8-10-2024

Antibiotic Resistance in Livestock: A Literature Review of Its Consequences and International Effort on Human Antimicrobial Agents Resistant Crisis

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Abstract

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Background: Despite their benefits, the overuse of antibiotics in livestock has resulted in negative consequences to human health and the augmenting of an antibiotic-resistant crisis. Countries worldwide have conducted analyses and confirmed the growth of bacterial strains immune to most antibiotics. The widespread use of antibiotics is shown in various sectors, including human medicine and agriculture, leading to the emergence of antibiotic-resistant bacterial strains.

Purpose: This comprehensive literature review focuses on finding the connection between the usage of antibiotics in livestock, the transfer of antibiotic resistance to humans through consumption and exposure, and international efforts to find solutions to antimicrobial alternatives.

Methods: A review of literature on "Antibiotic resistance in livestock" was conducted using the NIH and Google Scholar databases to identify relevant peer-reviewed articles and reports on antimicrobial use and resistance. Inclusion criteria were studies showing how antibiotic use in livestock impacts human health through meat consumption and farming exposure, and exclusion criteria were analysis of environmental contamination issues.

Conclusion: Antibiotic usage in livestock causes the development of antibiotic resistance in bacteria, which harms humans and wildlife populations. Therefore, limitations and regulations on the use of antibiotics are set to avoid drug-resistant evolution. In addition, some alternatives to antibiotics include pre-and-probiotics, vaccines, and essential oils to protect livestock against common diseases. Other alternatives to antibiotics may be more cost-efficient and may not be therapeutically effective as a lifelong course of antibiotics. However, it is an entirely separate problem to develop a feasible program for the subsidization of non-antibiotic treatment by the agricultural industry.

Key Words: Antibiotic-resistant-organism, Meat consumption and antibiotic resistance, Antibiotic-treated livestock, Global crisis of antibiotic resistance

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Introduction.

In 2018, the World Health Organization has declared resistance to antimicrobial factors as one of the most serious threats to public health globally (World Health Organization, 2018). This phenomenon has long been predicted by Alexander Fleming, the first microbiologist to discover antibiotics. During his Nobel lecture, he warned that poorly managed consumption of antibiotics would eventually lead to the evolution of antibacterial resistance among the population (Fleming, 1945) Today, Fleming's vision is becoming reality as the frequent introduction of antibiotics in agriculture has set the stage for a massive global evolution of drug-resistant microbes.

In livestock, antibiotics are used to treat, prevent, and control common diseases. Despite their benefits, the overuse of antