growth promoters (antibiotic growth promoter, or AGP): i.e., to speed up the weight increase of animals raised for meat production (WOAH, 2022). The World Health Organization (WHO) considers prophylactic, metaphylactic, and AGP treatments as non-therapeutic and, with other UN and intergovernmental agencies, suggests national governments introduce regulations to limit such practices and phase out AGP (IACG-AMR, 2019; WHO, 2017a, 2015).

When the first antibiotics were tested in farmed animals more than 70 years ago, it was discovered that treatments with sub-therapeutic doses could accelerate weight gain (Marshall and Levy, 2011). The intensification of animal production was greatly accelerated by this innovation. The emerging intensive animal farming industry also realized that blanket use of antibiotics in healthy herds allowed for greater densities of animals in conditions that minimally met their needs. When it became possible to hasten growth and lessen infection, it quickly became more practical and profitable to keep large numbers of animals in close confinement while also boosting productivity (Kirchhelle, 2018; Otte et al., 2007). One of the negative results of this intensification bolstered by the misuse of antibiotics was a decline in animal welfare conditions in factory farms (Rodrigues da Costa and Diana, 2022).

While antibiotics supported the development of factory farming, the continued expansion of this industry has in turn caused the exponential growth of AMU in farms. Intensive animal farming practices like high stocking densities, genetic selection for rapid growth, early weaning, and routine mutilations can significantly affect animal welfare in factory farms (Cowen, 2006; Dawkins, 2017; Nicks and Vandenheede, 2014). Under conditions of poor welfare farmed animals become more vulnerable to diseases, and the massive use of antibiotics, reducing the risk of infection, can avoid production losses for farmers.

Image: Envato Stock

There is a growing concern about the consequences that massive AMU in farms can have on human health (Emes et al., 2022; Marshall and Levy, 2011; Otte et al., 2007; Rohr et al., 2019; Waage et al., 2022). Most infectious diseases are transmissible between animals and humans, and the huge consumption of antibiotics in factory farms facilitates the development of resistant pathogens that can infect people but are difficult or impossible to treat with commonly used drugs.

Workers operating in farms, slaughterhouses, and other activities of the food supply chain, as well as their relatives and friends, are especially at risk of infections and becoming carriers of microorganisms non-susceptible to antibiotics (EFSA Panel on Biological Hazards (BIOHAZ) et al., 2021; Hassan et al., 2021; Hickman et al., 2021; Xiong et al., 2018). For these reasons, the Global Action Plan against AMR, jointly launched by the WHO, the FAO and the World Organization for Animal Health (WOAH), addresses the issue with a One Health approach and promotes a more prudent AMU in animal production (WHO, 2015).

However, the role played by factory farming in the spread of antibiotic-resistant diseases in the human population is still largely unexplored by scientific research (Emes et al., 2022; Escher et al., 2021; Ikhimiukor et al., 2022; Medina-Pizzali et al., 2021; Rohr et al., 2019), and the possibility of exhaustively defining its global burden and economic impacts still appears very limited (Hillock et al., 2022; Innes et al., 2019; Morel et al., 2020; Dadgostar, 2019). Based on these premises, this study had 3 main objectives:

- to assess the global AMU in livestock production and factory farms and provide information on the global AMU for human health care. This objective was developed in Chapter 1;
- to evaluate the share of antimicrobials used on factory farms for non-therapeutic treatments (i.e., the use as AGP, and for prophylactic and metaphylactic treatments of animals) addressed in Chapter 2;
- to investigate the relations between AMU in factory farms and the spread of infections resistant to antibiotic treatments in the human population, developed in Chapter 3, and estimate the current global contribution of factory farming to the economic burden of AMR on human health, and in future scenarios leading up to the year 2050, developed in Chapter 4.

The study focused on the three main terrestrial species (cattle, pigs, and poultry) and the six main aquatic species (carp, catfish, salmon, shrimp, tilapia, and trout) raised in factory farms.

Due to its global scope, the research was organized into seven geographical regions following the classification set by the Centre for Disease Dynamics, Economics and Policy (CDDEP): East Asia and the Pacific, Europe and Central Asia, Latin America and the Caribbean, the Middle East and North Africa, Northern America, South Asia, and Sub-Saharan Africa. The analysis answered four main research questions corresponding to the four chapters of this report. Each question built up to the overall aim of determining the consequences of AMU in factory farms on the insurgence of AMR diseases in the human population globally and evaluating the related costs.

Image: Mother pig in a steel cage for birthing on a factory farm in the EU. Credit: World Animal Protection.

i. What is the current global use of antibiotics in factory farms?

The first question was resolved in four steps. The first step involved reviewing the definitions and the characteristics of factory farming, to establish what to consider a factory farm in this study and the share of farm animals that could be covered by this definition regionally and globally. Then in step 2, we estimated the global and regional outputs of the major terrestrial and aquatic species raised on factory farms. In step 3, the levels of AMU on farms for the selected animal species were investigated by drawing on existing data and reports of antibiotic sales and use. A similar search was also performed for the human consumption of antibiotics. In the last step, the total AMU in global animal production by species and region and the factory farming shares were calculated.

ii. How much antibiotics are administered in factory farms for non-therapeutic treatments?

The second research question more narrowly focused on routine non-therapeutic uses of antibiotics on factory-farmed animals by developing the fifth step of the study. Two methods permitted us to identify the relevance of non-therapeutic treatments in the total AMU of factory farms.

iii. How does antimicrobial use on factory farms impact the spread of antibiotic-resistant infections on the human population?

The third research question developed the sixth step of the research by investigating the links between AMU in factory farms and the spread of AMR diseases in humans. The four bacteria most responsible for foodborne infections in humans caused by consumption or manipulation of animal products or contact with animals, i.e., Escherichia coli, Staphylococcus aureus, Campylobacter spp., and non-typhoidal Salmonella, were selected to examine the correlation between antibiotic-resistant infections from those pathogens and AMU in factory farming in 30 countries. The analysis was carried out through a Spatial Error Model.

iv. How might antibiotic use in factory-farmed animals increase public health costs related to AMR infections?

The answer to the last question was articulated in two final steps: the seventh and the eighth of the study. Based on existing data, the seventh step estimated the global and regional human burden associated with antibiotic-resistant infections from the four pathogens selected in the previous step, assuming they are all related to AMU in animal production. The burden was expressed as the number of deaths and Disability-Adjusted Life Years (DALYs): a concept which encompasses the Years of Life Lost (YLLs) and the Years Lost due to Disability (YLDs) resulting from a given disease. The contribution of factory farms to the global and regional burden was calculated in proportion to the AMU in factory farms estimated in Chapter 1.

The global economic damage was then evaluated by attributing to each DALY lost a monetary value corresponding to the global GDP per capita. The eighth step projected the global economic burden from AMR related to the use of antibiotics in factory farms over the next few decades to the year 2050 by considering forecasts on world demography, urbanization, consumption of animal products, and GDP per capita in two alternative scenarios. The first scenario assumed a business-as-usual situation where the level of AMU in animal production would not have changed over the examined period. The second scenario assumed that thanks to policy measures undertaken under the European One Health Action against AMR, the global AMU in factory farms would have declined with the same decreasing rate achieved in Europe in the last decade.

Image: Envato Stock

1. WHAT IS THE CURRENT GLOBAL USE OF ANTIBIOTICS IN FACTORY FARMS?

In four steps, this chapter estimated the total amount of antibiotics globally consumed on factory farms.

Step 1 assessed the global animal stock of cattle, pigs, poultry, and main farmed aquatic species.

Step 2 calculated the proportion of factory farms in the global stock of the selected species.

Step 3 provided information regarding the levels of antibiotic consumption for human health care and animal production and set reference values to calculate the total amount of antibiotics consumed by the selected animal species.

Step 4 estimated the global use of antibiotics in animal production and the share of factory farming in that amount.

1.1. Introduction

Food security is a principal objective for nations as it is a fundamental requirement for human life. Food security is "when all people at all times have access to sufficient, safe and nutritious food that fits their dietary needs and food preferences for an active and healthy life", as stated by the Food and Agriculture Organization of the United Nations (FAO) in 1996 (FAO, 2003). Food production is the first dimension of food security, which is a multidimensional concept. Farming's main task is to produce food (Borch and Kjærnes, 2016). Farms are essential in creating the relevant regulations and technologies because they are the first actors in the food supply chain (Ardakani et al., 2020; Bakucs et al., 2013).

Theoretically, a farm is a single-managed economic unit of agricultural output that comprises all maintained animals and all land used for agricultural production, regardless of title, legal structure, or size (FAO, 2005; Hartvigsen, 2014). According to an alternative definition, a farm is a civil or legal entity that manages agricultural holding operations taking significant resource-use decisions (FAO, 2005).

There are many different classifications of farms: e.g., family and non-family farms, specialized and diversified farms, conventional and commercial farms, and intense vs extensive farms are a few of these classifications. Family farming is "a method of arranging agricultural, forestry, fisheries, pastoral, and aquaculture production which is managed and maintained by a family and largely dependent on the family work force, including both women and men" (Graeub et al., 2016). Thus, family farms are often represented by relatively small-scale agricultural enterprises, while non-family farms typically have hired workers and more advanced technology (FAO, 2014a). Some authors indicate the primary characteristic of commercial farming in large-scale production, capital-intensive, high-yielding varieties used, monoculture, advanced technology, and paid labour (Herens et al., 2018; Smalley, 2013).

A different classification distinguishes specialized and diversified farming (IPES-Food, 2016). Farms that produce few types of outputs or just one or focus on a single step in the production process are defined specialized farms: for instance, in specialized pig production, farrow farms produce only piglets, weaners farms raise weaned pigs for 7-8 weeks, and fattening farms cover the last stage of breeding until pigs reach market weight. Specialized farms aim to boost productivity by specialization and production intensification, like industrial operations in scale and goals. Diversification, however, relates to farming in that farmers produce a variety of goods and alter their production through time and across farming grounds. Diverse agricultural practices are used to increase biodiversity, promote interactions between species, and ensure long-term fertility, healthy agro-ecosystems, and stable livelihoods (Bommarco et al., 2018; Giannetti et al., 2020; Grass et al., 2021; IPES-Food, 2016; Swarnam et al., 2018; Thornton and Herrero, 2014).

Another distinction is between intensive and extensive farming. An extensive farming system has low inputs and outputs (Gilbert et al., 2015). Many types of systems are included within each category; for instance, pastoral production is a type of extensive farming which involves grazing livestock outside, and where little or no medicine and other external inputs are used. Intensive farming, on the other hand, is characterized by larger yields from both crops and livestock depending on broad use of external inputs including medicine and feed.

Non-family, specialized, commercial, and intensive farms share features like production scale and higher use of inputs to optimize profit and can be designated as large-scale-high-input farms: this broad category includes what this study refers to as "factory farms", a concept described in greater detail in the following section. In contrast, family, diversified, traditional, and extensive farms can be grouped under a second category: small-scale-low-input farms. However, it is worth noting that the term "factory farm" falls under several definitions within these classification systems but is not a commonly recognized or used term by industry or governments.

Image: Envato Stock

1.2. What is factory farming?

1.2.1. Definitions

Factory farms are large, industrialized farms, particularly the ones that house large numbers of animals indoors to maximize production and minimize costs (Merriam-Webster Dictionary, 2021). The World Animal Protection (WAP) defines factory farming as systems where animal husbandry practices do not acknowledge the sentience of the animals and where negative animal welfare, environmental, social, and health impacts are significant yet not considered when calculating the costs of production (WAP, 2022). The factory farm business model is characterized by concentrated and highly corporatized management, streamlined processes, high production volumes, and a strong focus on cost minimization. Intensive livestock operations, industrial farming, and concentrated animal feeding operations (CAFOs) are other phrases used to characterize this type of animal production. The main characteristics of factory farms are described in the following sections.

Image: Factory farm at undisclosed location in EU. Credit: World Animal Protection / Tracks Investigations

1.2.2. Concentration

Because land is a limited resource in agriculture, factory farms house many animals in small areas. For instance, broilers and laying hens often reside in a space smaller than a typical sheet of paper. Laying hens are commonly housed in cages that are too small for them to flap their wings (FAWC, 2012; Shields and Greger, 2013). Mother pigs (or breeding sows) are housed in crates or stalls that are too tiny to turn around (WAP, 2021, p. 2021). The size of factory farms does not guarantee that animals live in conditions they need to behave naturally. Often the space available to animals limits their natural behaviour. High animal concentrations on factory farms have other negative consequences. As labour costs are also a limiting factor, factory farms have few workers overseeing large numbers of animals. Limited attention to animals can increase the risk of disease and injury. Additionally, large concentrations of animals create lots of manure and wastewater, which significantly impacts the quality of air, groundwater, and life for neighbouring communities (Otte et al., 2007).


Image: Cattle raised for meat in a feedlot. Undisclosed location. Credit: Getty Images

1.2.3. Intensification

In livestock production, intensification refers to technological advancements that increase input use efficiency and output per animal. Examples of these advancements include genetic selection, health interventions, and farm management (Steinfeld et al., 2006). For instance, chickens sold at markets today are twice as heavy as they were in 1955, mainly due to genetic selection that allows for more efficient conversion of feed to muscle mass (Tallentire et al., 2016).

Animals kept in high numbers on factory farms demand many inputs, including feed and fossil fuel, to fertilize, harvest, process, and transport the feed, animals, and their products. Furthermore, facilities like automated feeding and watering equipment are required because many factory farm operations take place indoors, which requires considerable availability of electric power. To make this high use of resources economically feasible, factory farms maximize productivity and efficiency through intensification.

1.2.4. Specialization

Factory farms need to be highly specialized to be effective. Thus, they often exclusively produce one type of product or focus on only certain stages of the production cycle. Specialization relies on genetic selection for productive traits that maximize production relative to inputs, but animals may pay a heavy price for this. For example, in chickens raised for meat, selection addressed rapid weight gain and larger muscle mass, which has led to stress on the heart and respiratory functions, weak immune systems, and poorer animal welfare (Rodenburg and Turner, 2012). Additionally, by promoting few selected animal breeds and strains with commercial objectives, many old breeds of domesticated species face the risk of extinction, with impacts on biodiversity (Drucker et al., 2001). The proportion of livestock breeds classified as being at risk of extinction increased from 15% to 17% between 2005 and 2015, and 58% of breeds have not been reported to the genetic mapping classification at FAO for the last ten years (FAO, 2015).

1.2.5. Integration

Large factory farms are increasingly held by fewer corporations that control the millions of animals in their care. The characteristic structure is vertical integration, which refers to the control of each step of an animal production system, even in the upstream and downstream stages of the supply chain: for example, feed production, genetics, animal farming, animal health management, transportation, slaughtering, and processing.

Contract farming is a practice where independent farmers cooperate commercially with these large organizations. The types of contract farming are varied. In the European poultry and pig industries, for example, farmers generally provide work, farm facilities, water, and electricity, while the integrator companies provide the genetics, feed, technical and veterinary assistance, and transportation. The companies maintain the ownership of the animals they give to farmers and take all decisions regarding farming practices. The price paid to the farmer remunerates the inputs he provides and is agreed upon in advance.

Market advantages of vertical integration include the possibility to strengthen economies of scale, ensure supply and more control over product quality and homogeneity.

Step 1: Estimating the global farmed animals of the selected species and in factory farms

1.3. Animal species mostly produced in factory farms

1.3.1. Selection of the farmed animal species considered in the study

The world databank for monitoring the status and trends of animal species and genetic diversity reports that five species: cattle, sheep, chickens, goats and pigs are widely distributed in all the world regions and have broad global herds (FAO, 2015). AMU on sheep and goat herds is still relatively low, and production is generally extensive, exploiting pastures and marginal land through agropastoral practices, which use few industrial inputs. Therefore, for this study, only cattle, pigs, poultry, and fish were considered because they represent the species mostly raised in factory farms, and the scientific literature suggests that they are the species receiving the most veterinary antibiotics (Tiseo et al., 2020). Regarding aquaculture, the study considered the six globally most farmed aquatic species: carp, catfish, salmon, shrimp, tilapia, and trout (FAO, 2020a; FAOSTAT, 2022)

1.3.2. Poultry

Poultry are domesticated birds including chickens, turkeys, geese, ducks, guineafowls, pigeons, quails, ostriches, and many other minor species can be raised for eggs, meat, feathers, and skin. Due to human population increase, wealth growth, and urbanization, the poultry industry, in particular, egg production from laying hens, chicken meat from broilers, and turkey meat, is the livestock industry with the quickest development (Figure 1.1), especially in developing countries (FAO, 2021).

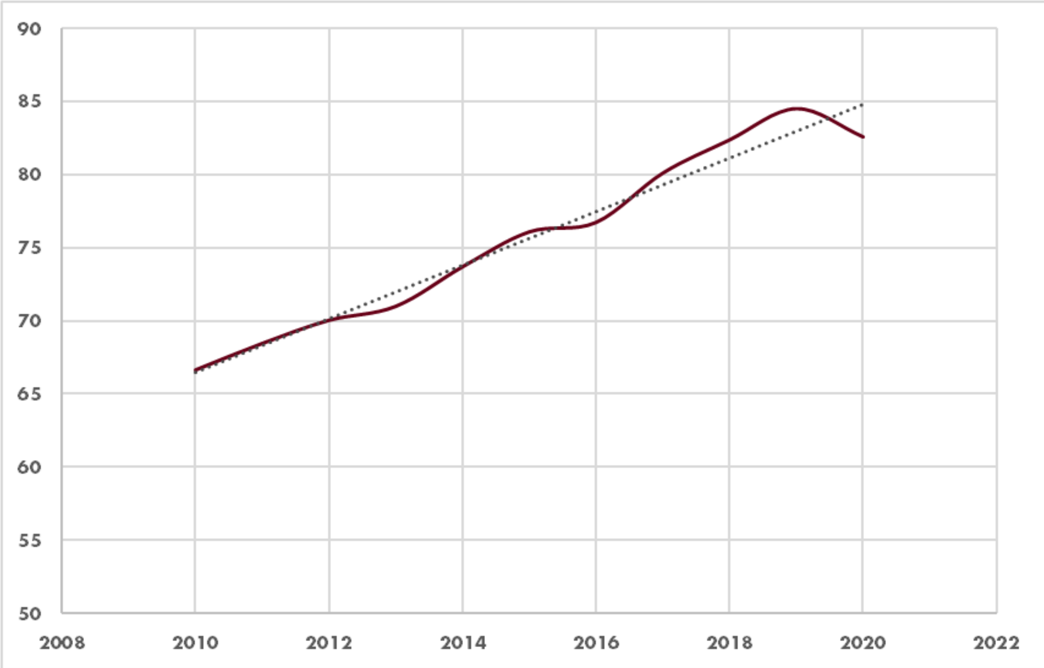


Figure 1.1 The trend of global poultry production in billion heads (FAOSTAT, 2022).

Chickens represent more than 90% of the world's poultry production and are the most widely bred species. Other relevant species include geese and ducks in Asia, turkey in North America, and guineafowl in Africa. Poultry meat is the second most consumed meat in the world after pork. However, in the coming years, global poultry meat demand is expected to overcome the pork demand, according to a report from the United States Department of Agriculture (USDA) (USDA, 2021). Global egg production is substantially growing, with the latest figures suggesting a 24% increase over the past decade.

Image: Intensive meat chicken farm, UK. Credit: World Animal Protection/Tracks Investigations.

1.3.3. Pigs

Pigs raised for meat are the most relevant category of animals in factory farms globally. The fast-growing species with high feed conversion rates, like pigs and poultry, are projected to contribute significantly to the growth of the livestock sector to meet the rising world demand for meat (FAO, 2014b). Figure 1.2 shows the global trend in pig production from 2010 to 2020. African Swine Fever (AFS), widely spread in China in 2019, is responsible for the significant decline in pig production in 2019.

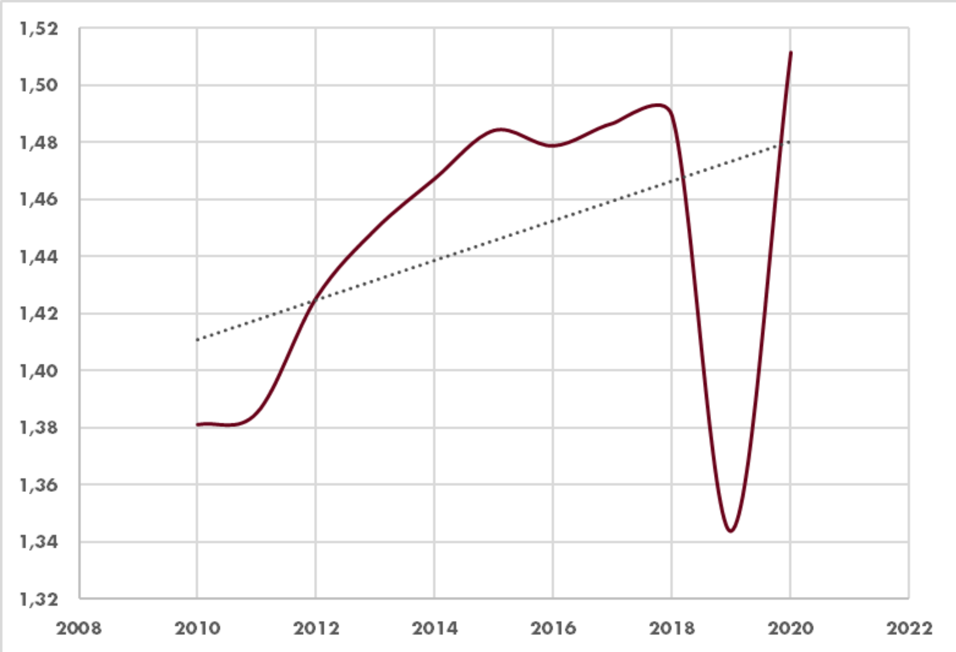


Figure 1.2 The trend of global pigs' production in billion heads (FAOSTAT, 2022)

1.3.4. Cattle

Cattle are mainly raised for milk (dairy cattle) and meat. The global demand for beef is rising since it is considered a high-quality source of protein and is popular in many countries and cultures. After chicken and pork, beef is the third most consumed meat in the United States (USA).

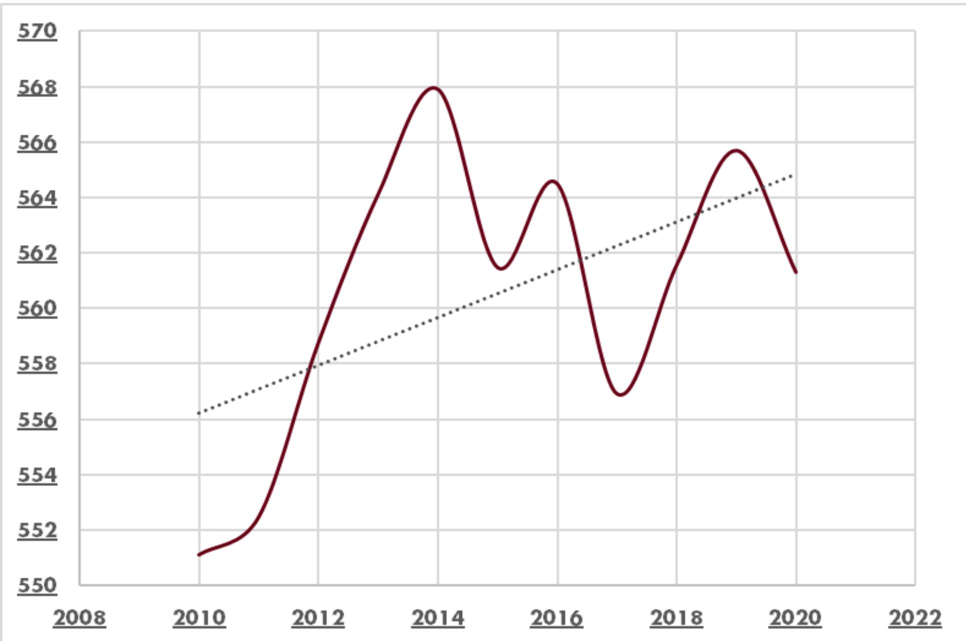


Figure 1.3 The trend of global cattle production in million heads (FAOSTAT, 2022)

The USA, Europe, Brazil, China, Argentina, India, and Australia are the principal beef-producing countries in the world. (Greenwood, 2021). Cow milk is considered an excellent source of vitamins and minerals, particularly calcium. Asia is the region that produces the most milk, followed by Europe, Latin America, and the Caribbean (FAO, 2020b). The global trend in cattle production from 2010 to 2020 is illustrated in Figure 1.3.

1.3.5. Farmed aquatic species

Fish products are appreciated as a rich source of animal protein and are considered an essential part of healthy diets. Many fish products contain omega-3 fatty acids and micronutrients, which are crucial for enhancing nutrition and health. In the last decades, the growing world demand for fish and other aquatic products is threatening the sustainability of fisheries in many regions and supporting the rapid development of aquaculture. This industry makes extensive use of technical inputs, including antibiotics (FAO, 2020a; UN Nutrition, 2021). Figure 1.4 below shows the global trend in output of all farmed fish species between 2010 and 2020.

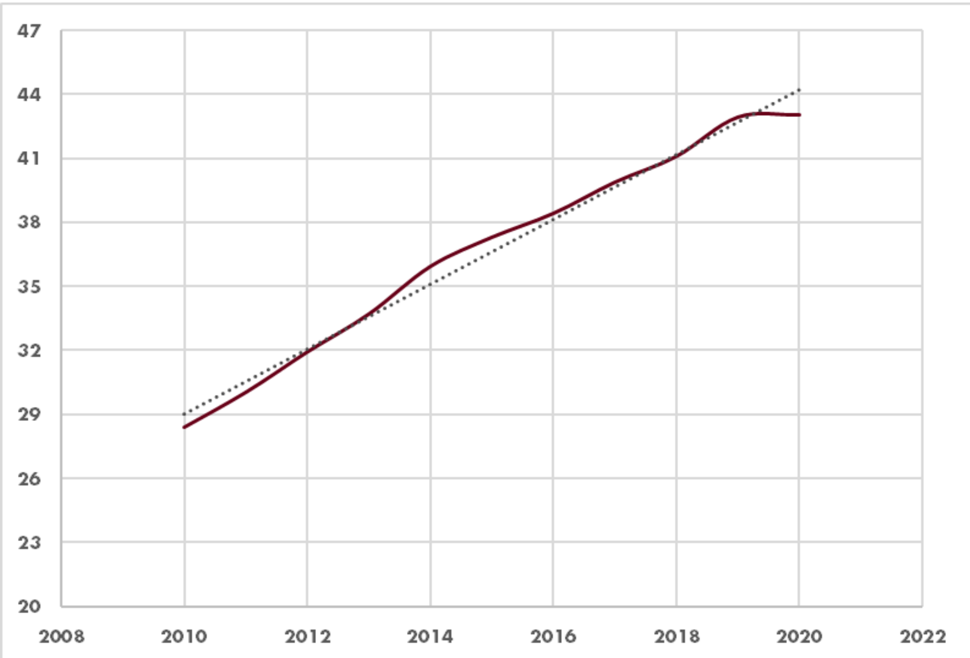


Figure 1.4 The trend of global aquatics production in million tonnes (FAOSTAT, 2022)

Image: Fish farm in Malaysia where fish are farmed in high densities. Credit line: World Animal Protection.

1.4. World regional distribution of animal production from the selected animal species

1.4.1. Data sources

To evaluate the global scale of factory farming, we collected data from several publicly available databases. The data were aggregated according to seven geographical regions, following classifications of the World Bank and the Center for Disease Dynamics, Economics and Policy (CDDEP): East Asia and the Pacific, Europe and Central Asia, Latin America and the Caribbean, Northern America, South Asia, the Middle East and North Africa, and Sub-Saharan Africa. Production data for the selected animal species and producing countries were obtained from the FAO Statistical Database (FAOSTAT) for 2018, 2019, and 2020: the three most recent years available at the time of the study (FAO, 2021).

1.4.2. Terrestrial animals

Table 1.1, Table 1.2, and Table 1.3 show the total poultry, pigs, and cattle production in the different world regions (annual average of the 2018-2020 period). Table 1.1 shows that 68% of the world poultry is produced in East Asia and the Pacific, North America, Latin America, and the Caribbean, with China, the USA, and Brazil as highest producing countries in those regions.

East Asia and the Pacific, Europe and Central Asia, and North America collectively produce 81% of the world's pigs (Table 1.2). The main producers are China, Germany, and the USA. Table 1.3 displays the global production of cattle, where South Asia, Sub-Saharan Africa, and Latin America and the Caribbean contribute to 65% of the total. The main producers are India, Brazil, and Chad.

Regions	Production (000 heads)	Share (%)
East Asia and the Pacific	41,842,288	35.89
North America	20,313,016	17.42
Latin America and the Caribbean	16,905,546	14.50
Europe and Central Asia	16,531,303	14.18
Middle East and North Africa	8,586,428	7.36
South Asia	7,979,534	6.84
Sub-Saharan Africa	4,427,022	3.80
World	116,585,137	100.00

Table 1.1 Global poultry production (thousand heads) and regional distribution (yearly average 2018-2020).

(Own elaboration from FAOSTAT, 2022)

Regions	Production (000 heads)	Share (%)
East Asia and the Pacific	1,310,000	55.37
Europe and Central Asia	518,000	21.85
Northern America	242,000	10.18
Latin America and the Caribbean	196,000	8.26
Sub-Saharan Africa	79,578	3.35
South Asia	21,637	6.84
Middle East and North Africa	1,463	0.06
World	2,368,678	100.00

Table 1.2 Global pig production (thousand heads) and regional distribution (yearly average 2018-2020).

(Own elaboration from FAOSTAT, 2022)

Regions	Production (000 heads)	Share (%)
Latin America and the Caribbean	527,879	25.46
Sub-Saharan Africa	448,657	21.64
South Asia	376,142	18.14
East Asia and the Pacific	255,634	12.33
Europe and Central Asia	273,979	13.21
Northern America	153,408	7.40
Middle East and North Africa	37,480	1.81
World	2,073,179	100.00

Table 1.3 Global cattle production (thousand heads) and regional distribution (yearly average 2018-2020).

(Own elaboration from FAOSTAT, 2022)

1.4.3. Aquatic species

Table 1.4 lists the main global producers of the aquatic species selected for this study. China alone covers more than half of the total world production, followed by Indonesia, Vietnam, India, and Bangladesh, which highlight the primary role of the Asian continent.

Countries	Production (000 tonnes)	Share %
China	24,813,227	56.39
Indonesia	4,008,193	9.11
Vietnam	2,326,263	5.29
India	2,004,579	4.56
Bangladesh	1,409,684	3.20
Norway	1,367,077	3.11
Egypt	1,160,671	2.64
Chile	911,000	2.07
Thailand	693,070	1.57
Ecuador	586,848	1.33
Iran	429,026	0.97
World	44,005,212	100.00

Table 1.4 Global production of the selected aquatic farmed species (thousand tonnes) and distribution by country (yearly average 2018-2020).

(Own elaboration from FAOSTAT, 2022)

Step 2: Calculating factory farms' relative share of the global animal production

1.5. Share of factory farms in the global animal production

The growing demand for products of animal origin is supporting a global expansion of factory farm production. We applied distinct methods to determine the current share of factory farms on the total output of the selected farmed species in the different regions. These methods were previously developed by various studies referenced in Appendix A (Table A1). In each region, for each species, we have adopted the production share of factory farms indicated in the referenced studies. However, whenever more accurate information was available for any country, we made the corrections needed.

Some countries were considered separately from their geographical region based on significant differences in the animal production systems compared to the regional standards. It was the case of Australia and New Zealand, located in the East Asia and Pacific region, but with a supply chain organization more like Western Europe. In the same region, for Japan and South Korea, we adopted the values of North America.

For North America, we used values estimated by the Sentience Institute, based on the definition of Concentrated Animal Feeding Operations (CAFO) from the US Environmental Protection Agency (USEPA). For Europe and Central Asia, we adopted the proportions of "specialised holdings" according to EUROSTAT data and definitions as a proxy for factory farms (for EUROSTAT, a "specialist holding" is a farm where one specific production provides at least two-thirds of the total output value). Corrections were conducted for pigs and poultry in France using estimations performed by interprofessional organisations.

For the other regions, we followed the estimations presented in the FAO report on "Global livestock production systems" (Robinson et al., 2011) using the approach of livestock densities for pigs and poultry. For cattle, we followed the estimations presented in the FAO report on "The State of the World Animal Genetic Resources" (FAO, 2007) by using the approach of "landless industrialized production systems", we aggregated the shares of industrial and mixed irrigated systems as a proxy for factory farms. We performed a robustness check using a method linking the national proportion of extensively raised animals to countries' GDP per capita (Gilbert et al., 2015) (see Table A. 2 in the Appendix).

Based on FAO production data and the cited methodologies, we estimated, for each region and globally, the proportion of the total animal production obtained in factory farms for the selected terrestrial species (see Table 1.5 and Figure 1.5). Regarding the aquatic species, given the technical characteristics and the organization of the aquaculture industry (Ahmad et al., 2021; Burridge et al., 2010; Reverter et al., 2020; Schar et al., 2020), we assumed that all the global production is from factory farming (Figure 1.5).

Regions	Poultry (%)	Pigs (%)	Cattle (%)
East Asia and the Pacific	79	69	42
Europe and Central Asia	86	74	65
Latin America and the Caribbean	64	17	34
Middle East and North Africa	57	6	34
Northern America	100	98	70
South Asia	30	8	34
Sub-Saharan Africa	29	21	34

Table 1.5 % share of factory farming in the regional production of the selected terrestrial species (yearly average 2018-20).

(Elaboration of data from different sources)

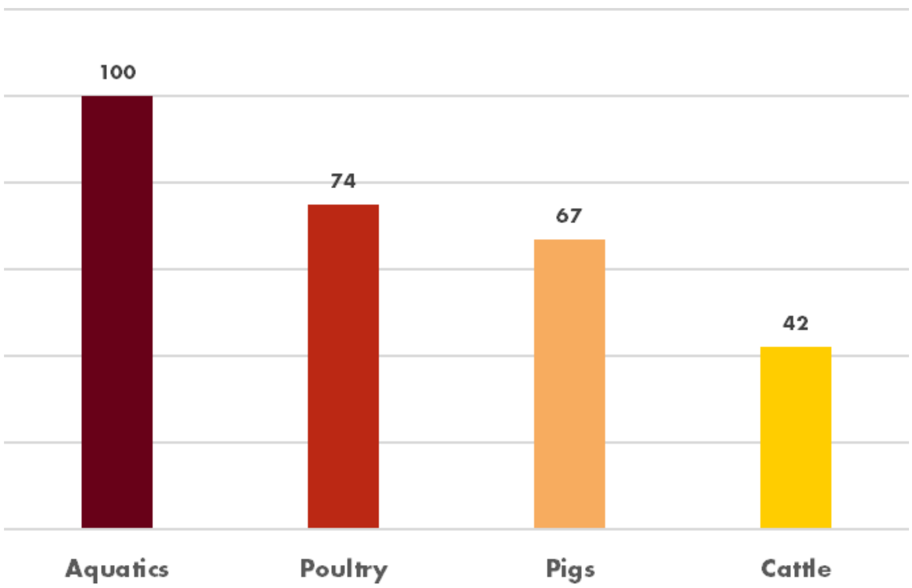


Figure 1.5 % share of factory farming in the global production of the selected species (yearly average 2018-20), (elaboration of data from different sources).

Step 3: Determining the amount of antibiotics consumed globally by humans and farmed animals

1.6. Antibiotic use in humans

The Defined Daily Dose (DDD) is a unit of measure defined by the WHO Collaborating Centre for Drug Statistics Methodology (WHOCCDSM) commonly used for statistics on drug consumption by human populations. According to the WHO, "the DDD is the assumed average maintenance dose per day for a drug used for its main indication in adults" (WHOCCDSM, 2021). This metric allows to analyse changes in drug utilization over time, make international comparisons on drug consumption, evaluate the effect of an intervention on drug use, document the relative therapy intensity with various groups of drugs, follow the changes in the use of a class of drugs, evaluate regulatory effects and effects of interventions on prescribing patterns (Hutchinson et al., 2004; WHO, 2022a).

We collected information for the analysis of human antibiotic usage, in DDD for 1,000 inhabitants, from the Center for Disease Dynamics, Economics & Policy (CDDEP) database reporting data from 2000 to 2015 and for the year 2020 from 67 countries distributed over the seven identified world regions. For the countries of the same region, we calculated the average consumption of the available years and the regional average.

Table 1.6 shows the results of seven regions and the global average: between 2000 and 2015, the average global annual consumption of antibiotics was 6,364 DDD per 1,000 inhabitants: major consumers were North America, Europe and Central Asia, and the Middle East and North Africa. However, from 2000 to 2015, the annual consumption decreased by 1.02% per year in North America, while it rose by 1.46% in Europe and Central Asia. The other regions that significantly increased consumption over that period were: East Asia and the Pacific, Sub-Saharan Africa and the Middle East and North Africa. The global average of the annual increase was 3.66%.

Image: Envato stock

Regions	Annual average consumption (DDD/1,000 inhab.)	Average annual variation (%)
East Asia and Pacific	6956.76	7.48
Europe and Central Asia	8226.14	1.46
Latin America and Caribbean	4022.28	3.37
Middle East and North Africa	7236.17	5.03
North America	9600.66	-1.02
South Asia	4327.78	2.3
Sub Saharan Africa	4179.16	6.98
Global average	6364.14	3.66

Table 1.6 Human consumption of antibiotics in world regions and globally (2000-2015 annual average consumption).

(Own elaboration from CDDEP, 2021)

The countries that utilized the most antibiotics were the USA, Turkey, Tunisia, South Korea, Pakistan, and South Africa. The latter was the largest consumer country. Figure 1.6 shows the trend of the global average, including data of the year 2020: the graph indicates that also after 2015, antibiotic consumption worldwide continued to rise (+15.1% in the global average between 2015 and 2020).

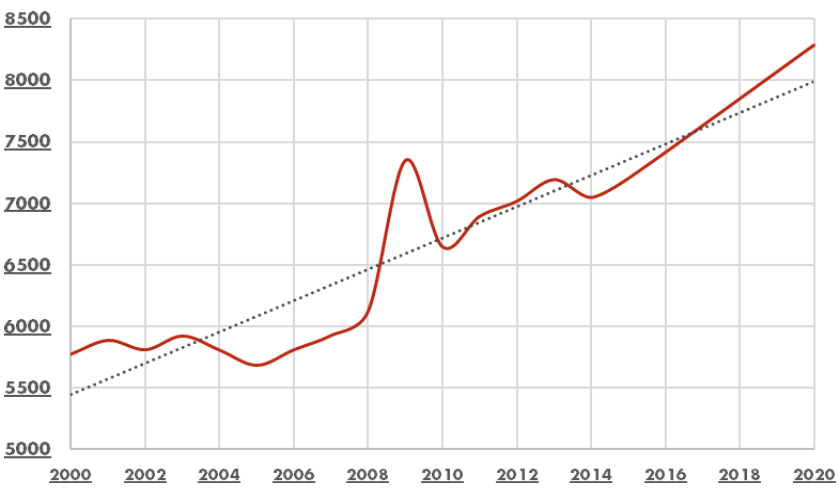


Figure 1.6 Trend in the calculated global average human consumption of antibiotics (DDD per 1,000 inhabitants), (Own elaboration from CDDEP, 2021)

1.7. Antibiotic use in farmed animals

The international statistics of AMU on farmed animals show national estimates of annual veterinary antimicrobial sales in mg of active principle per Population Correction Unit (PCU). The active principle is the constituent of an antimicrobial drug that determines its therapeutic effect. The PCU is an indicator of the animals' weight at treatment. PCUs are calculated by multiplying the numbers of animals by the theoretical weight at the time most likely for treatment (Average Weights at Treatment or AWT). Therefore, the statistics indicate the quantity of antimicrobial substance sold in one year per kg of animal standard live weight (or biomass) at treatment present in a country (EMA, 2011).

The CCDEP online database reports country data on AMU on farmed animals in 2013 and projections to 2030 (drawn from Van Boeckel et al., 2015). We aggregated these data at the regional level and calculated the regional averages reported in Table 1.7.

Regions	AMU mg/PCU (2013)
East Asia and the Pacific	97
Europe and Central Asia	58
Latin America and the Caribbean	57
Middle East and North Africa	61
North America	104
South Asia	39
Sub Saharan Africa	54

Table 1.7 Calculated regional averages of AMU on farmed animals in 2013.

(Own elaboration from CDDEP, 2021)

According to this source, major consumer countries of veterinary antibiotics in 2013 were China, South Korea, Spain, and Italy, while Sweden, Norway, New Zealand, Slovenia, and Finland were the countries that used less antibiotics for animal treatments. Global estimations on AMU on farmed animals are published annually by the WOAH based on information on sales of veterinary antibiotics collected from national governments (WOAH, 2022).

The last WOAH report estimated the amount of global antibiotic sales in 76,704 tonnes of active principle in 2018 (data from 109 countries): 58.2% of this amount was from 22 countries in Asia, the Far East and Oceania. The sales relative to the theoretical weight of treated animals resulted in 95.74 mg/PCU at the global level, with relevant differences between the WOAH regions (Table 1.8).

WOAH regions	Total sales (tonnes)	% Distri-bution	mg/PCU
Africa	1,477	1.9	20.78
Americas	22,887	29.8	96.29
Asia, Far East and Oceania	44,621	58.2	125.97
Europe	7,674	10.0	56.88
Global	76,704	100.0	95.74

Table 1.8 WOAH estimations on global sales of antimicrobials for farmed animals in 2018*.

* Data on total sales are from 24 countries in Africa, 19 in the Americas, 22 in Asia, the Far East and Oceania, 41 in Europe, and 109 globally (for three countries of the Middle East, data were not validated for the regional analysis). Data on mg/PCU are from 24 countries in Africa, 17 in the Americas, 21 in Asia, Far East and Oceania, 41 in Europe, and 106 globally (WOAH, 2022).

The last WOAH report also shows a historical series on global antibiotic sales per PCU over the 2016-2018 period in 72 countries. These data, which cover 65% of global animal biomass, indicate a decrease in global AMU by 28% over the period (Table 1.9).

These data appear encouraging; however, the WOAH warns that, because of the modality of the survey, they should not be considered representative of the antimicrobials consumed in any world region or country.

In 2009 the European Medicine Agency (EMA) launched a project on European Surveillance of Veterinary Antimicrobial Consumption (ESVAC) to develop a harmonised collection and reporting of data on AMU in animals in Europe. The ESVAC started publishing the results of its surveys on European sales of veterinary antimicrobials in 2011 (EMA, 2011) and currently collects data from 31 countries (EMA, 2022a). According to EMA estimations, between 2011 and 2021, the sales of veterinary antibiotics in Europe decreased from 161.9 to 86.2 mg of active principle per PCU, declining by 46.8%.

Year	Antibiotic sales (mg/PCU)	Variation from 2016 (%)
2016	128.85	-
2017	114.44	-11.2
2018	92.81	-28.0

Table 1.9 WOAH estimations on the trend in global sales of antimicrobials for farmed animals relative to animal weight at treatment*.

* Data from 12 countries in Africa, 9 in the Americas, 15 in Asia, the Far East and Oceania, 35 in Europe, 1 in the Middle East, and 72 globally (WOAH, 2022).

A problem of both the WOAH and the EMA surveys is that they report overall sales of veterinary antibiotics in a country or region relative to the total animal AWT but do not provide data on the use of antibiotics on specific farmed species. In the coming years, with the progressive implementation of the new European legislation on veterinary medicines, the EMA will start a systematic collection of AMU data by animal species and switch to providing statistics based on actual farm consumption and not on sales (EMA, 2022b).

Estimations of global AMU relative to the animal weight at treatment in 2017 were published by Tiseo et al. (2020) for farmed terrestrial species and by Schar et al. (2020) for farmed aquatic species. The results of these estimations for the species selected by our study are presented in Figure 1.7 and Figure 1.8.

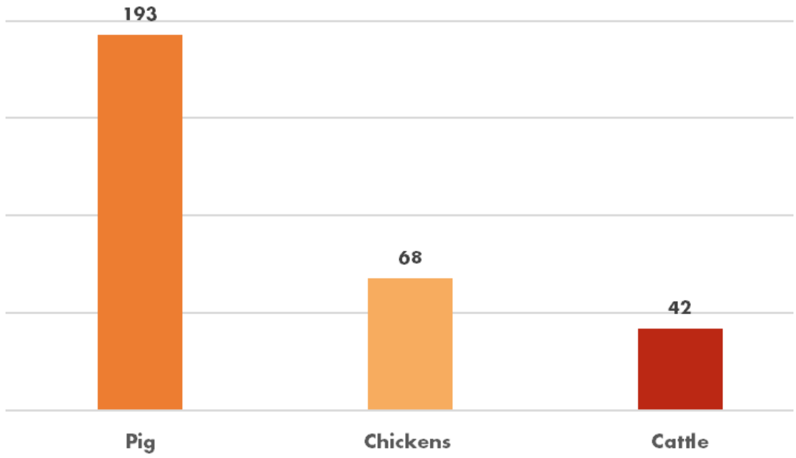


Figure 1.7 Global AMU relative to animal weight at treatment in selected farmed terrestrial species in 2017 (mg of active principles per kg of animal weight) (Tiseo et al., 2020).

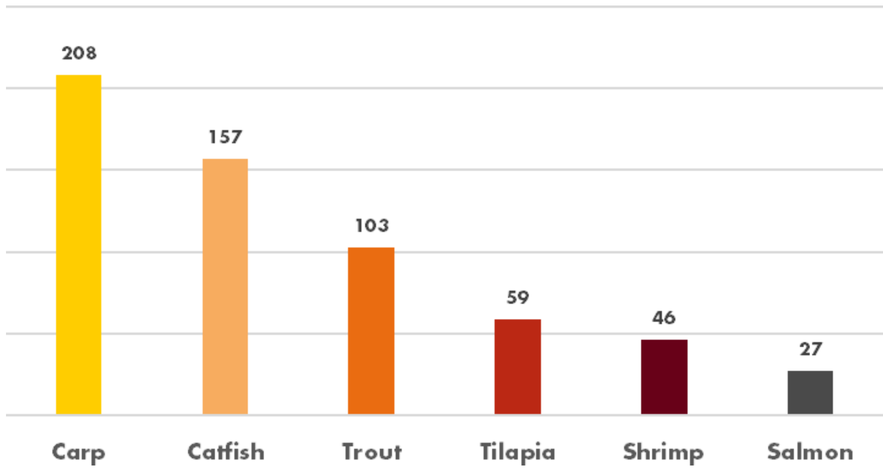


Figure 1.8 Global AMU relative to animal weight at treatment in selected farmed aquatic species in 2017 (mg of active principles per kg of animal weight) (Schar et al., 2020).

Image: Dairy cattle in India. Credit: World Animal Protection

1.8. Estimation procedure

To estimate global AMU on factory farms, first, we calculated regional and the global PCUs of the selected farmed animal species based on the animal AWT defined by EMA (EMA, 2011) and the heads defined in Section 1.4. The factory farms' shares on regional and global PCUs were assessed based on the percentages set in Section 1.5. Then, for each species, we multiplied the AMU in mg/PCU resulting from Tiseo's and Schar's evaluations (Figure 1.7 and Figure 1.8) by the regional and the global factory farm PCUs. For the selected aquatic species, we assumed that the PCUs were equal to the total production in kg, and all production was attributed to factory farms (see Section 1.5). Table 1.10 summarises the coefficients that were assumed to estimate regional and global AMU on the selected species.

Farmed animal species	AMU (mg/PCU)	AWT (Kg/head)
Cattle	42	425
Pigs	193	65
Poultry	68	1
Carp	208	*
Catfish	157	*
Salmon	27	*
Shrimp	46	*
Tilapia	59	*
Trout	103	*

Table 1.10 Assumed coefficients of AMU per PCU and AWT to estimate regional and global AMU on the selected species.

* For aquatic species, PCUs were assumed to equal the weight of total production.

(Own elaboration from different sources, see Section 1.8)

1.9. Global use of antibiotics on terrestrial species in factory farms

1.9.1. Global use of antibiotics on poultry in factory farms

Based on the procedure detailed in Section 1.8, Table 1.11 shows the annual average poultry PCUs and AMU in factory farms for poultry production over the 2018-2020 period. In this livestock sector, East Asia and the Pacific used the most antibiotics (38%), followed by North America (23%) and Latin America and the Caribbean (12%). The principal consumer countries are China, the USA, and Brazil. The estimated total annual AMU in poultry farming amounted to 7,928 tonnes of antibiotic active principles, of which 5,902 tonnes (74%) were in factory farms (Figure 1.9).

Regions	PCUs (000)	AMU (tonnes)
East Asia and the Pacific	33,046,612	2,247
North America	20,304,890	1,381
Latin America and the Caribbean	10,735,022	730
Europe and Central Asia	14,113,386	960
Middle East and North Africa	4,932,272	335
South Asia	2,369,922	161
Sub-Saharan Africa	1,288,263	88
World	86,790,367	5,902

Table 1.11 Estimated PCUs and AMU in poultry factory farms by region and globally (annual average 2018-2020)

(Own elaboration from different sources, see Section 1.8)

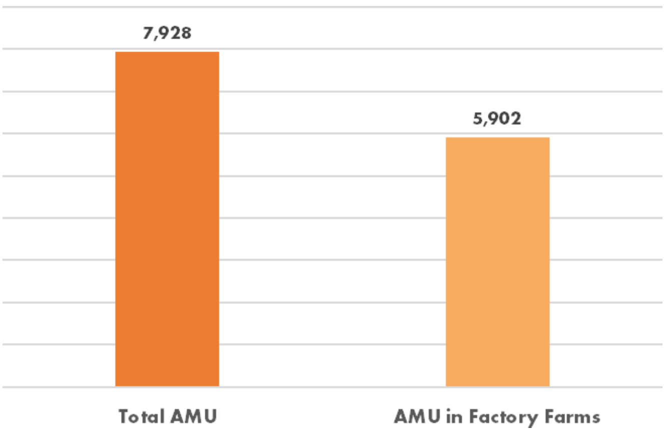


Figure 1.9 Estimated total AMU in global poultry production and in poultry factory farms (tonnes of active principles, annual average 2018-2020) (Own elaboration from different sources, see Section 1.8).

1.9.2. Global use of antibiotics on pigs in factory farms

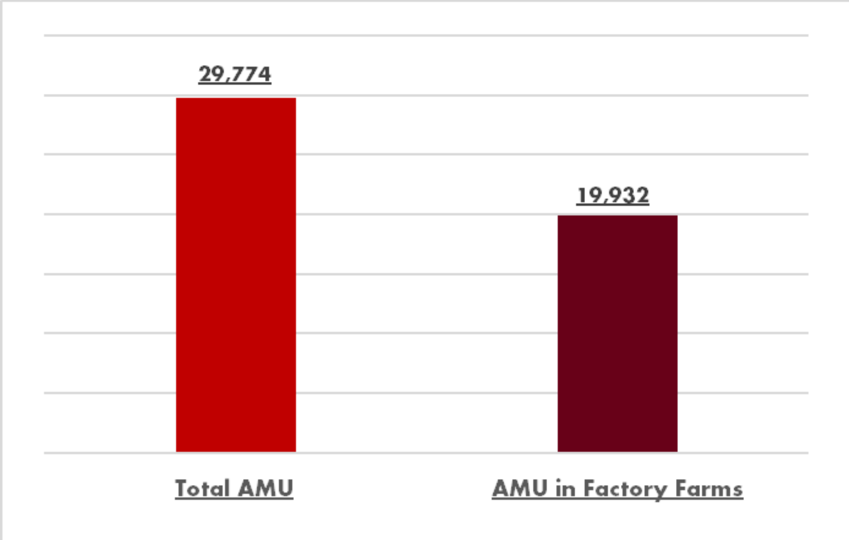
Table 1.12 shows the annual average pig PCUs and AMU in factory farms for pig production over the 2018-2020 period. In this livestock sector, East Asia and the Pacific used the most antibiotics (57%), followed by Europe (25%) and North America (15%). The main consumer countries are China, Germany, and the USA. The estimated total annual AMU in pig farming amounted to 29,774 tonnes of antibiotic active principles, of which 19,932 tonnes (67%) were in factory farms (Figure 1.10).

Regions	PCUs (000)	AMU (tonnes)
East Asia and the Pacific	58,991,883	11,385
Europe and Central Asia	25,460,436	4,914
North America	15,436,259	2,979
Latin America and the Caribbean	2,179,931	421
Sub-Saharan Africa	1,086,246	210
South Asia	113,919	22
Middle East and North Africa	5,325	1
World	103,273,999	19,932

Table 1.12 Estimated PCUs and AMU in pig factory farms by region and globally (annual average 2018-2020)

(Own elaboration from different sources, see Section 1.8)

Figure 1.10 Estimated total AMU in global pig production and in pig factory farms (tonnes of active principles, annual average 2018-2020) (Own elaboration from different sources, see Section 1.8).



1.9.3. Global use of antibiotics on cattle in factory farms

Table 1.12 shows the annual average cattle PCUs and AMU in factory farms for cattle production over the 2018-2020 period. In this livestock sector, East Asia and the Pacific used the most antibiotics (21%), followed by Sub-Saharan Africa (18%) and South Asia (15%). The estimated total annual AMU in cattle farming amounted to 37,006 tonnes of antibiotic active principles, of which 19,932 tonnes (42%) were in factory farms (Figure 1.11).

Regions	PCUs (000)	AMU (tonnes)
Latin America and the Caribbean	76,951,581	3,232
Europe and Central Asia	75,077,817	3,153
Sub-Saharan Africa	65,402,998	2,747
South Asia	54,832,062	2,303
North America	45,875,489	1,927
East Asia and the Pacific	45,186,779	1,898
Middle East and North Africa	5,463,598	229
World	368,790,324	15,489

Table 1.13 Estimated PCUs and AMU in cattle factory farms by region and globally (annual average 2018-2020)

(Own elaboration from different sources, see Section 1.8)

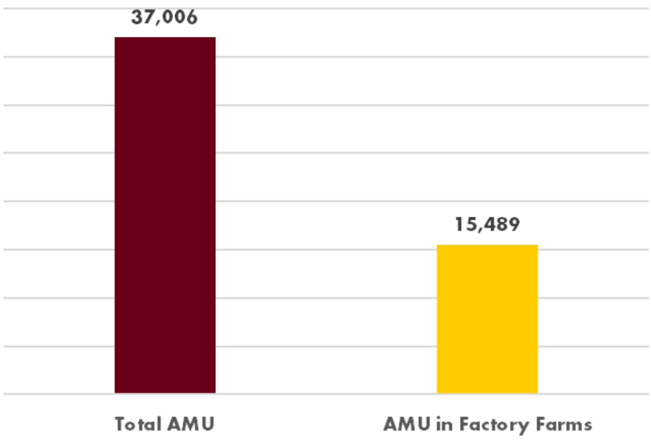


Figure 1.11 Estimated total AMU in global cattle production and in cattle factory farms (tonnes of active principles, annual average 2018-2020) (Own elaboration from different sources, see Section 1.8).

1.10. Global use of antibiotics on aquatic species in factory farms

Table 1.14 shows the annual average PCUs of the selected aquatic species and the respective AMU over the 2018-2020 period. In this sector, 100% of global production was attributed to factory farms, and global AMU resulted in 5,834 tonnes of antibiotic active principles. Most antibiotics were used in carp, catfish, and tilapia production. China alone produced more than 50% of the selected aquatic species and was the principal antibiotic consumer of this industry.

Table 1.14 Estimated global PCUs and AMU on selected aquatic species (annual average 2018-2020)

(Own elaboration from different sources, see Section 1.8)

Species	PCUs (000)	AMU (tonnes)
Carp	19,376,757	4,030
Catfish	6,007,475	943
Tilapia	6,166,596	364
Shrimp	7,019,773	323
Trout	944,386	97
Salmon	2,827,840	76
Total	42,342,826	5,834

Image: Fish farm in Malaysia where fish are farmed in high densities. Credit line: World Animal Protection.

1.11. Synthesis of results

Table 1.15 shows the global AMU on the selected farmed animals and the part attributed to factory farms estimated by this study as the annual average for the 2018-2020 period. Global AMU resulted in 80,542 tonnes of antibiotic active principles, of which 47,157 tonnes, or 58.5% consumed in factory farms. 87.6% of factory farms' AMU was administered on terrestrial species: pigs 42.3%, cattle 32.8%, and poultry 12.5%. Aquatic species consumed 12.4% of total factory farms' AMU.

Farmed animals	Global AMU (tonnes)	AMU in Factory Farms (tonnes)
Terrestrial species	74,708	41,323
- Cattle	37,006	15,489
- Pigs	29,774	19,932
- Poultry	7,928	5,902
Aquatic species	5,834	5,834
Total	80,542	47,157

Table 1.15 Estimated global AMU in tonnes of active principles (annual average 2018-2020)

(Own elaboration from different sources, see Section 1.8)

2. HOW MUCH ANTIBIOTICS ARE ADMINISTERED IN FACTORY FARMS FOR NON-THERAPEUTIC TREATMENTS?

This chapter aims to determine the amounts of antibiotics used in factory farming for non-therapeutic purposes (step 5): i.e., prophylaxis, metaphylaxis, and use as Antibiotic Growth Promoters (AGP). We applied two methods: the first used the information available in the scientific literature, and the second compared the use of antibiotics in organic and non-organic farms. Both gave similar results.

Image: Antibiotics are extensively used in factory farming to promote fast growth or to prevent animals getting sick. Credit: KOOKLE/Shutterstock.

2.1. On the relevance of limiting non-therapeutic treatments on farmed animals

Veterinary therapeutic use of antibiotics implies that treated animals show clinical symptoms of infections or sickness. The utilization of antibiotics for metaphylaxis, prophylaxis, and as AGP is considered non-therapeutic (AVMA, 2022; EMA, 2022b; Johnston, 1998; Tang et al., 2017; WHO, 2019, 2017a). Antibiotics are administered as metaphylactic treatments to groups of animals that do not show clinical symptoms of infections when they are in contact with infected animals to minimize the risk of disease spreading. Prophylactic treatments intend to prevent the spread of a disease before its symptoms appear in animals on the farm. The administration of antibiotics as AGP, usually with water or feed, aims to speed up animal weight growth, boost productivity, and lower sickness and death rates (Allen et al., 2013; Butaye et al., 2003; Getabalew et al., 2020).

AGP use in farmed animals creates public health concerns (WHO, 2019). The increasing global population and per capita income are driving a growing demand for products of animal origin, which is anticipated to nearly double in some countries by 2030 and will contribute to expanding antibiotic consumption in animal farming (Van Boeckel et al., 2015). Many antibiotics used in human health care are the same as or closely similar to those used on farmed animals (WHO, 2019).

The WHO recommends limiting the veterinary use of antibiotics critical to human health. The most obvious path toward resistant microbial strains that endanger human health would seem to be the use of medically necessary antibiotics as growth promoters (Hughes and Heritage, 2004). But around 90% of all antibiotics used in farmed animals are reportedly given at non-therapeutic concentrations, and a significant proportion of them are utilized as AGP (Hosain et al., 2021; Wu, 2018). Traces of antibiotics currently used on farmed animals can be found in water and soil due to overuse despite the increasingly tighter limits imposed on their usage (Robles-Jimenez et al., 2021). A WHO report published in 2017 noted that the use of antibiotics in farmed animals in several countries accounted for approximately 80% of all antibiotic consumption, primarily to promote the growth of healthy animals (WHO, 2017a).

To maintain the efficacy of antibiotics critical for human treatments, the WHO asks farmers to stop routinely using antibiotics to boost growth and prevent diseases in healthy animals. When choosing antibiotics for use in animals, the WHO recommends the “least important” to human health rather than those defined as “critically important antimicrobials” (CIAs). The WHO urges a general decrease in the use of CIAs in farmed animals and to phase out AGP use and limit the other non-therapeutic treatments (WHO, 2018, 2017a).

2.2. AMU on farmed animals by antibiotic class

According to the 6th WOAH report on “Antimicrobial Agents Intended for Use in Animals”, 109 countries responding to the survey reported sales of 69,455 tonnes of antibiotics for use on animals (including terrestrial and aquatic farmed animals, and companion animals) in 2018. On this basis, taking into consideration the coverage of the survey in the respondent countries, the WOAH estimated 76,704 tonnes of total antibiotic sales in 2018, as mentioned in Section 1 (WOAH, 2021).

Table 2.1 shows the distribution of the sales in volume by antibiotic class. The table also indicates the classes that may include antibiotics classified by the WHO as CIAs, “Highly Important Antimicrobials” (HIAs), and “Important Antimicrobials” (IAs). WHO defines CIA as an antimicrobial class that is the sole, or one of limited available therapies, to treat serious bacterial infections in people, or is used to treat infections in people caused by bacteria that (condition 1) may be transmitted to humans from non-human sources, or (condition 2) may acquire resistance genes from non-human sources. HIAs are antimicrobial classes used in humans which meet the conditions (1) and (2) of CIAs but not both. IAs are antimicrobial classes used in humans which do not meet any of the CIAs’ conditions (WHO, 2018). The table shows that many antibiotics used on farmed animals may belong to CIA or HIA categories.

Classes	% of the total sales volume reported
Tetracyclines**	40.5
Penicillin***	14.1
Macrolides***	8.8
Polypeptides	7.3
Sulfonamides**	5.1
Amphenicols**	4.9
Aminoglycosides***	4.0
Pleuromutilin*	2.5
Fluoroquinolones	2.3
Quinoxalines	2.0
Lincosamides**	1.9
Glycophospholipids	0.4
Cephalosporins 3-4 gen.***	0.5

Table 2.1 Distribution of the global sales of veterinary antibiotics by antibiotic class in 2018 (109 countries)

*** The class may include CIAs; ** the class may include HIAs;

* the class may include IAs (WHO, 2018; WOAH, 2022)

In 2018, in the 109 countries of the survey, Tetracyclines accounted for 40.5% of the total sale volume of veterinary antibiotics, followed by penicillins (14.1%), macrolides (8.8%), polypeptides (7.3%), sulfonamides (5.1%), amphenicols (4.9%), aminoglycosides (4.0%). The agents reported in the table covered more than 94% of the total volume of veterinary antibiotic sales.

2.3. The non-therapeutic uses of antibiotics

Intensive animal farming introduced AGP in husbandry practices early after the discovery of antibiotics (Hughes and Heritage, 2004). However, in the 1950s, international concern over antibiotic residues in food and AMR proliferation started to rise, and in the early 1970s the first regulations were set in several countries. But in most States, this was not considered a priority compared to cost reduction in food production (Kirchhelle, 2018). In 1986, Sweden was a pioneer in outlawing AGP use on farmed animals twenty years before the EU ban (Cardinal et al., 2021). The EU gradually phased out AGP between 2003 and 2006, but it was difficult to determine how much it influenced the overall antibiotic use in farms, since most EU countries did not monitor AMU. For instance, after the AGP outlawing in the Netherlands, one of the few countries collecting AMU statistics, total antibiotic sales initially maintained their upward trajectory: this because farmers expanded AMU for prophylaxis, replacing a large portion of previous AGP usage (Mevius and Heederik, 2014; Nunan, 2022). Since January 2022 in the EU, the new regulations on veterinary medicines and medicated feeds strongly limit other routine antibiotic uses. For example, prophylactic mass treatments are no longer allowed. These new rules imply that crucial organic norms on antibiotic usage now apply to all the EU farms: a significant step forward for antibiotic regulation on farmed animals in Europe (ASOA, 2021, 2019).

Since the European AGP ban, many other countries have phased out growth promoters. According to the WOAH's 2016 report, 96 of the 130 surveyed countries no longer permit AGP use (ASOA, 2017; Johnson, 2009; Robles-Jimenez et al., 2021). The AGP use of antibiotics relevant to human care has been banned in the USA since January 2017. However, numerous therapeutic doses of antibiotics used for short periods to treat, prevent, and control specific bacterial infections are still permitted (CIDRAP, 2020).

AGPs treatments are still a farming practice in many countries, despite the risks related to AMR spreading (Muurinen et al., 2021). According to some authors, the principal users of antibiotics in farms in 2030 will be large meat-producing countries that in many cases have not banned AGP (Okocha et al., 2018; Robles-Jimenez et al., 2021).

The laws on AGP use have weak enforcement in the USA, Canada, Australia, and New Zealand: for instance, some restrictions are only voluntary. In many countries that have restricted or banned AGPs, it is still possible to carry out many routine prophylactic treatments. A study on the Belgian pig industry revealed that 93% of mass medication instances were prophylactic. However, six EU countries (Denmark, Finland, Iceland, Norway, Sweden, and the Netherlands) had already discontinued group prophylactic treatments before the recent European ban (ASOA, 2017).

An analysis of the proportion of antibiotics used for group treatments and individual treatments reveals the various approaches to the use of antibiotics in cattle in Europe. The proportions of antibiotics administered as premixes (medicated feed), oral powders, and oral solutions (in feed or water) among the 31 countries surveyed by the EMA-ESVAC project were respectively 22.5%, 7.4% and 57% in 2020. These products are mainly used for group therapies, according to the EMA. The proportion of veterinary antibiotics used for group treatments varies significantly amongst countries. Group treatments are used in 1.3%, 9.1%, and 10.9% of cases in Iceland, Norway, and Sweden, respectively, but for 96%, 94.9%, 93.7%, and 93.4% of treatments in Cyprus, Hungary, Portugal, and Poland, respectively (Nunan, 2022).

Unfortunately, no breakdown of treatments into those that are purely prophylactic versus metaphylactic is provided in the EMA-ESVAC reports or national reports on farm antibiotic use. There is also very little information on this topic in the scientific literature. The countries that use veterinary antibiotics for group treatments at a disproportionately high rate are also likely to use veterinary antibiotics at a disproportionately high rate overall (Nunan, 2022). In Ireland, oral medication accounted for 38.1% of veterinary antibiotic sales in 2018, while premix sales were 29.2% (Martin et al., 2020). Sales of antibiotics for cattle decreased by 43% in Europe between 2011 and 2020 but it was as high as 60% in some countries (EMA, 2022a). Over the past five years, antibiotic use in livestock has decreased by 50% in the UK (ASOA, 2022). In the Netherlands, challenging goals for reducing antibiotic use in farmed animals were set in 2009, and all prophylactic group treatments were outlawed in 2011. Over the past ten years, the use of antibiotics decreased by almost 70% thanks to these limits (Nunan, 2022).

Image: Pigs are amongst the most intensively farmed animals on the planet. Credit: World Animal Protection.

In other parts of the world, rates of non-therapeutic use are more worrying. More than 60% of farmers in South Asian countries, like India and Bangladesh, use antibiotics without a prescription (Manyi-Loh et al., 2018). Antibiotics are administered to cattle in Uganda at rates of 40% and 3.3% for prophylaxis and AGP, respectively (Mikecz et al., 2020).

In the USA, according to the USDA (2015), between 40% and 62% of pigs were given AGP, 51% received antibiotics to prevent disease, and 90% of all antibiotics were administered for non-therapeutic uses. A survey revealed that the majority of antibiotics marketed in the USA were for use in animal feed and water (CIDRAP, 2020; USDA, 2015). The use of injectable antibiotics, usual for metaphylaxis protocols, accounted for 4% of all antibiotic sales and distribution in the USA cattle farming. The most widespread use of antibiotics is in feed and water, which accounts for 74% and 22% of total sales, respectively (Dennis et al., 2018).

Antibiotic use in China, in mg per PCU, is more than five times greater than the global average. The widespread use linked to growth promoters in feed and veterinary use on farms is one of the key causes of the relatively higher consumption. A lack of veterinarian support and direction at the farm level is also partially responsible for excessive veterinary antibiotics utilization. According to the ministerial bulletin in China, 53% of antibiotics used by farmers in 2018 were for AGP (OECD, 2019; Schoenmakers, 2020). China banned the AGPs in July 2020, however, there are fears that this is leading to increased use of therapeutic and other type of group treatments (Wen et al., 2022).

Step 5: Estimating the amount of antibiotics used for non-therapeutic treatments

2.4. Estimations of non-therapeutic antimicrobial use on farmed animals

To estimate the global proportions and volumes of antibiotics used for non-therapeutic purposes in farmed animals, data were collected from the scientific literature (method 1) and reported in Table B1 in Appendix B. Another technique to estimate the non-therapeutic use of antibiotics is to compare the percentages of antibiotics used in intensive farming systems with the use of antibiotics in organic and less intensive agricultural systems (Zwald et al., 2004). A core element of organic farming is the avoidance of frequent preventative treatment in favour of good husbandry practices, the use of suitable breeds, and a healthy diet. For instance, four times fewer antibiotics are used on organic farms in the UK than the national average. Non-organic pig farms in Denmark use almost ten times more antibiotics than organic pig farms (ASOA, 2021).

Table 2.2 shows the percentages of non-therapeutic antibiotics used for each region using method 1: 86.90% of antibiotics are administered for non-therapeutic purposes in Europe and Central Asia. In Sub-Saharan Africa, data available for Uganda were used as a proxy to demonstrate that 46% of antibiotics are for non-therapeutic purposes. In North America, 94% of antibiotics are used for non-therapeutic purposes assuming that Canada applies the same antibiotic use as the USA.

Assumptions were also made for other regions for which we did not find data on antibiotic use in the literature: i.e., East Asia and the Pacific, Latin America and the Caribbean, and the Middle East and North Africa. These assumptions were based on the percentages of antibiotic use found in developing countries in South Asia, where 90% of antibiotics administered are for non-therapeutic treatments. The analysis finds that an average of 84% of antibiotics globally utilized in farms are for non-therapeutic purposes.

Regions	% of non-therapeutic AMU on total
East Asia and the Pacific	90.00
Europe and Central Asia	86.90
Latin America and the Caribbean	90.00
Middle East and North Africa	90.00
Northern America	94.00
South Asia	90.00
Sub-Saharan Africa	46.00
Global average	84.22

Table 2.2 Estimation of the share of non-therapeutic AMU on the total AMU on farmed animals found in the scientific literature for the different world regions and global average (method 1).

(Own elaboration from different sources)

Method 2 used available data from the UK comparing antibiotic use on organic and non-organic farms to estimate the percentage of non-therapeutic antibiotic use. (ASOA, 2021). Table B2 of Appendix B shows the quantity of antibiotics used in the United Kingdom (UK) on organic and non-organic farms by species.

Table 2.3 displays the proportions of non-therapeutic antibiotics based on the information of Table B2: column 1 of Table 2.3 contains literature information (Tiseo et al., 2020) about the total amount of antibiotics used (in mg per kg of liveweight at treatment or PCU) in non-organic farming. Column 2 shows that non-organic farms use antibiotics more frequently than organic farms, based on the UK situation. By dividing column 1 by column 2, column 3 calculates the overall antibiotic usage (mg per PCU) on organic farms, while column 4 calculates the non-therapeutic use (mg per PCU) on non-organic farms (column 1 - column 3). The percentages of non-therapeutic antibiotics used in non-organic farms are determined in column 5 by dividing the outcomes of column 4 by column 1, then multiplying the result by 100. This method is based on the following assumptions:

- all the AMU in organic animal farms is exclusively for therapeutic treatments;
- all the AMU in conventional animal farms that exceeds the quantity used in organic farms is for non-therapeutic treatments.

Based on these two methods, we inferred that more than 80% of overall AMU on factory farms is for non-therapeutic purposes. Figure 2.1 shows the total amount of antibiotics used worldwide in factory farming for non-therapeutic purposes.

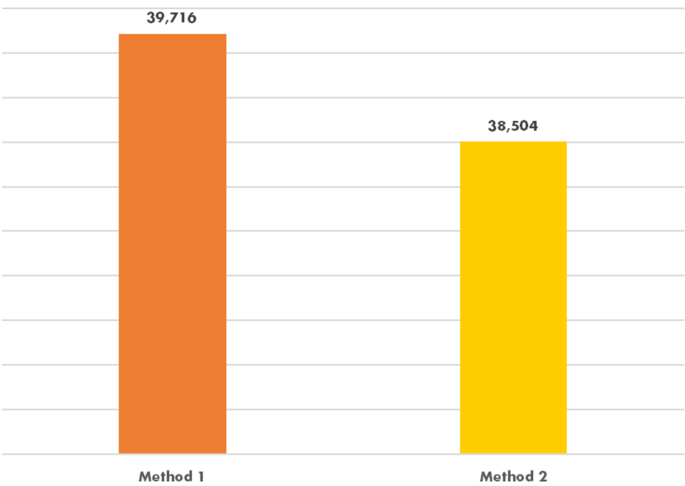


Figure 2.1 Estimated AMU for non-therapeutic treatments in factory farms (tonnes of active principles - annual average 2018-2020), (Own elaboration).

The amount was calculated by multiplying the estimated proportions of antibiotics used for non-therapeutic purposes from method one (84.22%) and method two (81.65%) by the overall AMU on factory farms that we estimated in Chapter 1 (47,157 tonnes).

Species	AMU in non-organic farming (global data)(mg/PCU) (1)	AMU in non-organic farms / AMU in organic farms (data from the UK) (2)	AMU in organic farming (mg/PCU) (3) = (1)/(2)	Non-therapeutic AMU in non-organic farming (4) = (1) - (3)	Percentages of non-therapeutic AMU in non-organic farming (5) = (4) x 100 / (1)
Poultry	68	5.76	11.81	56.19	82.63
Pig	193	77.46	2.49	190.51	98.71
Cattle	42	2.75	15.28	26.72	63.62
Average	-	-	-	-	81.65

Table 2.3 Estimation of the share of non-therapeutic AMU on the total AMU on farmed animals based on data on AMU in UK organic farms (method 2).

(Own elaboration from: Tiseo et al., 2020; and ASOA, 2021)

3. HOW DOES ANTIMICROBIAL USE ON FACTORY FARMS IMPACT THE SPREAD OF ANTIBIOTIC-RESISTANT INFECTIONS ON THE HUMAN POPULATION?

This chapter covers Step 6 of the study. We collected information on the pathogens causing antibiotic-resistant infections in humans from food of animal origin to investigate the links between the use of antibiotics on farmed animals and the spread of AMR in the human population. Then, we developed a statistical model to identify the main variables of AMR insurgence along the food supply chain.

Step 6: Investigating links between the use of antibiotics in factory farms and the spread of resistant infections in humans

3.1. Antibiotic use on farmed animals and AMR spreading

A rising number of infections are becoming harder to cure, and in some cases impossible, as antibiotics lose their effectiveness (Silbergeld et al., 2008). The WHO indicates AMR as one of the major global hazards to public health (AMR Collaborators, 2022). Resistant bacteria can harm human health directly or transferring AMR to other bacteria. Several authors highlight the interconnectedness between human and animal health, and laboratory evidence demonstrated that AMR spread from animals and the environment to humans (Economou and Gousia, 2015; Mencía-Ares et al., 2021; Mitchell et al., 2021; Pinto Ferreira, 2017; Ramos-Tanchez, 2021).

Although AMR is a natural phenomenon, the growing consumption of antibiotics for use on humans and

animals drives its rapid increase. Factory farming contributes to AMR spread through the massive use of antibiotics that has become part of its husbandry practices (Aarestrup, 2015; Economou and Gousia, 2015; Mencía-Ares et al., 2021; Mitchell et al., 2021).

The prolonged and extensive use of antibiotics on farmed animals can increase the risk of resistant infections in humans. It may occur through the spread of resistant germs across the food supply chain, and through direct and indirect contact with animals (Emes et al., 2022; Landers et al., 2012; Mencía-Ares et al., 2021; Van Boeckel et al., 2015, 2017).

Many scientists agree that the inappropriate use of antibiotics in farmed animals is related to the spread of

AMR. The global antibiotic demand from the veterinary sector overcomes the one for human health care, and the gap may broaden due to increasing industrialization of animal farming, poor husbandry standards, high stocking densities, and low levels of animal health and welfare (Aarestrup, 2015; Okocha et al., 2018; Wegener, 2003).

Farmed animals can be important reservoirs for foodborne pathogens such as Escherichia coli,

Staphylococcus aureus, Campylobacter, and non-typhoidal Salmonella. Escherichia coli has been found in pigs, broiler chickens, and cattle, raising continued concerns about its spread in farmed animals. One of the most prevalent bacterial infections in both humans and animals is caused by Staphylococcus aureus. Campylobacter is one of the leading causes of foodborne disease worldwide and can be found in poultry, pigs, and cattle. Lastly, one of the most significant foodborne infections is salmonellosis, caused by Salmonella spp., for which poultry, cattle, and aquatics can act as reservoirs (Economou and Gousia, 2015)

Understanding the connection between antibiotic usage in farmed animals and resistant infections is crucial

for lowering the risk of ineffective therapies. There is a debate regarding the benefits and drawbacks of AMU farmed animals, even for non-therapeutic purposes. This debate is also fuelled by the uncertainties regarding the links between resistant infections in humans and AMR spread from animals and the environment, as well as the numerous factors that can influence AMR insurgence (Emes et al., 2022; Marshall and Levy, 2011; Okocha et al., 2018).

To gain insight on these connections, we collected data on resistant infections in humans caused by Escherichia coli, Staphylococcus aureus, Campylobacter, and non-typhoidal Salmonella. which are common bacteria affecting poultry, pigs, cattle, and aquatics. Then we developed a statistical model to identify the key variables that might influence the emergence of resistant infections from the selected bacteria in humans.

Image: Piglet in confinement conditions at undisclosed location in Latin America. Antibiotics are administered to piglets to promote fast growth, contributing to AMR. Credit: World Animal Protection

3.2. Resistant infections in humans

3.2.1. Data collection and processing

We collected data on the resistance of Escherichia coli and Staphylococcus aureus to the different antibiotics from the CDDEP online database for the years and the countries available between 2000 and 2018 (CDDEP, 2021), and data on Campylobacter and Salmonella resistance from the Surveillance Atlas of Infectious Diseases of the European Centre for Disease Prevention and Control (ECDC) for the years and the countries available from 2000 to 2020 (ECDC, 2021). A weighted average was calculated using the resistance percentages and the number of tests for isolates (total numbers of analysis done to test resistance for a specific bacterium in each country and year) and we obtained a global and regional estimate of the amount of bacterial resistance to the antibiotics. Table C1 in Appendix C presents the countries included in each region, the type of bacteria, and the number of isolate tests done. Table C2 shows the antibiotics used in farmed animals categorized as CIAs and HIAs for human health by the ResistanceBank for Livestock at CDDEP.

The ECDC classifies resistance to antibiotics into seven categories, from rare to extremely high. Figure 3.1 illustrates the level of resistance using ECDC colour coding. The brown colour indicates extremely high resistance to antibiotics (when resistance is greater than 70%), the pink colour very high resistance (more than 50% to 70%), the purple colour high resistance (more than 20% to 50%), the blue moderate resistance (more than 10% to 20%), the yellow low resistance (more than 1% to 10%), the orange very low resistance (more than 0.1% to 1%), and the light blue represents situations where resistance is less than 0.1%.

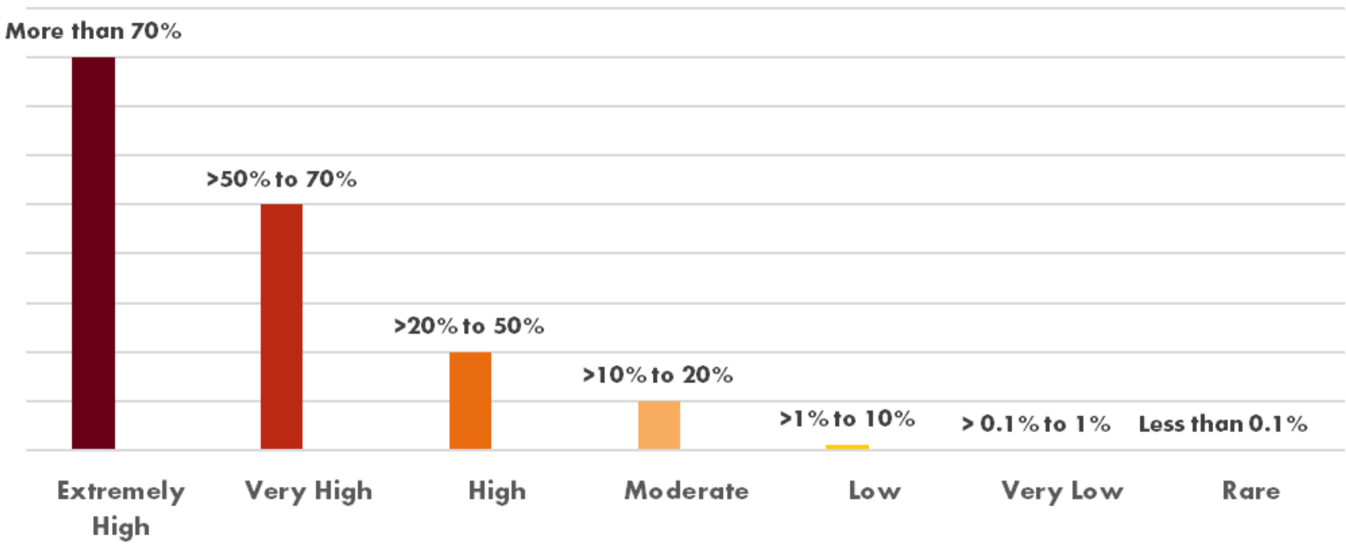


Figure 3.1 ECDC classification of the levels of AMR according to test positivity (ECDC, 2021)

3.2.2. Escherichia coli resistance to antibiotics

Escherichia coli may be resistant to many antibiotics, including aminoglycosides, amoxicillin-clavulanate, ampicillin-sulbactam, carbapenems, cephalosporins (3rd Gen), fluoroquinolones, glycylcyclines, macrolides, piperacillin-tazobactam, and polymyxins. Table 3.1 shows the estimated Escherichia coli resistance to each antibiotic by region. Interestingly, there was a 56% resistance to ampicillin-sulbactam in Vietnam and a 60% resistance to macrolides in India.

The resistance to all antibiotics is averaged out by region in Figure 3.2, with South Asia showing the highest rate (46%). Except for North America, in every region, high levels of antibiotic resistance were recorded for one or more than one antibiotic.

Figure 3.3 shows the antibiotic resistance rates of E. coli by antibiotic class. The data collected show that resistance is more common to aminopenicillins (73%). Escherichia coli resistance to all antibiotics is rising globally according to more than 7 million isolate tests (Figure 3.4). Between 2000 and 2018, resistance increased from about 27% to about 40% (high resistance) (CDDEP, 2021).

Antibiotics	East Asia and the Pacific	Europe and Central Asia	Latin America and the Caribbean	The Middle East and North Africa	North America	South Asia	Sub-Saharan Africa
Aminoglycosides	32.50	15.71	18.92	14.09	11.29	48.46	34.78
Aminopenicillins	78.18	61.90	76.37	80.22	48.66	89.62	78.04
Amoxicillin-clavulanate	27.81	46.65	39.85	-	20.45	65.36	56.90
Ampicillin-sulbactam	56.00	-	-	-	-	-	-
Carbapenems	4.63	0.97	1.06	8.33	0.02	9.30	13.50
Cephalosporins (3rd gen)	46.00	20.78	27.01	52.47	8.76	60.98	45.13
Fluoroquinolones	44.92	27.65	44.77	47.99	-	68.78	56.37
Glycylcyclines	1.68	-	0.33	-	-	1.09	0.00
Macrolides	-	-	-	-	-	60.00	-
Piperacillin-tazobactam	9.37	19.13	9.07	-	4.94	19.03	45.50
Polymyxins	1.44	-	0.49	11.07	-	36.78	0.49

Table 3.1 Escherichia coli resistance to antibiotics by region and antibiotic class (% values)

(Own elaboration from CDDEP, 2021)

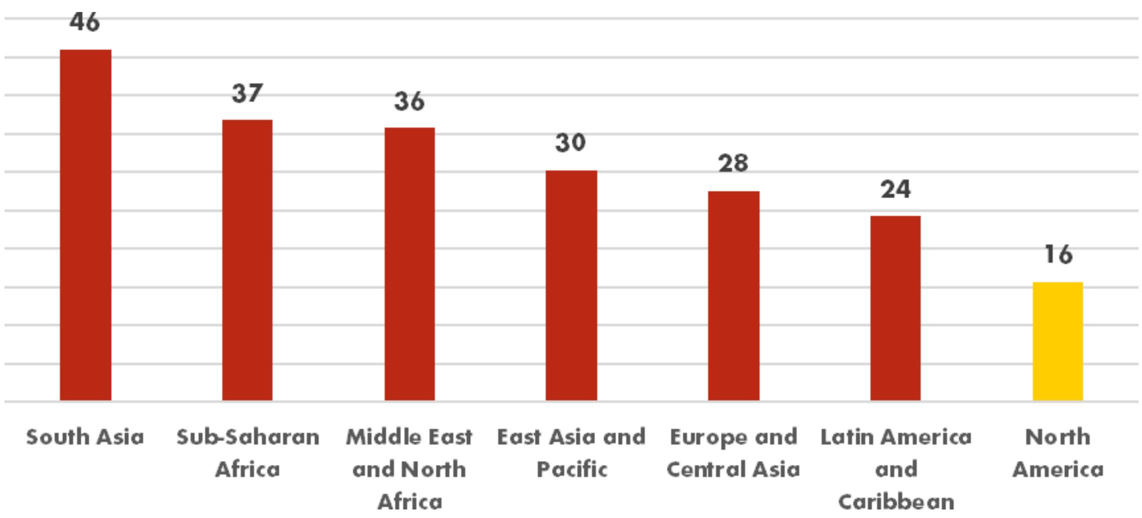


Figure 3.2 Escherichia coli resistance to all antibiotics by region (% values), (Own elaboration from CDDEP, 2021).

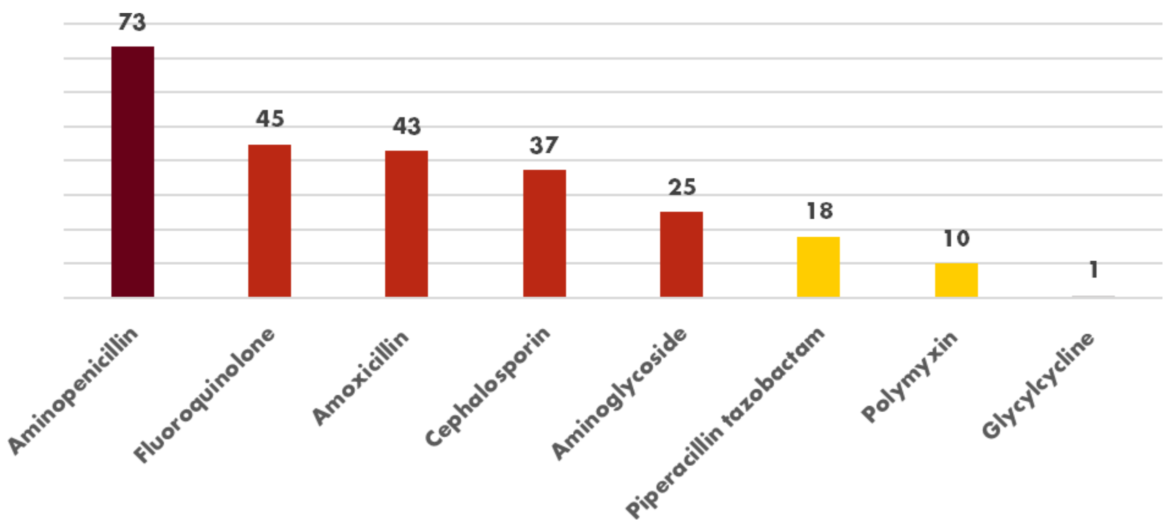


Figure 3.3 Escherichia coli global resistance to antibiotics by antibiotic class (% values), (Own elaboration from CDDEP, 2021).

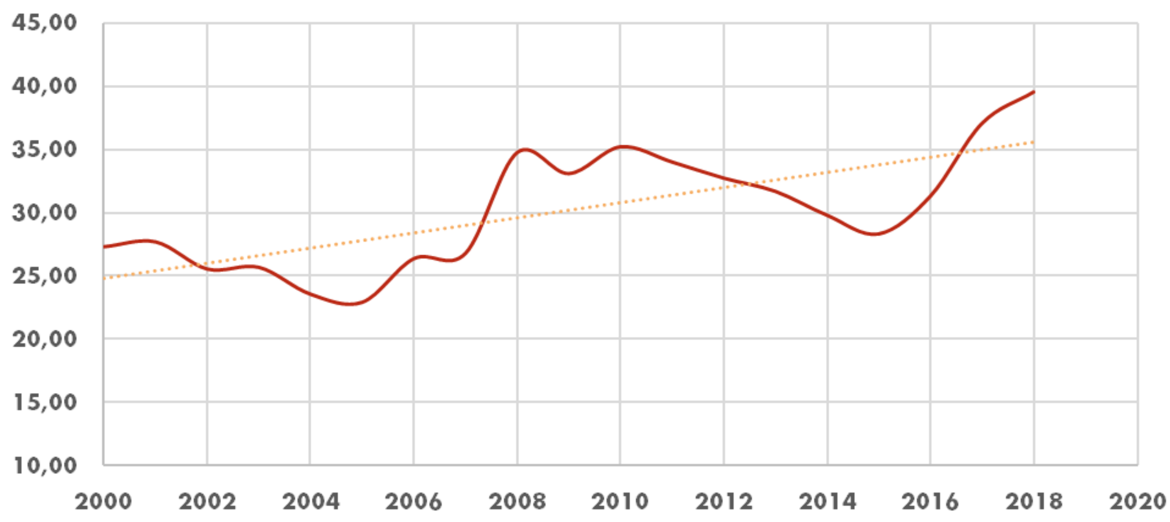


Figure 3.4 The trend of Escherichia coli global resistance to all antibiotics (% values), (Own elaboration from CDDEP, 2021)

3.2.3. Staphylococcus aureus resistance to antibiotics

Staphylococcus aureus tested resistant to fluoroquinolones, linezolid, macrolides, oxacillin (MRSA), rifampicin, and vancomycin. India in particular recorded resistance to aminoglycosides, aminopenicillins, amoxicillin-clavulanate, carbapenems, 3rd-generation cephalosporins, and piperacillin-tazobactam. Table 3.2 shows the regional distribution of Staphylococcus aureus AMR.

Figure 3.5 displays the average regional distribution of Staphylococcus aureus AMR, with South Asia showing the highest rate of resistance (41%), followed by the Middle East and North Africa (39%). Other areas have displayed a blue condition, denoting a moderate level of AMR.

Figure 3.6 reports global AMR in Staphylococcus aureus. The resistance to macrolides resulted very high (56%), the resistance to fluoroquinolones and oxacillin high at 48% and 36%, respectively, and the resistance to linezolid and vancomycin very low (less than 1%). Interestingly, in India, resistance to carbapenems, aminoglycosides, aminopenicillins, amoxicillin-clavulanate, and 3dr-generation cephalosporins tested very high and high (Figure 3.6).

Based on about 1.36 million tests globally conducted, between 2000 and 2018, Staphylococcus aureus showed an increasing slope in antibiotic resistance.

Resistance increased from 25% in 2000 to more than 30% in 2018, as shown in Figure 3.7, indicating a high resistance situation.

Antibiotics	East Asia and the Pacific	Europe and Central Asia	Latin America and the Caribbean	The Middle East and North Africa	North America	South Asia	Sub-Saharan Africa
Aminoglycosides	-	-	-	-	-	44.37	-
Aminopenicillins	-	-	-	-	-	92.07	-
Amoxicillin-clavulanate	-	-	-	-	-	43.08	-
Carbapenems	-	-	-	-	-	55.03	-
Cephalosporins (3rd gen)	-	-	-	-	-	48.28	-
Fluoroquinolones	-	19.25	-	-	-	77.73	-
Linezolid	0.63	0.44	0.53	-	0.00	0.76	0.00
Macrolides	-	-	-	-	43.37	68.60	-
Oxacillin (MRSA)	44.98	20.43	37.75	39.27	32.73	51.66	27.78
Piperacillin-tazobactam	-	-	-	-	-	6.00	-
Rifampicin	0.64	12.94	6.19	-	3.03	9.00	6.00
Vancomycin	0.24	0.13	0.21	-	0.00	0.52	-

Table 3.2 Staphylococcus aureus resistance to antibiotics by region and antibiotic class (% values)

(Own elaboration from CDDEP, 2021)

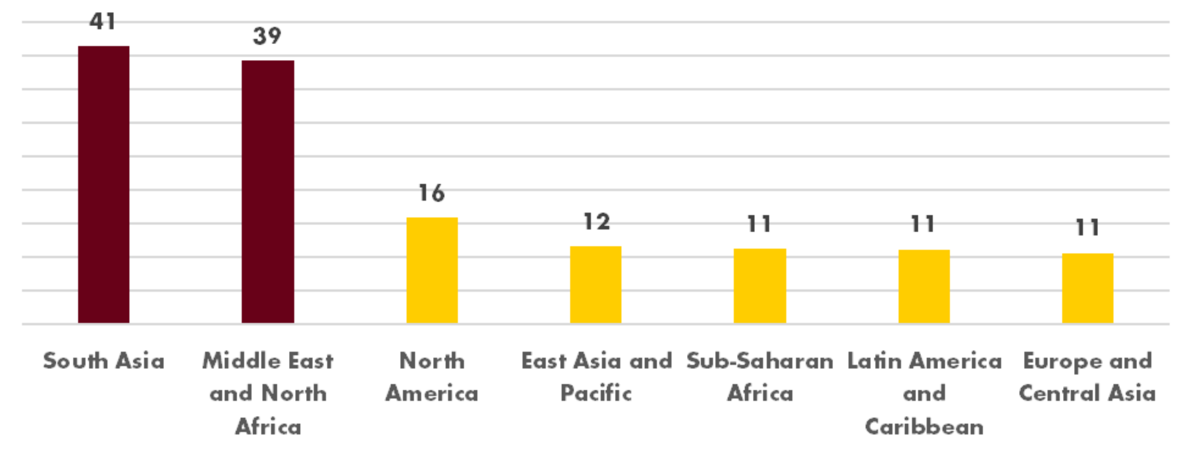


Figure 3.5 Staphylococcus aureus resistance to all antibiotics by region (% values), (Own elaboration from CDDEP, 2021).

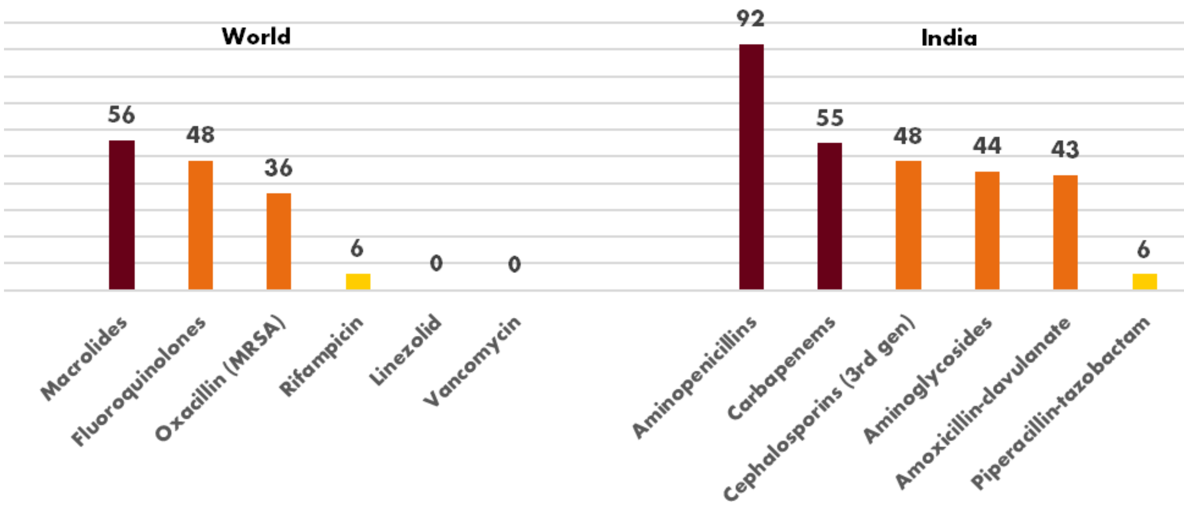


Figure 3.6 Staphylococcus aureus resistance to antibiotics by antibiotic class at global level and in India (% values), (Own elaboration from CDDEP, 2021).

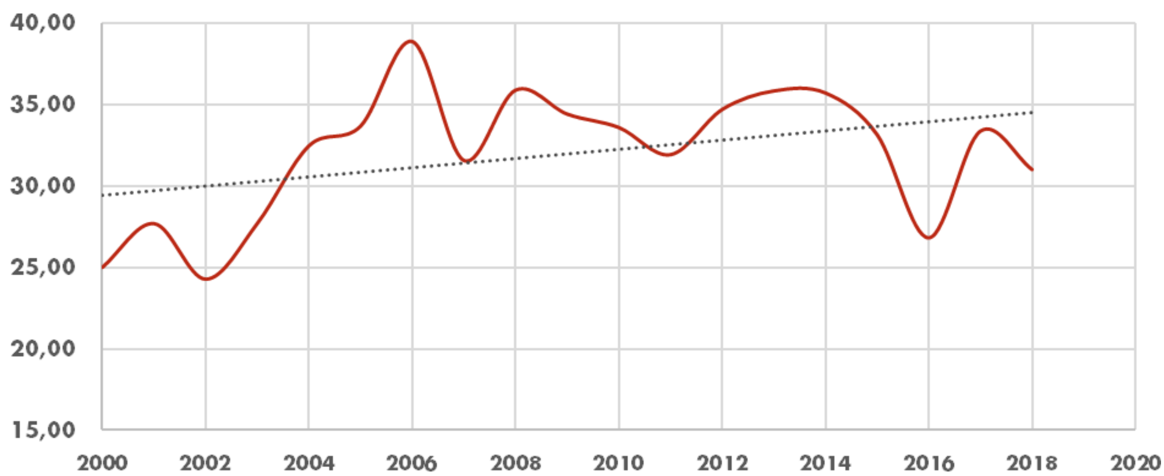


Figure 3.7 The trend of Staphylococcus aureus global resistance to all antibiotics (% values), (Own elaboration from CDDEP, 2021)

3.2.4. Campylobacter resistance to antibiotics

Data collected by ECDC from 2013 to 2020 showed that Campylobacter coli and Campylobacter jejuni are resistant to ciprofloxacin, erythromycin, gentamicin, and tetracycline (ECDC, 2021). Table 3.3 shows he resistance of Campylobacter coli and Campylobacter jejuni to antibiotics in the EU. Very high resistance to ciprofloxacin was observed for Campylobacter jejuni (67%) and extremely high resistance to ciprofloxacin for Campylobacter coli (77%). Tetracycline resistance was extremely high in both Campylobacter species (67% and 50%, respectively). Erythromycin resistance in Campylobacter coli is moderate (15%), while that in Campylobacter jejuni is low (2%). For both species, gentamicin resistance was very low.

Antibiotics	Campylobacter coli	Campylobacter jejuni
Ciprofloxacin	77.49	66.69
Tetracycline	67.35	49.52
Erythromycin	15.16	2.05
Gentamicin	2.79	1.99

Table 3.3 Campylobacter resistance to antibiotics in the EU (% values)

(Own elaboration from ECDC, 2021)

Figure 3.8 contrasts the typical antibiotic resistance of Campylobacter coli and Campylobacter jejuni in the EU (between 2013 to 2020). Figure 3.8 illustrates extremely high resistance to ciprofloxacin and very high resistance to tetracyclines. For both Campylobacter coli and Campylobacter jejuni the prevalence of resistance to all antibiotics rose between 2013 and 2020.

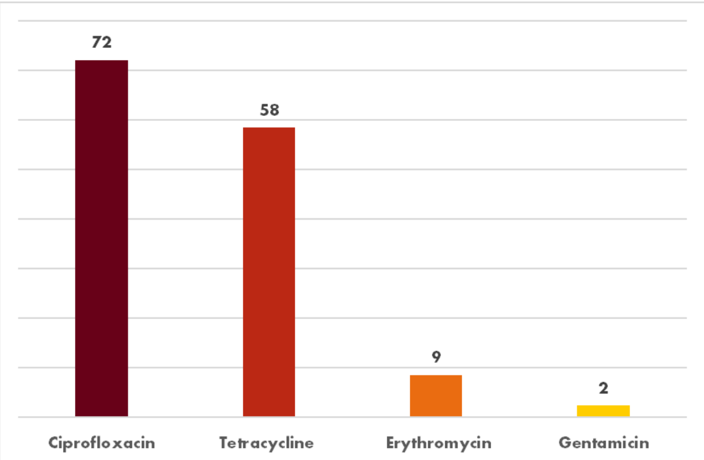


Figure 3.8 Campylobacter aureus resistance to antibiotics by antibiotic class in the EU (% values), (Own elaboration from ECDC, 2021).

Figure 3.9 shows the rise in antibiotic resistance in the EU, from 33% (high resistance) in 2013 to over 37% (high resistance) in 2020.

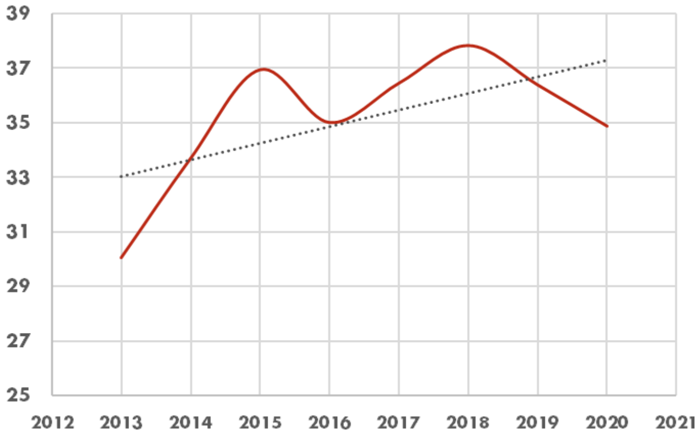


Figure 3.9 The trend of Staphylococcus aureus resistance to all antibiotics in the EU (% values), (Own elaboration from ECDC, 2021)

3.2.5. Salmonella resistance to antibiotics

Salmonella antibiotic resistance tests only started in 2019 in the EU (ECDC, 2021). The data show resistance to the active principles listed in Table 3.4. Salmonella resistance to sulfamethoxazole, ampicillin, and tetracyclines increased from 2019 to 2020 (high resistance), and there is moderate resistance to ciprofloxacin.

Antibiotics	2019	2020
Sulfamethoxazole	29.00	30.10
Ampicilin	25.80	25.80
Tetracycline	25.60	31.20
Nalidixic acid	16.70	13.10
Colistin	14.20	7.10
Ciprofloxacin	13.50	14.10
Co-trimoxazole	7.20	6.50
Trimethoprim	7.00	6.10
Chloramphenicol	5.60	6.40
Gentamicin	2.30	1.60
Cefotaxime	1.80	1.80
Ceftazidime	1.20	0.80
Tigecycline	1.10	0.20
Azithromycin	0.80	0.80
Cefotaxime + Ciprofloxacin	0.50	0.50
Meropenem	0.00	0.00

Table 3.4 Salmonella resistance to antibiotics in the EU (% values)

(Own elaboration from ECDC, 2021)

Figure 3.10 shows that overall resistance to all antibiotics used in the EU to treat Salmonella is low (less than 10%).

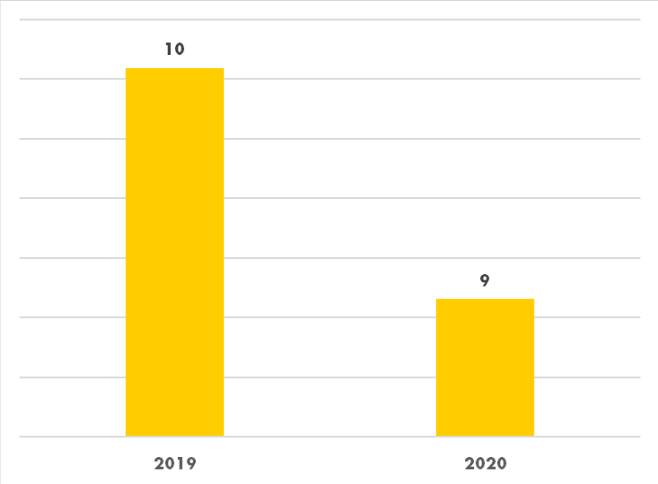


Figure 3.10 Salmonella resistance to antibiotics in the EU (% values), (Own elaboration from ECDC, 2021).

3.3. AMR in farmed animals

To analyse AMR on the selected farmed animal species, we used data on AMR testing published by governmental organizations and scientific journals from 2000 to 2021 and gathered by the CDDEP Resistance Bank (see Figure 3.11) (CDDEP, 2021). We found high and very high levels of AMR. Among poultry, pigs, and cattle, positive tests on Escherichia coli resistance to antibiotics was in average 54.74%, 53.72%, and 41.96%, respectively. Staphylococcus aureus resistance was 43.30% in poultry, 53.85% in pigs, and 40.70% in cattle. Salmonella resistance was 65.57% in poultry, whereas Campylobacter resistance was 49.49% in poultry, 45.56% in pigs, and 36.33% in cattle. Figure 3.12 shows the level of resistance of the four bacteria by antibiotic classes that are all classified by the WHO as CIAs and HIAs. (WHO, 2018).

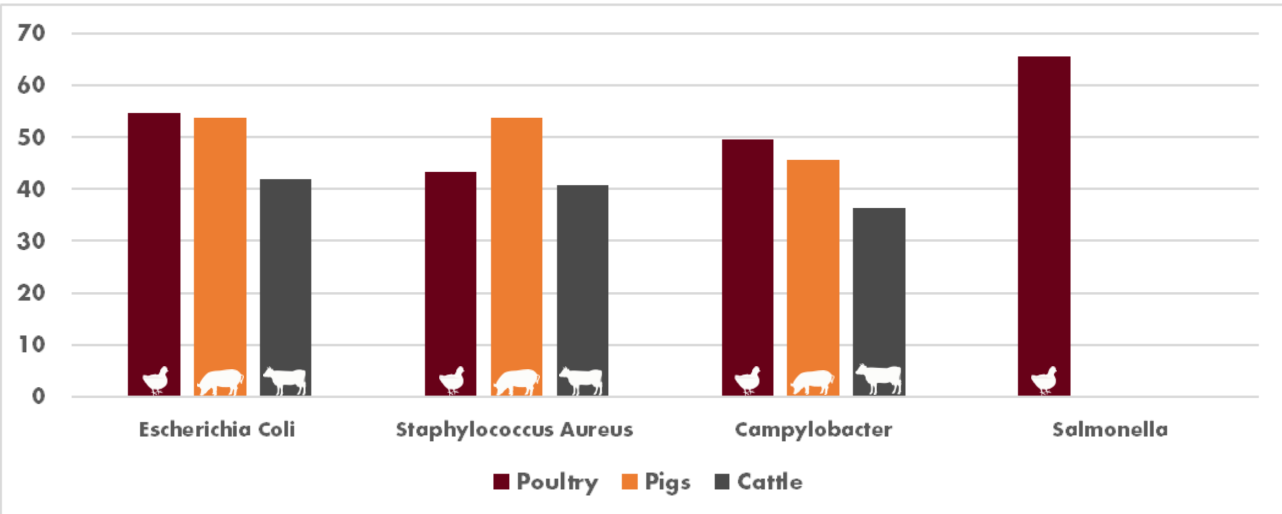


Figure 3.11 Resistance to all antibiotics in farmed animals by species (% values, averages from data published between 2000 and 2021), (Own elaboration from CDDEP, 2021).

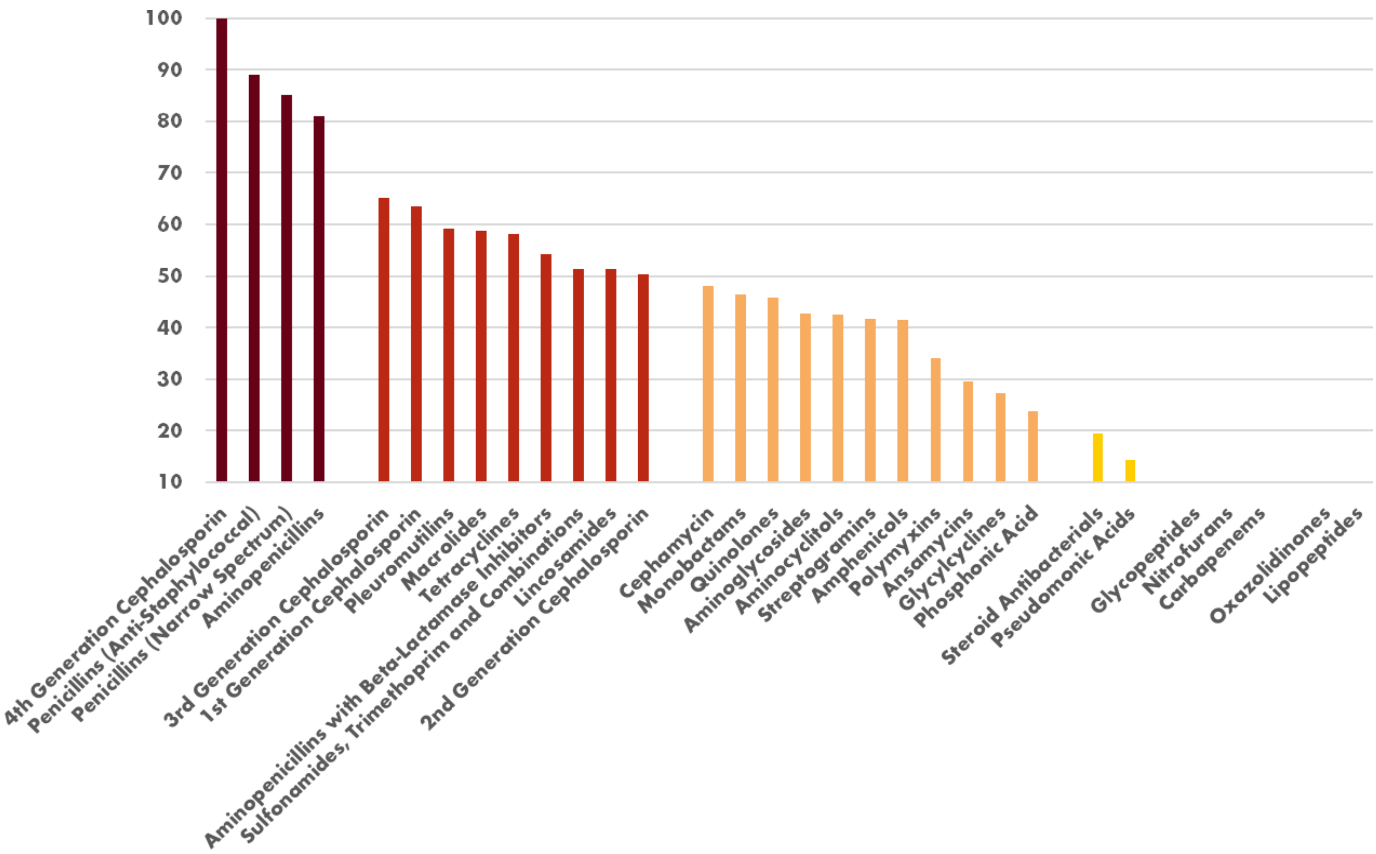


Figure 3.12 Resistance to antibiotics in farmed animals by antibiotic class (% values, averages from data published between 2000 and 2021), (Own elaboration from CDDEP, 2021).

3.4. Modelling the effects of AMU in factory farming on resistant infections in humans

The primary objective of the modelling is to identify how AMU on factory farms impacts resistant infections in humans. We first determined which countries in each region are the principal producers of poultry, pigs, cattle, and aquatics (carp, catfish, salmon, shrimp, and tilapia). In total, the analysis included data from 30 countries.

Table 3.5 lists the top producers of the selected farmed species worldwide from 2010 to 2020 based on information on production available in the FAO database in those years. Results show that the chosen poultry-producing countries accounted for almost 60% of global poultry production: 40% in the USA, China, and Brazil.

The selected countries produced more than 70% of the world total pigs, half from China and the USA, and more than 50% of the world's cattle, of which Brazil, India, the USA, and China delivered around 40%, and more than 90% of the farmed aquatics sold worldwide, with China alone producing about 60%.

Poultry		Pigs		Cattle		Aquaculture	
Country	Share (%)	Country	Share (%)	Country	Share (%)	Country	Share (%)
USA	17.86	China	47.55	Brazil	13.39	China	58.24
China	17.37	USA	7.80	India	12.28	Indonesia	7.51
Brazil	7.14	Germany	3.53	USA	6.66	Vietnam	5.06
India	3.39	Brazil	3.31	China	5.69	India	3.71
Russia	2.88	Spain	3.12	Ethiopia	3.60	Norway	2.85
Iran	2.65	Russia	2.35	Mexico	2.21	Bangladesh	2.61
Mexico	2.41	Mexico	1.41	Russia	1.73	Chile	2.06
UK	1.21	Denmark	1.30	Chad	1.45	Egypt	2.02
South Africa	1.18	India	0.83	France	1.35	Thailand	1.64
France	1.11	Malawi	0.41	Germany	0.99	Ecuador	1.10
Spain	0.87	Cyprus	0.04	UK	0.72	Brazil	0.62
Morocco	0.80	Ethiopia	0.00	Italy	0.54	UK	0.44
Italy	0.74	-	-	Iran	0.46	Philippines	0.46
Nigeria	0.51	-	-	Egypt	0.36	USA	0.41
-	-	-	-	-	-	Nigeria	0.39
-	-	-	-	-	-	Iran	0.45
-	-	-	-	-	-	Mexico	0.33

Table 3.5 Positions of the countries selected for the Chapter 3 analysis as world producers of poultry, pigs, cattle, and aquaculture (% shares on total global production, 2010-2020 period).

(Own elaboration from FAOSTAT, 2022)

The level of antibiotic resistance of the selected bacteria in human infections was estimated for each country using a weighted average and included in the model as the dependent variable. Since the ECDC considers an AMR level of 20% or more, we built the model with resistance levels of 20% or higher (high, very high, and extremely high). While there are numerous contributing factors to AMR, we used the WHO definition of the primary causes of AMR in humans to determine the independent variables (WHO, 2021).

According to WHO, the main drivers of AMR include the misuse and overuse of antimicrobials, lack of access to clean water, sanitation, and hygiene (WASH) for both humans and animals, scarce infection and disease prevention and control in healthcare facilities and farms, poor access to quality, affordable medicines, vaccines and diagnostics, lack of awareness and knowledge, and lack of legislation enforcement. We used two variables to examine antibiotic misuse and overuse: antibiotic usage in humans (extracted from CDDEP Resistance Bank) and antibiotic use on factory farms (our estimation).

A dummy variable[2] represented the absence of access to WASH. Poor access to WASH contributes to almost 800,000 deaths annually in low- and middle-income countries (WHO, 2022b). Thus, a dummy equal to zero was for the low-income countries in the selected year, and one was for all other countries. According to the World Bank definition, a high-income country has a Gross National Income (GNI) per capita of more than 12,056 US$ (The World Bank, 2022a).

We considered the percentage of GDP for health expenditures as a proxy for poor prevention of infections and diseases, scarce control in healthcare facilities and farms, and poor access to quality, affordable medicines, vaccines, and diagnostics. The source for this data was the World Bank (The World Bank, 2022b). Another dummy variable represented lack of awareness and knowledge, and lack of enforcement of legislation. When a country has laws regulating antibiotic use, such as prohibiting the use of AGPs in farmed animals, the dummy equals one and zero for the other cases.

We included GDP per capita based on Purchased Power Parity (PPP) into the model as the consumers' income because the demand for food of animal origin grows with rising consumer affluence. We collected data from the publicly available World Bank database (The World Bank, 2022c). The final dataset had 2010-2020 data for the 30 main world producing countries of the selected animal species. We used the Spatial Regression Model since AMR can spread among humans, animals, and the environment. The assumption of independent observations is frequently inaccurate, and there may be dependencies between observations made at several locations or regions (Alzahrani et al., 2020). Examples of such a dependency between the variable of interest and an outcome include pollution levels and health outcomes (Alzahrani et al., 2020; Moscone and Tosetti, 2014).

We examined the spatial correlation with the Moran's I test to validate spatial dependency statistically rather than theoretically. There was a spatial correlation in the data on AMR in humans across the various countries included in the model, according to the results of Moran's I test (0.022 p-values: 0.000).

[2]A Dummy variable is an artificial variable created using 0 and 1 values. Dummy variables are used in regressions for qualitative variables (sex, colour, etc.) and sub-groups variables split based on a definition.

Typically, data including time-series observations of geographic units are indicated as spatial panels (zip codes, regions, states, countries, etc.). Spatial components must be included in economic models to account for spatial dependence, which may be integrated into linear regression models using the Spatial Lag Model (SLM) and Spatial Error Model (SEM). The SLM assumes that the dependent variable is reliant on the dependent variable seen in the nearby units as well as many other observed local characteristics. The SEM, on the other hand, hypothesizes that the error terms are spatially linked, and that the dependent variable depends on a set of observed local characteristics. Regression estimations of the model parameters may be biased and inconsistent if spatial effects are ignored (Ardakani et al., 2020).

To understand how AMU in factory farming can affect AMR in humans, we built a spatial panel econometric regression model. Using the Robust Multiplier Lagrange test, we decided between an SLM and an SEM (9.834 p-values: 0.002). The results led to the selection of an SEM. The optimal model was chosen using log-likelihood, Akaike information criterion (AIC), and Bayesian information criterion (BIC) statistics as well. Finally, we choose SEM as the estimation method. The SEM assumes that the dependent variable depends on many observed neighbourhood features. For instance, concerning this research, if a country imposes limitations on meat import from other countries, the exporting countries must alter their production techniques to comply with those limitations. In other words, customers of both countries will profit from the improvement in meat quality.

Table 3.6 summarizes the model's findings. We used skewness, kurtosis, and Breusch-Pagan tests to determine whether the residuals were normal and heteroscedastic. The findings show that there is no correlation between the AMR in humans and AMU in humans, as well as with health expenditures. The countries with access to WASH for both humans and animals have 12% lower rates of antibiotic resistance in humans than the others. The countries with some restrictions on the use of antibiotics in farmed animals had 7% fewer cases of AMR in humans.

AMU on factory farms and consumer income are highly important and positively correlated with AMR in humans. According to the findings, a global increase in AMU in farmed animals of 1,000 tonnes will result in a 21% increase in AMR in humans.

The GDP per capita based on PPP assumes that rising consumer incomes cause a rise in the demand for foods derived from animals, which in turn causes an increase in AMR in humans. According to the value of this coefficient, the AMR might rise by 13.5% if consumer income rises by 100 US$.

Our findings show that the use of antibiotics in farmed animals is strongly and positively connected with AMR in humans, indicating that the overuse or improper use of antibiotics in farmed animals will raise AMR in humans. Additionally, rising AMR in humans is correlated to rising per capita income due to the anticipated financial impact of eating foods derived from animals. These two highly associated characteristics suggest that the overuse and abuse of antibiotics in farmed animals will likely result in a significant increase of AMR spread to humans. Although the use of antibiotics in farmed animals for non-therapeutic purposes is currently banned in some countries, other countries do not implement this legislation, allowing for cross-border effects at the continental and global levels.

Number of Observation = 323 Sigma = 0.24 Log Likelihood = - 3.3118806 Dependent Variable: Antibiotics Resistance in Humans %					
Independent Variables:	Coefficient	Standard Error	P > I Z I	[95% Confidence Interval]	
Antibiotics Use in Humans (DDD)	0.032	0.042	0.437	-0.050	0.115
Antibiotics Use in Factory Farms (tonnes)	0.021	0.007	0.005	0.006	0.036
Wash Infrastructure (Dummy)	-0.121	0.065	0.064	-0.249	0.007
Expenditures in Health (% of GDP)	0.052	0.032	0.110	-0.012	0.115
Lack of Legislation (Dummy)	-0.077	0.041	0.061	-0.158	0.004
GDP per Capita based on PPP (US$)	0.135	0.027	0.000	0.081	0.188
Intercept	-2.266	0.527	0.000	-3.299	-1.232
Lambda	-1.768	0.273	0.000	-2.303	-1.233
Wald Test of Lambda = 0 Chi2 (1) = 41.904 (0.000)					
AIC = 24.624 BIC = 58.623					

Table 3.6 Results of the Spatial Error Model (dataset includes 30 producers between 2010 to 2020).

(Own elaboration)

4. HOW MIGHT ANTIBIOTIC USE IN FACTORY FARMED ANIMALS INCREASE PUBLIC HEALTH COSTS RELATED TO AMR INFECTIONS?

This chapter covers steps 7 and 8 of the research. In step 7, the human burden from AMR related to AMU in livestock production was calculated based on data on deaths and DALYs publicly available. In step 8, the contribution of factory farming to that burden was estimated and evaluated in monetary terms. The estimation was projected to the year 2050 after setting two alternative scenarios related to a business-as-usual and a more-prudent-AMU perspective.

4.1. Introduction

4.1.1. The burden "attributable to", and "associated with" AMR

AMR causes significant damage to human and animal health and the economy. Therapies become ineffective with resistant pathogens, and patients suffer more severe infections, complications, prolonged hospitalizations, and increasing medical costs and risks of death. (Hay et al., 2018; HIQA, 2021; Yang et al., 2020).

To evaluate the burden of AMR on human society, scientists compare the current situation in which people suffer more serious infections or even die due to the loss of antibiotics' efficacy with two alternative scenarios. The first scenario assumes that the antibiotics have not lost efficacy, so they evaluate how many deaths or time lost by patients in a state of disability due to prolonged illness would have decreased in this hypothetical situation compared to reality. In this case, scientists talk of a burden "attributable to" AMR, which means compared to a theoretical counterfactual where drug-susceptible infections replace drug-resistant infections.

The second scenario compares patient deaths or lost time due to resistant infections to a hypothetical situation where none of these infections would have occurred. In this case, scientists talk of a burden "associated with" AMR, which means compared to a theoretical counterfactual where no infection replaces the drug-resistant infections (AMR Collaborators, 2022).

A recent study estimated that, in 2019, 1.27 million people died from causes "attributable to" AMR (i.e., first scenario) and 4.95 million from causes "associated with" AMR (i.e. second scenario) (AMR Collaborators, 2022).

Image: Meat chicken suffering and unable to stand due to fast growth. Antibiotics are administered to meat chickens to promote fast growth, contributing to AMR. Credit: World Animal Protection

4.1.2. An indicator of disease burden: the DALY

The DALY is an indicator used to evaluate how diseases affect people's quality of life over time. They were elaborated in the 1990s by the World Bank and Harvard University (Lajoie, 2015). One DALY can be thought of as one year of life lost by one person, and 0.5 DALYs as one year spent by one person in a state of 50% of disability (WHO, 2020, 2017b). Thus, the burden of a given disease expressed in DALYs is the sum of the years lost by affected people due to deaths that occurred before their respective life expectancy terms (years of life lost, or YLL), plus the time spent in a state of disability caused by the disease before full recovery or death (years lost due to disability, YLD).

$$DALY = YLL + YLD;$$

DALY is a metric that has the advantage of allowing comparisons between different types of diseases (for example, communicable diseases versus non-communicable diseases) based on their impacts on populations (Grandjean and Bellanger, 2017; Maertens de Noordhout et al., 2017; McDonald et al., 2012).

4.1.3. Contents of this Chapter

Foodborne diseases are a significant global cause of morbidity and mortality (Hald et al., 2016).The prevalence of AMR in foodborne bacterial pathogens, and how such resistance may impact treatments' efficacy are raising concerns (Colavecchio et al., 2017). When considering the implementation of health policies and treatments against AMR, it is vital to quantify the illness burden caused by AMR because it increases both morbidity and mortality (Majumder et al., 2020; Pezzani et al., 2021; Tsuzuki et al., 2021). The financial cost of treating AMR infections represents a heavy burden on society (HIQA, 2021): for example, it has been estimated that, in the USA, the cost of AMR amounts to 55 billion US$ per year (Dadgostar, 2019). This chapter presents:

1. a calculation, in terms of DALYs, of the global burden of AMR in Escherichia coli, Staphylococcus aureus, non-typhoidal Salmonella, and Campylobacter, under the hypothesis that all infections are related to the use of antibiotics in farmed animals (step 7),

2. a calculation of the part of the burden that could be imputed to factory farms, based on the share of the global antibiotic consumption estimated for factory farming (step 7),

3 an estimation of the current global economic cost due to the productivity losses in humans affected by the resistant bacteria examined for the part ascribed to factory farms (step 8),

4 a projection to the year 2050 of the future global economic costs under two different scenarios (step 8):

- a business-as-usual scenario, where the global consumption of antibiotics per unit of animal biomass (mg/PCU) continues at the current levels,
- a second scenario in which the measures undertaken at the global level for a more prudent use of antibiotics in farmed animals obtain the same achievements, in terms of antibiotic consumption per unit of animal biomass (mg/PCU) obtained in Europe during the last decade.

Step 7: Estimating the burden of AMR infections related to the use of antibiotics on factory farms

4.2. Deaths and DALYs from the selected resistant bacteria

4.2.1. The no-infection counterfactual and other basic assumptions

The sources of data used in this study estimated the global AMR burden in terms of deaths and the DALYs by comparing the current situation to both conterfactuals described in Section 4.1.1: i.e., the drug-susceptible scenario for the burden "attributable to" AMR, and the no-infection scenario for the burden "associated with" AMR.

The Institute for Health Metrics and Evaluation (IHME) of the University of Washington reports the burden of AMR using both counterfactuals and suggests that the results, which may be very different, will set bounds on the maximum impact of an intervention to control AMR (AMR Collaborators, 2022; GBD 2019 AMR Collaborators, 2022). Some researchers underline that the counterfactual for assessing the burden of AMR depends on the type of intervention we are estimating. Among the proposed intervention typologies, the most suitable for our analysis were the following: "livestock vaccination, infection control, food-animal handling changes, and other measures to reduce animal-to-human transmission of infection. To the extent that such measures are used as part of a One Health strategy to reduce human exposure to foodborne pathogens, the no-infection counterfactual appears most relevant" (de Kraker and Lipsitch, 2022). Then, we chose to assess the burden to society of AMU in factory farms as associated with AMR, using data from the no-infection scenario.

Data on the global and regional burden of resistant Escherichia coli, Staphylococcus aureus, and non-typhoidal Salmonella are available for 2019, but there are no data on resistant Campylobacter. For this bacterium, we extrapolated the burden from the USA country case. According to the Centres for Disease Control and Prevention (CDC), in the USA, 200 persons die each year from Campylobacter infections, with a 35% prevalence of resistant Campylobacter (CDC, 2019). Lacking other estimations our study assumed that 35% of deaths and DALYs caused by Campylobacter worldwide result from resistant strains.

4.2.2. Deaths and DALYs from resistant bacteria

Table 4.1 shows that in 2019, globally, 403 thousand deaths were attributable to infections from resistant Escherichia coli, Staphylococcus aureus, and non-typhoidal Salmonella and 1,604 million deaths were associated with the same resistant bacteria. More than half of those deaths were related to Escherichia coli, around 45% to Staphylococcus aureus, while non-typhoidal Salmonella had a minor role. According to the IHME data, Escherichia coli and Staphylococcus aureus were the two most lethal resistant pathogens, responsible for more than 30% of the total deaths related to AMR.

Data on the regional distribution and incidence of deaths (Table 4.2) indicate a global incidence of 49 and 197 deaths per 1 million persons, respectively, for the deaths attributable to AMR and those associated with AMR. According to the HIME data, in proportion to the population, the deaths from AMR had the highest incidence in Europe and Central Asia, followed by Latin America and the Caribbean and Sub-Saharian Africa. The lowest incidence was recorded in the Middle East and North Africa, preceded by East Asia and the Pacific, and South Asia. The other regions show incidence values that were closer to the global value.

Table 4.3 shows that in 2019 the global burden attributable to resistant infections from Escherichia coli, Staphylococcus aureus, and non-typhoidal Salmonella amounted to 13.7 million DALYs and the burden associated with the same diseases to 54.3 million DALYs. Such values represented about 28% of the global DALYs from resistant infections. The data on regional distribution and incidence of the burden (Table 4.4) show values of 1.7 and 6.9 thousand DALYs per million persons, respectively, for the infections attributable to and associated with the three resistant pathogens. Compared to deaths, the DALYs incidence indicates that Sub-Saharian Africa was the most affected region, followed by South Asia. The lowest incidence resulted in Middle East and North Africa, preceded by East Asia and the Pacific, and North America.

Pathogens	Deaths associated with AMR (N.)	Deaths associated with AMR (N.)	Deaths attributable to AMR (%)	Deaths associated with AMR (%)
Escherichia coli	828,589	828,589	54.3	51.7
Non-typhoidal Salmonella	27,148	27,148	1.4	1.7
Staphylococcus aureus	748,410	748,410	44.3	46.7
Total deaths	1,604,147	1,604,147	100.0	100.0
As % of total deaths from AMR	32.4	32.4		

Table 4.1 Global deaths attributable to and associated with the selected resistant bacteria in 2019.

(Own elaboration from IHME, 2022)

World regions	Deaths attributable to AMR (%)	Deaths associated with AMR (%)	Deaths attributable to AMR – Incidence per 1 Mio persons	Deaths associated with AMR – Incidence per 1 Mio persons
East Asia, and the Pacific	21.1	21.2	34.2	136.7
Europe and Central Asia	13.7	14.9	80.3	348.8
Latin America and the Caribbean	8.1	8.3	67.4	275.9
Middle East and North Africa	6.1	5.6	25.3	92.2
North America	5.5	5.9	56.7	243.1
South Asia	27.9	25.3	57.7	208.4
Sub-Saharan Africa	17.6	18.8	60.5	257.1
World	100.0	100.0	49.4	197.0

Table 4.2 Global deaths attributable to and associated with resistant Escherichia coli, non-typhoidal Salmonella, and Staphylococcus aureus in 2019, percentage distribution and incidence per 1 million persons by region.

(Own elaboration from IHME, 2022)

Pathogens	DALYs attributable to AMR (N.)	DALYs associated with AMR (N.)	DALYs attributable to AMR (%)	DALYs associated with AMR (%)
Escherichia coli	7,515,126	28,024,911	55.1	51.6
Non-typhoidal Salmonella	264,254	1,394,696	1.9	2.6
Staphylococcus aureus	5,870,683	24,859,926	43.0	45.8
Total DALYs	13,650,064	54,279,533	100.0	100.0
As % of total DALYs from AMR	27.8	27.6		

Table 4.3 Global DALYs attributable to and associated with the selected resistant bacteria in 2019.

(Own elaboration from IHME, 2022)

World regions	DALYs attributable to AMR (%)	DALYs associated with AMR (%)	DALYs attributable to AMR - Incidence per 1 Mio persons	DALYs associated with AMR - Incidence per 1 Mio persons
East Asia and the Pacific	15.8	15.9	895.5	3,586.8
Europe and Central Asia	7.8	8.4	1,608.2	6,906.9
Latin America and the Caribbean	6.0	6.2	1,756.6	7,176.5
Middle East and North Africa	6.2	5.8	898.8	3,323.4
North America	2.9	3.2	1,064.2	4,568.3
South Asia	31.4	28.9	2,277.2	8,332.1
Sub-Saharan Africa	29.7	31.6	3,568.2	15,080.3
World	100.0	100.0	1,730.3	6,884.6

Table 4.4 Global DALYs attributable to and associated with resistant Escherichia coli, non-typhoidal Salmonella, and Staphylococcus aureus in 2019, percentage distribution and incidence per 1 million persons by region.

(Own elaboration from IHME, 2022)

4.2.3. Estimation of the global burden associated with Campylobacter infections

As previously mentioned, lacking data on the global burden from resistant Campylobacter infections, for this element of the evaluation, we extrapolated the information available from the country case of the USA to estimate a global prevalence of 35% in total worldwide deaths and DALYs from Campylobacter infections. According to IHME data, we calculated the following amounts referred to the "no-infection" scenario for the year 2019:

- global deaths associated with resistant Campylobacter infections: 48,678;
- global DALYs associated with resistant Campylobacter infections: 2,557,744.

4.2.4. Estimation of the global burden of AMR related to farmed animals and the contribution of factory farming

In 2019, the global burden from resistant Escherichia coli, Staphylococcus aureus, Campylobacter, and non-typhoidal Salmonella infections resulted in:

- 1.65 million deaths associated with AMR;
- or 56.84 million DALYs associated with AMR.

According to our hypotheses, this burden is related to AMU in farmed animals. On this basis, we estimated that the contribution of factory farming to the burden was equal to the share of factory farms in the global use of veterinary antibiotics, as calculated in Chapter 1 (Table 4.5).

Global burden from AMR related to AMU in farmed animals:	
- Deaths associated with AMR (a) =	1,652,825;
- DALYs associated with AMR (b) =	56,837,277;
Share of factory farms in total AMU (c) =	59%;
Contribution of factory farming to the global burden:	
- Deaths associated with AMR = (a x c) =	975,167;
- DALYs associated with AMR = (b x c) =	33,533,993.

Table 4.5 Estimation of the contribution of factory farms in the global burden of AMR related to AMU on farmed animals (year 2019)

(Own elaboration)

4.3. Estimation of the global economic burden from AMR related to AMU in farmed animals and contribution of factory farming

Individuals are the active contributors to the economy, and the GDP measures the overall result of economic activities in a given area (region, country, continent, whole world, etc.) over a certain period. When individuals become inactive due to YLD or YLL, their contribution to the economy, therefore to the GDP, is lost (Dalal and Svanström, 2015). Assuming, on the one hand, the DALYs as a measure of the total time lost for economic activities, over a given period, by the individuals living in an area because of one or more diseases and, on the other hand, the GDP per capita as the value of the average contribution of individuals to the economy, the economic damage suffered by this society in terms of productivity losses can be evaluated as the product of the DALYs lost multiplied by the GDP per capita of the area over the period. (Brown, 2008; Dalal and Svanström, 2015; Mathers and Loncar, 2006). Our study found that in the year 2019, at the global level, 56.84 million DALYs associated with AMR could be related to AMU in farmed animals, and the contribution of factory farms to this amount was 33.53 million DALYs (Section 4.2.4).

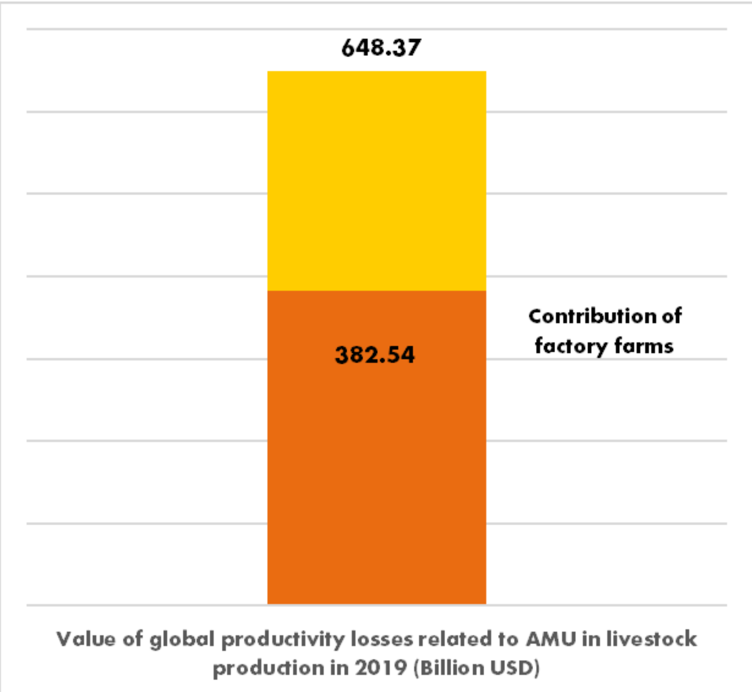


Figure 4.1 Value of global AMR productivity losses related to AMU in farmed animals and contribution of factory farming in 2019 (billion USD), Source: (Own elaboration from: IHME, 2022; The World Bank, 2022d, 2022e)

According to The World Bank data, in 2019, the global GDP per capita was 11,407.48 US$ (The World Bank, 2022d) which, multiplied by the DALYs indicated above, gives a global productivity loss of 648.37 billion US$ related to AMU in farmed animals and 382.54 billion US$ as the contribution of factory farming (Figure 4.1). Respectively, such values correspond to 0.74% and 0.43% of the global GDP of 2019, estimated by the World Bank at 87,652.86 billion US$. (The World Bank, 2022e)

4.4. Projection to the year 2050 of the contribution of factory farming to the global economic burden from AMR related to AMU in farmed animals

4.4.1. Basic assumptions for projections and scenario building

To estimate the value of productivity losses from AMR related to AMU on factory farms in the future, we should quantify the future AMU impact in terms of DALYs.

The regression analysis in Chapter 3 showed a highly positive correlation between AMU in factory farming and AMR detected for the four selected bacteria: then, we assumed that a variation in AMU on factory farms causes a similar variation in the levels of AMR detected in the selected bacteria, as well as in the related human infections and the consequent disease burden calculated as the number of DALYs. With those hypotheses and defining AMU as the product of the total animal biomass multiplied by the average dose administered to animals per unit of biomass, in mg per PCU, it is possible to set the following equations:

$$AMR = f(AMU) = f(PCUs \times mg/PCU); \quad \Delta AMR = \Delta PCU$$

if:

$$\Delta AMR = \Delta DALYs$$

then:

$$\Delta DALYs = \Delta PCU + \Delta mg/PCU$$

Using the above relations, we set two scenarios to project the DALYs associated with AMR from the selected bacteria.

4.4.2. Scenario One: business-as-usual

Scenario One refers to a business-as-usual situation: it assumes no significant change occurs in the AMU practices in farms worldwide over the 2019-2050 period. Globally, the amount of antibiotics consumed per unit of animal biomass, or PCU, will be the same as estimated for 2019 over the whole period. Under this hypothesis, the changes in the global AMU depend on the variations in the global animal biomass, i.e. in the global amount of livestock measured as PCUs. According to previous assumptions, the variations in PCUs will determine similar variations in the total AMU worldwide, hence, in the global DALYs related to farmed animals. On this basis, global PCU variations can be detected by changes in global meat consumption and DALYs are assumed to vary depending on changes in meat consumption.

According to estimations from the Organization for Economic Cooperation and Development (OECD), the global consumption of cattle, pig, and poultry meat grew from 146 thousand tonnes in 1990 to 312 thousand tonnes in 2021 and is expected to reach 347 thousand tonnes in 2029 (OECD, 2022; OECD/FAO, 2021). The historical data and future projections indicate that global meat consumption is rising at an annual rate of 2.26% (see Figure D1 in Appendix D). We used this rate to assess the future variation of global deaths and DALYs related to AMU in farmed animals for Scenario One. Table 4.6 shows the results of the estimation.

4.4.3. Scenario Two: more prudent AMU

In 2015, the WHO and other intergovernmental world agencies launched a Global Action Plan on AMR (WHO, 2015). Regarding the farming sector, the global plan focus on increse public awareness on AMR risks, monitoring AMU on farms, promote best animal health management practices, and improve governance coordinating the various measures. With this initiative, the WHO urged its member to adopt national plans against AMR in line with the global action: in 2022, on a total of 166 countries monitored by the specific Country Self-Assessment Survey, only 17 had not yet started to develop an action plan (TrACSS, 2022).

After banning AGPs in 2006, the EU has developed its actions since 2011 (European Commission, 2011). The current European One Health Action Plan Against AMR started in 2017 with the objectives of making the EU a best practice region, boosting research, development and innovation, and shaping the global AMR agenda (European Commission, 2017a). In the farming sector, the EU action supported a considerable progression of the European legislation. For example, traceability and monitoring of AMU on farms has been considerably improved, with the electronic prescriptions of veternary drugs, and strict limitations have been imposed on non-therapeutic treatments (European Commission, 2022).

While most of the new European legislation on veterinary medicines is being enforced gradually by 2030, the EU Member States have long since embarked on a path of change in farms' animal health management leading to reduction of AMU (ECDC/EFSA/EMA, 2021). A diminishing trend of AMU on farmed animals have been recorded by the EMA-ESVAC project in its annual survey on veterinary antibiotic sales in 31 European countries (EMA, 2022a) and the WOAH in its last global survey covering 72 countries worldwide for the 2016-2018 period (WOAH, 2022). These are the main international statistics on AMU on farmed animals available.

The second scenario intends to project this diminishing trend that implies strengthening the implementation of the global strategy against AMR. For the Scenario Two estimation, we decided to reproduce the EU experience of the last decade, for which the quantity and reliability of available data are better. According to ESVAC data (EMA, 2021), between 2011 and 2020, the sales of antibiotics in the EU, as mg of active principle per PCU, dropped on average by 5.78% per year, and this figure was assumed as the global decreasing rate for the antibiotic consumption per PCU in Scenario Two. However, a limit to global decrease was set at the level of relative antibiotic consumption reached by Sweden in 2020.

In Scenario Two, the AMU decrease per unit of animal biomass is counterbalanced by the increase of the global animal biomass. The latter is linked to the growing consumption of animal products, and this depends on demographic trends and the average income per capita. We assumed that global PCUs increase over the analyzed period at the same rate foreseen for meat consumption in Scenario One (i.e. 2.26%). The combination of the two effects, decreasing AMU per PCU, on the one hand, and increasing PCUs, on the other hand, results in an average annual decrease of the global AMU in farmed animals of 3.51%. Considering the assumptions made in Section 4.4.1, this also corresponds to the decreasing rate of global deaths and DALYs related to AMU in farmed animals of Scenario Two. Table 4.6 shows the future projections estimated for the two scenarios.

Table 4.6 Projected deaths and DALYs related to AMU in farmed animals

Year	Scenario One business as usual*		Scenario Two more prudent AMU*	
	Million deaths	Million DALYs	Million deaths	Million DALYs
2019	0.97	56.84	0.97	56.84
2022	1.06	60.78	0.89	51.05
2030	1.33	72.70	0.70	38.35
2040	1.78	90.92	0.52	26.82
2050	2.38	113.72	0.39	18.76

*The burdens calculated in the two scenarios follow a variation in the estimated global farm AMU from 47.1 thousand tonnes of antibiotic-active substances in 2019 to 115.6 thousand tonnes in 2050 for Scenario One (+145.4%) and 19.1 thousand tonnes for Scenario Two (-59.5%).

(Own elaboration from: IHME, 2022; OECD 2022)

4.4.4. Projections of factory farming contribution to global farmed animals and AMU

Globally, there is a growing demand for food of animal origin due to population growth and economic expansion (Van Boeckel et al., 2015). Hence, the production of farmed animals is becoming increasingly intensive and industrialized (Price et al., 2015). The share of people residing in towns approaches 60% of the total world population: urban population is growing at an annual rate of 1.8%, while the growth rate of the global rural population is nearly zero. According to United Nations' (UN) forecasts, by 2050, the world's urban population will have increased by almost half to close to 6.7 billion people, while the rural population should fall by 10% to around 3.1 billion people (United Nations, 2022). On this basis, the demand of urban consumers is expected to play an increasing role in food markets, driving further development of industrial-scale farming and food-supply chain organization (Schar et al., 2020; Vorley et al., 2015).

In this study, we consider the level of urbanization as the share of the urban population on the total population, and the rate of urbanization as the rate at which that share is changing (Satterthwaite et al., 2010). Economic growth and urbanization are strongly correlated. Urban residents consume more animal products and processed food delivered through integrated agro-industrial systems and supermarket chains. Urbanization has a considerable impact on global food markets, and large-scale animal production is driven by rising incomes and a growing population in towns and cities. (Regmi and Dyck, 2022; Zhang et al., 2017). On this basis, we predicted the proportion of factory farms in global animal production to increase in parallel with the rate of urbanization.

The UN estimated the global rate of urbanization between 1950 and 2020 and produced forecasts for the 2021-2050 period (see Figures D2 and D3 in Appendix D). The urban world population increased from 29.61% of the total in 1950 to 56.17% in 2020, and is expected to reach 68.36% by 2050. Consequently, between 1950 and 2020, the percentage of urban population on the total increased by an average annual rate of 0.9%, and it will rise by 0.7% annually in the 2020-2050 period.

Assuming that the share of factory farms in total livestock production and the level of urbanization change at a similar annual rate, we estimated that, by 2050, factory farms rear 71.8% of global PCUs and use this same proportion of veterinary antibiotics compared to global AMU on farms (Table 4.7).

Year	Contribution of factory farming to global PCUs and AMU (%)
2019	58.5
2022	59.8
2030	63.0
2040	67.2
2050	71.8

Table 4.7 Projections of the contribution of factory farms to global PCUs and AMU

(Own elaboration from (FAOSTAT 2021, FAO Fishery Database, 2022, United Nations, 2022)

4.4.5. Projections of the global GDP and GDP per capita

We projected the GDP per capita by using the below equation. FV stands for future value, PV for present value, i for growth rate, and n for the period in years:

$$FV = PV(1 + i)n$$

The World Bank calculated that between 1961 and 2021, the average annual growth rate for the global GDP per capita was 1.9% (The World Bank, 2022f). Assuming this rate for projections, we estimated the future global average GDP per capita over the 2019-2050 period. The future values of global GDP were then calculated by multiplying the projected GDP per capita by the UN forecasts on the future global population (Table 4.8).

Year	Period N. of years	Global GDP per capita (US$)	Global GDP (billion US$)
2019	-	11,407	88,926.80
2022	3	12,061	95,940.57
2030	11	13,994	119,661.72
2040	21	16,850	155,194.10
2050	31	20,289	198,265.29

Table 4.8 Projection of global GDP per capita and global GDP

(Own elaboration from: The World Bank, 2022d, 2022e, 2022f; United Nations, 2022)

4.4.6. Projections of the AMR burden related to factory farms (Scenarios One and Two)

We calculated the future global economic burden of AMR related to AMU in farmed animals by multiplying the projected global DALYs resulting in the two scenarios (Table 4.6) by the estimated global average GDP per capita of the corresponding years (Table 4.8).

The contribution of factory farming to the projected global economic burden was then estimated by assuming our forecasts of the share of factory farms in total AMU (Table 4.7).

The estimation results are displayed in Figure 4.2 for the two scenarios, starting from 2019 and projected to 2022, 2030, 2040, and 2050. In Scenario One (business as usual), where there are no significant changes in animal health management globally (AMU per PCU is considered steady at the current levels), global AMU grows following the increase of livestock production and the consumer demand of animal products, the contribution of factory farming to the value of human productivity losses for AMR related to AMU in livestock production rises from 382.54 billion US$ in 2019 to more than one trillion US$ in 2040, and 1.67 trillion US$ in 2050. The cumulative cost for human societies will be 28.14 trillion US$ over the whole period. From a value corresponding to 0.43% of the global GDP in 2019, the contribution of factory farming to the estimated losses would attain a value equal to 0.84% of the global GDP in 2050 (Figure 4.3).

In Scenario Two (more prudent AMU), assuming that policies and measures undertaken at the global level to counter AMR succeed to reduce AMU at the same annual rate achieved in the EU during the last decade, the contribution of factory farming to the value of global human productivity losses for AMR related to AMU in farmed animals will decrease to 306 billion US$ in 2040, and 275 billion US$ in 2050, with cumulative savings of 17.69 trillion US$ over the 2019-2050 period if compared to Scenario one. The contribution of factory farming to the estimated losses would decline to a value corresponding to 0.14% of the global GDP in 2050 (Figure 4.3).

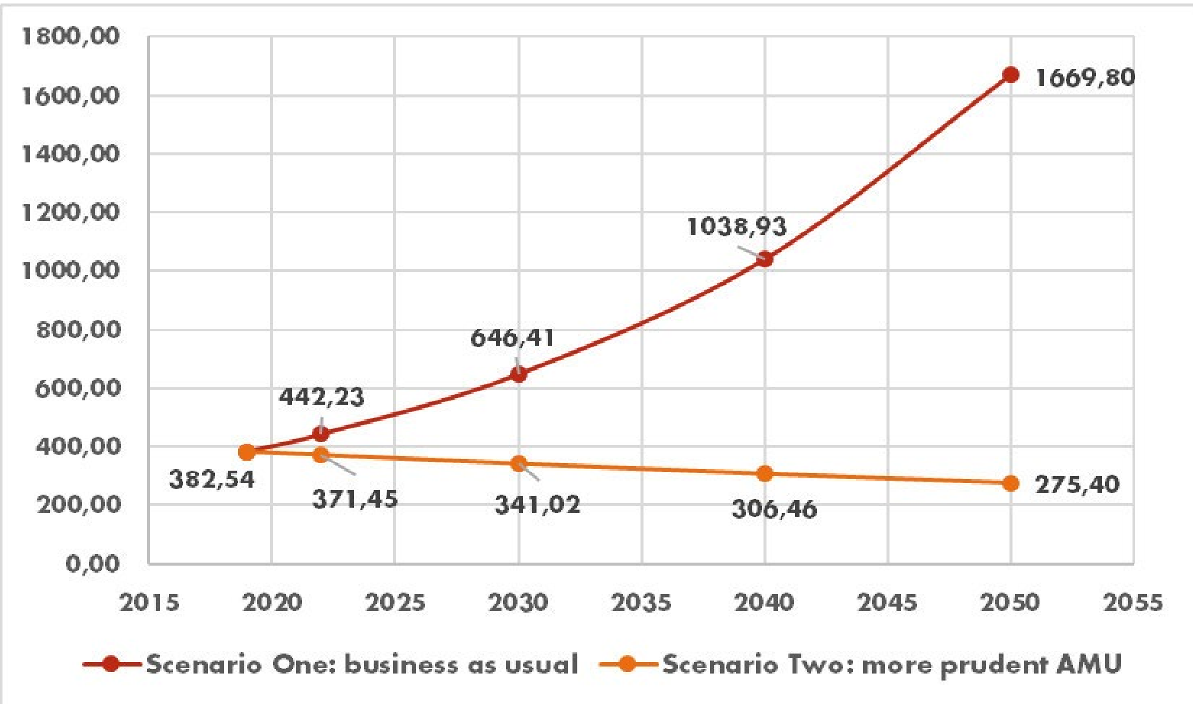


Figure 4.2 Contribution of factory farms to the global economic burden related to AMU in farmed animals (projected values in billion US$), (Own elaboration)

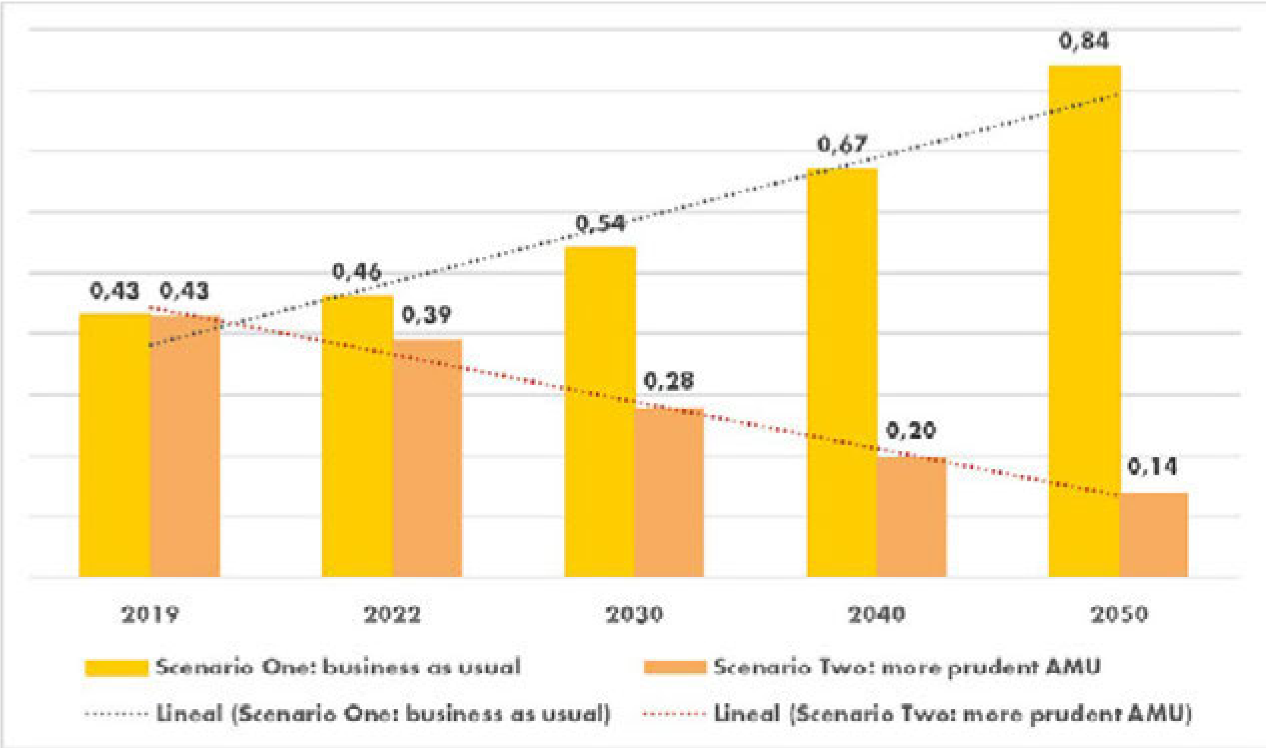


Figure 4.3 Contribution of factory farms to the global economic burden related to AMU in farmed animals (projected percentages of the global economic losses on the global GDP), (Own elaboration)

DISCUSSION AND CONCLUSIONS

The use of antibiotics in farmed animals

This study was designed to evaluate the economic impact of antibiotic resistant infections related to the use of antimicrobials in factory farming on society. Antibiotic resistance is a natural phenomenon, but the scientific literature attests the correlation between its emergence and the use of antibiotics in medical and veterinary care (D'Costa et al., 2011), and potential links between AMU in farmed animals and the spread of resistant infections in humans (Chokshi et al., 2019). In many countries, antibiotics are still used on farmed animals, not only against the spread of diseases but also as AGPs (Hickman et al., 2021). The AMU for farmed animals broadly exceeds the use in human medicine. Several studies that addressed this issue attributed from 60% to around 75% of global antibiotic consumption to animal husbandry (Okocha et al., 2018; Tiseo et al., 2020; Wegener, 2003).

Estimation of the global use of antibiotics on farmed animals and factory farms

Over the last decades, the growth of urban population and per capita income in many developing countries has led to an expansion of the industrial-scale production of food of animal origin, especially in regions that experienced this phenomenon only marginally during the 20th century. However, there are no international standard classifications or homogeneous systematic collections of data about different types of farmed animals. Based on the analysis of different national and regional sources and FAO data (FAOSTAT, 2022), our study estimated that, over the 2018-2020 period, factory farms raised 74.4% of poultry, 66.9% of pigs, and 41.9% of cattle globally. For aquaculture, we assumed that all global production of the six examined species (i.e., carp, catfish, salmon, shrimp, tilapia, and trout) is from factory farms.

We calculated the consumption of antibiotics using previous estimations on the total mg of active substances used per kg of animal biomass (or PCU) in the different species at the global level (Schar, 2020; Tiseo, 2020). The results show a global annual consumption of 80,541 tonnes of antibiotics, of which 47,156 tonnes or 58.5% on factory farms (2018-2020). As a comparison with figures produced by more detailed national surveys, in 2020, the sales of veterinary antimicrobials resulting from the EMA-ESVAC survey in 31 European countries were 5.6 thousand tonnes (EMA, 2021), in the USA, the FDA survey indicated an amount of 10.5 thousand tonnes for the same year (FDA, 2021), and the Nippon AMR One Health Report (NAOR) about one thousand tonnes for Japan in 2018 (The AMR One Health Surveillance Committee, 2021).

The non-therapeutic use of antibiotics in farmed animals

A report published in 2017 by the WHO noted that the use of antibiotics as growth promoters has a primary role in the consumption of these drugs (WHO, 2017c). 90% of all antibiotics used in farmed animals are administered at non-therapeutic concentrations, with a significant portion as AGPs (Hosain et al., 2021; Wu, 2018).

Our study found that more than 80% of global AMU on farms is for non-therapeutic purposes. For this estimation, we applied two different methods: the first was based on information from the literature on non-therapeutic uses in several countries and regions; the second utilised data from a survey comparing AMU in organic and conventional UK farms. With the first method we obtained a result of 84% of non-therapeutic treatments on global AMU, with the second 81%.

Correlation with AMR

Although most antibiotics are sold worldwide for usage on farmed animals, the scientific literature on the human burden from AMR from this practice is scarce, and the issue remains relatively unknown (Aarestrup, 2015; Bonten and Mevius, 2015; Tang et al., 2017). We investigated the correlation between the use of antibiotics and the spread of resistant infections in humans by using a spatial model, which also considers the cross-border effects of AMR at the global level, e.g., via international trade and people movements.

We focused on AMR caused by foodborne pathogens Escherichia coli, Staphylococcus aureus, Campylobacter, and non-typhoidal Salmonella, because of their relation with AMR in farmed animals (Heredia and García, 2018). Data on AMR from the four bacteria resulted from tests on isolated cultures collected by the CDDEP from a group of 30 countries selected among the first producers of the examined farmed animal species. We calculated the farms' AMU in the selected countries with the procedure applied for Chapter 1 estimations.

According to our findings, there is a robust correlation between the two variables. A global increase in AMU on factory farms of 1,000 tonnes results in a 21% increase in human resistant infections (r(323)=0.021, p=0.005). These results reinforce the outcomes of other studies exploring the links between farms' AMU and resistant infections in human patients (Emes et al., 2022; Godijk et al., 2022; Kim and Ahn, 2022; Lazarus et al., 2015; Nüesch Inderbinen et al., 2022; Sirichokchatchawan et al., 2021; Tang et al., 2017; Ye et al., 2016)

The review conducted as part of the research showed that tested Escherichia coli resistance to aminopenicillins is very high in human infections (73%). WHO categorized them as CIA. They are administered regularly on farmed animals (CDDEP ResistanceMap, 2021). On the contrary, Escherichia coli resistance to glycylcyclines is 1%. These antibiotics are rarely administered to animals (CDDEP ResistanceMap, 2021). They were developed to overcome microbial resistance to tetracyclines, one of the most widely used veterinary antimicrobial class. To saufguard glycylcyclines' efficacy, EMA reccomended restrictions on the veterinary use (EMA, 2013).

We found high Escherichia coli resistance to one or more antibiotics in many regions.

Staphylococcus aureus resistance to macrolides (CIA) in humans resulted extremely high, and this drug is frequently administered on farmed animals, while resistance to linezolid and vancomycin is low in humans (less than 1%) and these drugs are not utilized on farmed animals (CDDEP ResistanceMap, 2021). In the EU, Campylobacter resistance to ciprofloxacin and tetracycline is extremely high (ECDC, 2021). Ciprofloxacin and tetracyclines are also frequently used on farmed animals. This empirical data supports the findings of the statistical model used in this research, indicating that the most used antibiotics in both humans and farmed animals can significantly increase AMR in humans.

Considering the other factors that influence AMR, our results shows that the increase of AMR in humans is also correlated with rising individual income, finding a 13.5% increase when consumer income rises by 100 US$ (r(323)=0.135, p=0.000).

The model also indicates that countries with access to clean water, sanitation, and hygiene for both humans and animals have 12% lower rates of AMR in humans (r(323)=-0.121, p=0.064). Furthermore, the countries with some restrictions on antibiotics use in farmed animals had 7% fewer cases of AMR in humans than those without regulations (r(323)=-0.077, p=0.061).

Disease burden, cost of human productivity losses, and contribution of factory farming

Based on data from IHME (2022), our study calculated that, in 2019, resistant infections from the four examined bacteria globally caused 403 thousand deaths attributable to AMR (i.e., compared to a counterfactual where the drug-resistant infections are replaced by drug-susceptible infections), and 1.604 million deaths associated with AMR (i.e., compared to a counterfactual where drug-resistant infections are replaced by no infections). The global burden of these infections amounted to 13.65 million DALYs attributable to AMR and 56.84 million DALYs associated with AMR. Estimated global incidence per 1 million people resulted in 49.4 deaths and 1,730.3 DALYs attributable to AMR, and 197 deaths and 6,884.6 DALYs associated with AMR.

We assumed that all the burden globally associated with resistant Escherichia coli, Staphylococcus aureus, Campylobacter, and non-typhoidal Salmonella was related to AMU on farmed animals. On this hypothesis, we quantified the potential contribution of factory farming in 975 thousand deaths and 33.5 million DALYs associated with AMR. We obtained these figures by multiplying the global burden by the share estimated for factory farming on the global AMU in farmed animals (58.8%). Compared to other diseases, in terms of DALYs, the calculated burden is lower only to those indicated by the IHME database for cardiovascular diseases and diabetes mellitus and higher than AIDS, malaria and the most common cancers at the global level.

Assuming the global GDP per capita as the cost of one DALY, we calculated the economic value of global productivity losses from the people affected by AMR related to farmed animals at 648.37 billion US$ in 2019. Factory farms' contribution was 382.54 US$, corresponding to 0.43% of the global GDP. This evaluation does not consider other costs globally incurred by society that are not possible to quantify within the limits of this study due to the lack of available information: e.g., among the health costs, we could mention the costs of hospitalization and medical care, and resource use from patients, families, and other sectors (e.g., public social help). Further costs relate to livestock productivity losses, costs of veterinary care, and environmental contaminations from the spread of resistant pathogens. Other authors have highlighted the complexity of making a comprehensive estimate of the potential AMR costs (Dadgostar, 2019; Hillock et al., 2022; Innes et al., 2019; Morel et al., 2020; Shrestha et al., 2018).

Cost projections to 2050

Our projections indicate that in a business-as-usual scenario (Scenario One), where the amount of antibiotic administered per kg of animal biomass (PCU) remains constant over the 2019-2050 period, the global burden of the AMR related to AMU in farmed animals rises to 113.72 million DALYs in 2050 (no-infection counterfactual). In a more-prudent-AMU scenario (Scenario Two), where the implementation of policy strategies against AMR succeeds in reducing the AMU per unit of animal biomass globally with the same diminishing annual rate achieved by the EU in the last decade, the burden lowers to 18.76 million DALYs in 2050.

Both scenarios foresee a growth of globally farmed animals at an annual rate of 2.26% over that period and a share of factory farming in the global AMU rising from 58.5% to 71.8%, in parallel to its contribution to global animal production. The projected estimations of the economic value of the burden consider an annual growth in the global average GDP per capita of 1.9%. With those assumptions, under the business-as-usual scenario (Scenario One), the contribution of factory farming to the economic burden of AMR related to AMU in farmed animals rises to more than 1 trillion US$ in 2040 and 1.67 trillion US$ in 2050: about 4.3 times higher than in 2019. The 2050 economic burden corresponds to 0.84% of the global GDP estimated for that time, and the cumulative cost to human societies between 2019 and 2050 amounts to 28.14 trillion US$.

In the more-prudent-AMU scenario (Scenario Two), following the decrease of the global burden of AMR related to veterinary AMU, the value of factory farms' contribution declines to 275.4 billion US$ in 2050, corresponding to 0.14% of the estimated global GDP in 2050. Compared to the business-as-usual scenario, the more-prudent-AMU scenario would generate 17.69 trillion US$ of cumulative savings for society over the 2019-2050 period from the contributions of factory farming to global AMR burden.

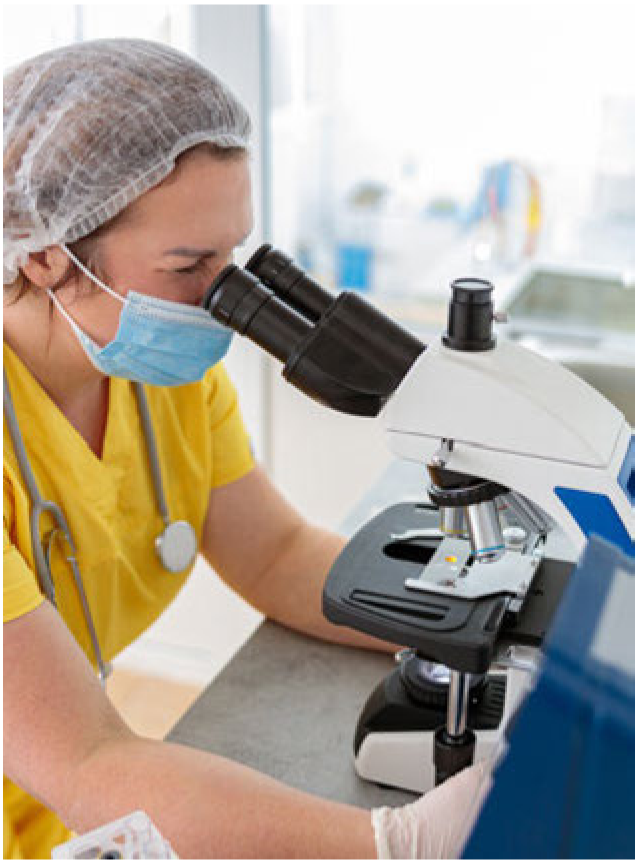
The projection of the AMR burden assumed that, over the period, global animal production will rise at the same rate as meat consumption, which we estimated from the OECD statistics and forecasts 1990-2029. We also assumed that the factory farming share in global animal production grows at the same increasing rate as the global urban population.

These hypotheses and other study limitations, described in detail in the following section, are mainly due to the lack of data and information necessary to develop the required evaluations.

Beyond the limitations, the study results show that if the AMU reduction achieved by European farms over the last decade becomes global, by 2050, the global AMR burden related to AMU in farmed animals may decrease significantly, although the market demand for animal products driven by rising population and per capita income, is set to grow.

Limitations of the study

The study objectives required carrying out many evaluations for which, in many cases, the needed data and information are non-available yet. This knowledge gap was a considerable constraint for our analysis. More generally, it is also a limitation for the actions addressing the overuse of antibiotics in factory farming, the impacts on public health, and the related costs. The lack of data made it necessary to develop the research based on a considerable number of hypotheses and assumptions, which constitute the main limitations of this research. We have summarized them in this section by following the four chapters of the study.



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Chapter 1

- Estimating the factory farming share of global animal production (Section 1.5). Lacking international standard definitions and classification methods for "factory farms" (the term, in general, is not used in livestock statistics and scientific literature), we assessed the share of factory farm production on the global outcome of animal farming based on the information available from different sources at the country or regional level. Therefore, the assessment was not homogeneous, and the evaluation of the factory farming share in one country or region might have been influenced by the diversity of criteria and definitions applied by the sources. For the selected aquatic species, we assumed that all the global production is from factory farms.

- Estimating the PCUs and the AMU on farmed animals and in factory farms (Sections 1.7-1.11). We calculated the regional and global PCUs by using one standard weight at treatment for all the animals of a given farmed species. Within one species, we made no distinctions between the different categories of animals (for example, regarding cattle, the same PCUs were attributed to adult cows, heifers, bulls, and calves), the regions, and the production systems (e.g., factory farms and other types of farms). For aquatic species, we assumed the weight of final products as PCUs. Similarly, to estimate global AMU, we used a standard annual dosage administered in mg of antimicrobials' active principles per PCU for each species without differentiating animal categories, regions, production systems, and between the dosages dispensed in factory farms and no-factory farms.

Chapter 2

- Assessing the non-therapeutic AMU by factory farms (Section 2.4). We developed the assessment with two distinct methods. With the first method, we used different sources according to data available for the countries and regions, making wide extrapolations in some regions where data were lacking. Then, problems of consistency of the assessment might arise due to the diversity of criteria used in the different sources and the extrapolations. In the second method, we used the results of a study on the differences in AMU between organic and conventional animal farms. We assumed that all the AMU in organic farms was therapeutic, and the difference between AMU in conventional and organic farms, in terms of mg per PCU, was non-therapeutic. We extrapolated our findings at the global level, with problems of accuracy of the final evaluation.

Chapter 3

- Analyzing the level of AMR affecting humans in countries and regions (Sections 3.2 and 3.4). We evaluated the level of AMR affecting humans in terms of the percentage of isolated bacterial cultures that tested positive in a country over one year (Section 3.2). The evaluation accuracy depends on the number of tests available in the country and the extent of the historical series. We extrapolated regional values from the country data but regions were differently covered. Some countries involved in the modelization (Section 3.4) for their role as relevant producers of commodities of animal origin had no available data regarding tests on isolates. For these countries, we assumed the regional data. Then, the data introduced in the model for the dependent variable (AMR affecting humans) might be influenced by these biases.

- Data on AMU in factory farms for the Spatial Error Model (Section 3.4). The model's most relevant independent variable for the analysis is the level of AMU in factory farms. For this variable, we needed ten-year historical series from the countries involved. Such data were not available. Then, we estimated the AMU based on FAOSTAT data on animal production in the different countries, applying the method used in Chapter 1 and considering, for each country, the share of factory farms in total animal production assessed for the respective region. The lack of data on AMU directly collected in factory farms might affect the consistency of the model outcomes.

Chapter 4

- Estimation of the global burden from AMR related to AMU in animal production and the contribution of factory farming (Section 4.2). Lacking more accurate information, we assumed that all the resistant infections from Escherichia coli, Staphylococcus aureus, Campylobacter, and non-typhoidal Salmonella, and only those resistant infections, were globally related to AMU in animal production. Therefore, we calculated all the global deaths and DALYs from the resistant four bacteria as related to AMU in farms. Regional and global data on resistant Campylobacter infections were not available. For these infections, we could find only data from the USA that we extrapolated at the global level. To evaluate the contribution of factory farming to the AMR burden, we assumed that it was proportional to the portion of global farm AMU dispensed in factory farms estimated in Sections 1.8-1.11. The consistency of the estimate depends on the occurrence of these assumptions.
- Assumptions for the projection of costs related to AMU in factory farms to 2050 (Section 4.4). The two scenarios set up for cost projection assumed that (1) the global number of farmed animals (and PCUs) increases at an annual rate of 2.26%, corresponding to the increase in global meat consumption estimated by the OECD for the 1990-2029 period; (2) the global average GDP per capita, taken as the value for one DALY, increases by 1.9% annually, corresponding to the increase of the global average GDP per capita estimated by The World Bank for the 1960-2020 period; (3) the share of factory farming on total animal production increase at the same growth rate of the global urban population, estimated by the FAO for the 2020-2050 period. Scenario Two (Section 4.4.3) considered an annual 5.78% reduction of farm AMU per PCU over the 2020-2050 period, corresponding to the decrease recorded by the EMA-ESVAC project over the 2011-2021 period. The predictive potential of our projection is subject to these hypotheses.

Conclusions

The WHO and other intergovernmental public health organizations stress the need to avoid the overuse of antibiotics in humans and farmed animals to safeguard the efficacy of these medicines crucial for human and animal health. Our study found that more than 80% of global AMU on farmed animals is not for individual therapies but for prophylaxis or metaphylaxis or to promote animal weight gains. AGP use is not related to animal health management but to enhance production performances. For this reason, the WHO suggests its phasing out in the absence of risk analysis. Animal welfare, farm biosecurity, vaccines, alternative medications, and integrators can contribute to consistently reducing antibiotic prophylaxis and metaphylaxis.

The WHO Global Action Plan against AMR recommends that national authorities implement plans to counter AMR insurgence and spread and indicate a set of coordinated measures covering different types of actions for the livestock sector: increase of stakeholders' and consumers' awareness, monitoring of AMU in farms and AMR across the agro-food supply chain, improvement of farm best practices for animal welfare and health management, and tightening AMU regulation and strengthening governance by harmonizing the initiatives of all public and private actors involved (WHO, 2015).

After banning AGPs in 2006, the EU launched its first Action Plan against AMR in 2011 and the second in 2017 with a reinforced One Health approach (European Commission, 2017a). The EU Plan aims to make Europe a best-practice region for AMU, boost research and innovation and contribute to shaping the global agenda against AMR. Among the most significant EU initiatives in the livestock sector there are the establishment of a standardized farm AMU monitoring and traceability system throughout Europe (European Union, 2021), the guidelines provided to Member States to design their national plans (European Commission, 2017b), the new regulations limiting both the use of critically important antimicrobials (CIAs) and the recourse to non-therapeutic treatments (European Union, 2019a, 2019b), and the introduction of the AMR issue within the European Common Agricultural Policy, by setting a target of 50% reduction of AMU in European farms by 2030 (European Commission, 2022, 2020). EU and Member States' initiatives led to a 43.2% reduction in the sales of veterinary antibiotics per PCU in Europe between 2011 and 2021 (EMA, 2022a).

The estimates made for this study indicate the real possibility of significantly reducing AMU in farms globally over the coming decades, despite the increase of the world's urban population and income, suggesting a continued growth of the international trade of products of animal origin. A worldwide extension of the advancements that Europe has attained in recent years would reverse the current trend of antibiotic consumption for animal use and decrease the social and economic costs of AMR caused by AMU on farmed animals.

Compared to a business-as-usual situation, our more-prudent-AMU scenario projects global savings for avoided productivity losses from deaths and disabilities that we cumulatively estimated at 17.7 trillion US$ between 2019 and 2050. On the other hand, the continuation of the current levels of AMU per livestock unit would multiply by more than four times the cost of the disease burden over the period.

The global implementation of the more-prudent-AMU scenario proposed in this study is not an easy achievement. But the European experience indicates that it is feasible and the measures recommended by the Global Action Plan can bring effective results. National governments should take decisions based on this perspective and collaborate to improve the operation of the Global Action Plan.

National plans should stimulate stakeholders to adopt knowledgeable and site-specific measures to improve animal welfare, prevent and control animal infections and safeguard the effectiveness of veterinary treatments. The pharmaceutical industry and public-sector research should intensify investments in novel antimicrobials and explore alternatives to antibiotics at risk of becoming obsolete due to AMR in farms. Possible options include vaccines, immune modulators, bacteriophages, endolysins, hydrolases, infeed enzymes, prebiotics, probiotics, peptides, organic acids, and phytochemicals. The prevention of disease through proper husbandry, improved biosecurity and animal welfare, genetics, and feeding, as opposed to the frequent use of prophylactic medications, is a fundamental strategy for lowering AMU in factory farming.

AGPs and other non-therapeutic treatments should be phased out globally, and strict limitations required for CIAs' use. The examples of countries and livestock systems adopting more stringent measures on farm AMU suggest the possibility of limiting antibiotic prophylaxis and avoiding significant reductions in animal performances and health conditions when animal welfare and farm biosecurity are adequately improved (Diana et al., 2019; Emborg et al., 2001; Grundin et al., 2020; Laine et al., 2004; Wierup, 2001). Concerning the possible economic impacts, the information available in the scientific literature did not find any evidence of disruption in production costs and farm income related to the application of these measures (Belay and Jensen, 2022; Jensen et al., 2021; Lawson et al., 2008; Laxminarayan et al., 2015; McEwen et al., 2018; Pasquali et al., 2021; Roskam et al., 2019; van Asseldonk et al., 2020). On the contrary, there is evidence that animal welfare and farm biosecurity practices can be cost-effective ways to reduce AMU in farms (Albernaz-Gonçalves et al., 2022; Collineau et al., 2017; Rodrigues da Costa and Diana, 2022, 2022; Rojo-Gimeno et al., 2016).

Governments should cooperate to establish harmonized regulations and metrics to monitor, trace, and optimize AMU in farms. Food supply chain transparency regarding the use of antibiotics in food-producing animals should enable better-informed consumer choices on this issue.

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Appendix A

Table A. 1 Methodological references used to estimate the share of animals raised in factory farm on total farmed animals

Region or Country	Reference Method
Northern America	https://www.sentienceinstitute.org/us-factory-farming-estimates
Latin America and the Caribbean	For pigs and poultry: Method based on livestock densities (Robinson et al. 2011). For dairy and beef: Method based on the proportion of industrial + mixed irrigated systems (FAO, 2007).
Western, Southern, and Northern Europe	Eurostat: Share of Specialised farms
France	Correction for pigs and poultry according to https://www.animal-cross.org/animaux-delevage/elevage-industriel/
Eastern Europe and Central Asia	Eurostat: Share of Specialised farms (calculated only with data from Eastern Europe and extrapolated for Central Asia)
Central Asia	Correction for poultry and pigs according to (Robinson et al. 2011)
South Asia	For pigs and poultry: Method based on livestock densities (Robinson et al. 2011). For dairy and beef: Method based on the proportion of industrial + mixed irrigated systems (FAO, 2007).
India	Correction for poultry and pigs according to (Robinson et al. 2011)
China	Correction for poultry and pigs according to (Robinson et al. 2011)
Japan and South Korea	Correction: We adopted the same values of North America based on the similarity of livestock production systems.
East Asia and the Pacific	For pigs and poultry: Method based on livestock densities (Robinson et al. 2011). For dairy and beef: Method based on the proportion of industrial + mixed irrigated systems (FAO, 2007).
Australia and New Zealand	Correction: We adopted the same values as Western Europe, based on the similarity of livestock production systems.
The Middle East and North Africa	For pigs and poultry: Method based on livestock densities (Robinson et al. 2011). For dairy and beef: Method based on the proportion of industrial + mixed irrigated systems (FAO, 2007).
Sub-Saharan Africa	For pigs and poultry: Method based on livestock densities (Robinson et al. 2011). For dairy and beef: Method based on the proportion of industrial + mixed irrigated systems (FAO, 2007).

(Own elaboration)

Table A. 2 Estimates of the share of animals raised in factory farm on total farmed animals based on countries' GDP per capita

Regions	Poultry (%)	Pigs (%)
East Asia and Pacific	84.45	52.25
Europe and Central Asia	89.90	79.26
Latin America and the Caribbean	87.57	50.29
Middle East and North Africa	83.60	92.18
Northern America	90.00	95.00
South Asia	51.33	50.00
Sub-Saharan Africa	65.29	48.97

(Own elaboration from: Gilbert et al., 2015)

Appendix B

Table B. 1 Percentages of antibiotics administered on farmed animals as premixes, orally, and via feed or water (Method 1)

Region or Country	Year	Premixes (A)	Oral (B)	Feed or Water (C)	(A) + (B) + (C)	Source
Europe	2020	22.50%	7.40%	57%	**86.90%**	(Nunan, 2022)
United Kingdom	2018	-	-	73%	**73.00%**	(POST, 2018)
Ireland	2018	29.20%	38.10%	-	**67.30%**	(Martin, 2020)
South Asian	2021	-	-	-	**90.00%**	(Hosain et al., 2021)
Uganda	2020	-	-	-	**46.00%**	(Mikecz et al., 2020)
USA	2019	-	-	94%	**94.00%**	(CIDRAP, 2020)

Table B. 2 Antibiotic use in organic and non-organic UK farms (mg per PCU) (Method 2)

Species	(A) Non-Organic Farms (mg/PCU)	(B) Organic Farms (mg/PCU)	(A) / (B)
Dairy	22.50	10.66	2.11
Beef	24.40	7.22	3.38
Pigs	110.00	1.42	77.46
Broilers	17.00	2.95	5.76
Average	**31.00**	**7.46**	**4.16**

(ASOA, 2021)

Appendix C

Table C. 1 Number of AMR tests on isolated bacterial cultures of Escherichia coli, Staphylococcus aureus, Campylobacter, and non-t. Salmonella in the different world regions with indication of the countries that provided data

Region	Countries	Bacteria	Total tests (N.)
East Asia and the Pacific	Australia, Cambodia, China, Indonesia, Japan, Korea, Laos, Malaysia, Myanmar, Nepal, New Zealand, Philippines, Taiwan, Thailand, and Vietnam.	Escherichia coli, and Staphylococcus aureus	1,332,283
Europe and Central Asia	Austria, Belarus, Belgium, Bosnia and Herzegovina, Bulgaria, Croatia, Cyprus, Czech Republic, Denmark, Estonia, Finland, France, Georgia, Germany, Greece, Hungary, Iceland, Ireland, Italy, Kosovo, Latvia, Lithuania, Luxembourg, Macedonia, Montenegro, Netherlands, Norway, Poland, Portugal, Romania, Russia, Serbia, Slovakia, Slovenia, Spain, Sweden, Switzerland, Turkey, and the United Kingdom.	Escherichia coli, and Staphylococcus aureus (all countries) + Campylobacter and non-t. Salmonella (only in the EU countries)	6,087,453
Latin America and the Caribbean	Argentina, Brazil, Chile, Ecuador, Mexico, and Venezuela.	Escherichia coli, and Staphylococcus aureus	158,599
Middle East and North Africa	Bahrain, Egypt, Iran, Jordan, Lebanon, Malta, Oman, Saudi Arabia, Sudan, Tunisia, and the United Arab Emirates.	Escherichia coli, and Staphylococcus aureus	35,288
North America	Canada and the United States.	Escherichia coli, and Staphylococcus aureus	1,167,477
South Asia	India, Pakistan, and Sri Lanka.	Escherichia coli, and Staphylococcus aureus	65,010
Sub-Saharan Africa	Ghana, Kenya, Madagascar, Malawi, Mali, Nigeria, South Africa, Zambia, and Zimbabwe.	Escherichia coli, and Staphylococcus aureus	195,655

(CDDEP, 2021; ECDC, 2021)

Table C. 2 Critically important antibiotics (CIAs) and highly important antibiotics (HIAs) for human health used on farmed animals

Critically important antibiotics (CIAs)	Highly important antibiotics (HIAs)
Aminoglycosides	Amphenicols
Cephalosporins (3rd and 4th)	Cephalosporins (1st and 2nd)
Aminopenicillins	Cephamycin
Ansamycins	Lincosamides
Carbapenems	Penicillins
Glycopeptides	Streptogramins
Glycylcyclines	Sulfonamides, Trimethoprim and Combinations
Macrolides	Tetracyclines
Monobactams	
Oxazolidinones	
Phosphonic Acid	
Polymyxins	
Quinolones	

(CDDEP ResistanceMap, 2021)

Appendix D

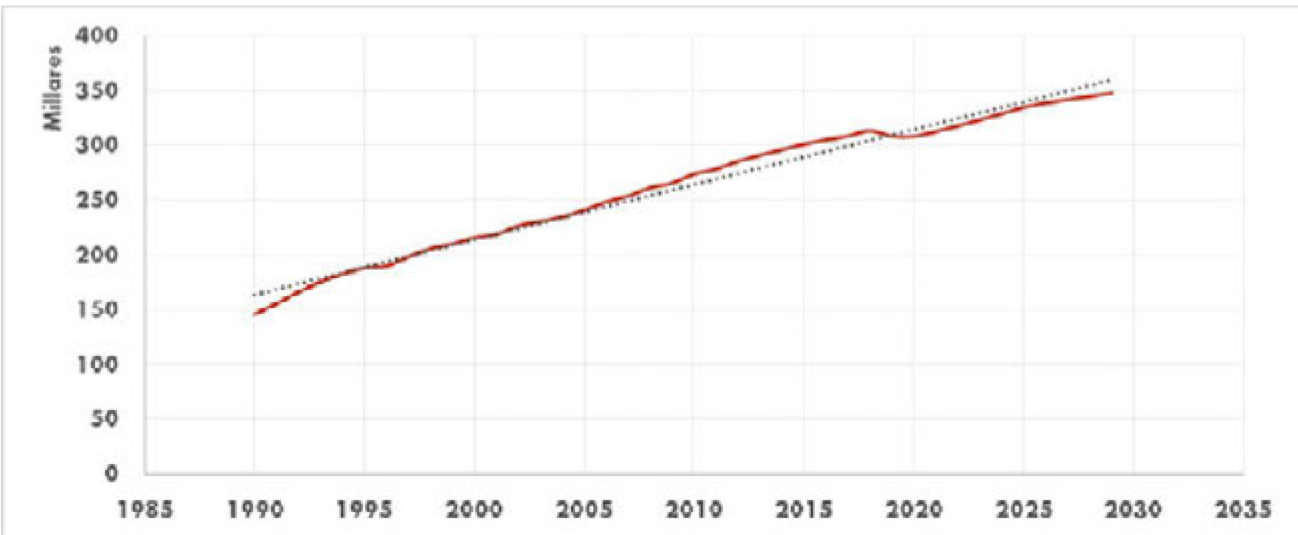

Figure D. 1 Trend of global meat consumption (OECD, 2022)

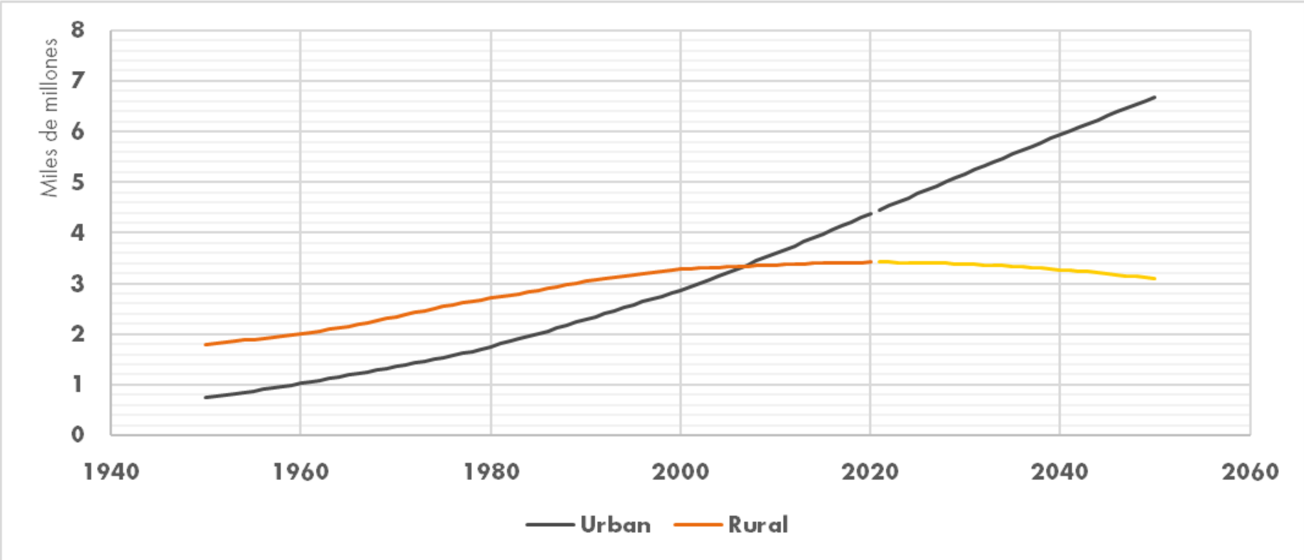

Figure D. 2 Trend of global urban and rural population (United Nations, 2022)

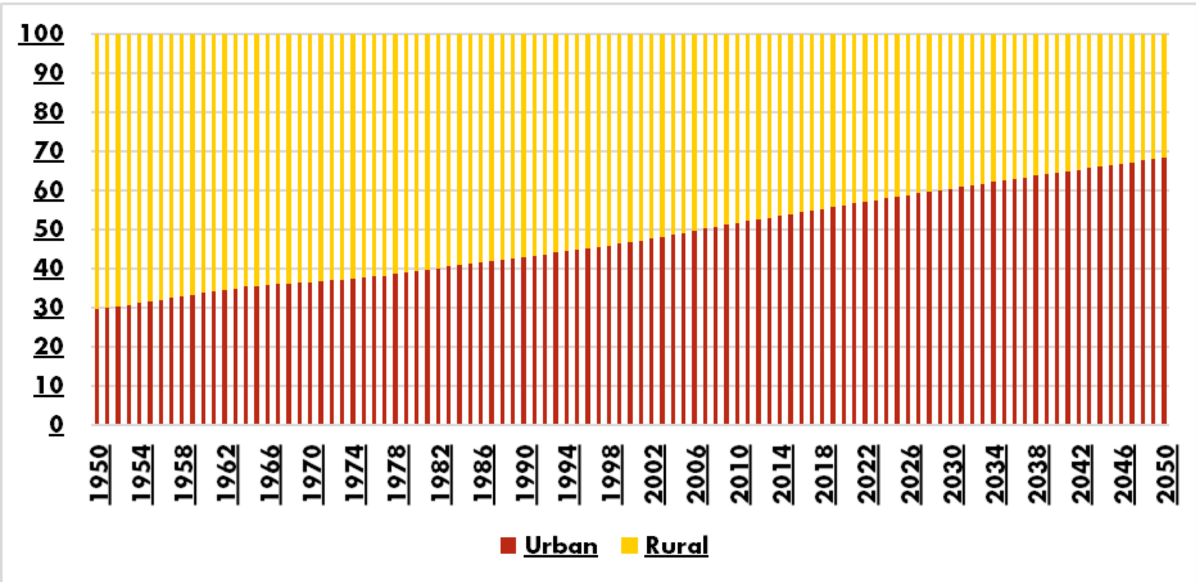

Figure D. 3 Trend in the distribution of urban and rural population (United Nations, 2022)

This research was produced by a group of researchers of the Department of Agricultural and Food Sciences, University of Bologna for World Animal Protection. The views and opinions expressed in this report do not reflect the views or positions of the Dept. of Agricultural and Food Sciences of the University of Bologna.

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World Animal Protection is an international animal welfare organization. Our mission is to create a better world for animals. From the frontlines of disaster zones to the boardrooms of large corporations, we are fighting to create better lives for all animals. World Animal Protection is registered with the Charity Commission as a charity and with Companies House as a company limited by guarantee. World Animal Protection is governed by its Articles of Association. Charity registration number 1081849. Company registration number 4029540. Registered office 222 Gray's Inn Road, London WC1X

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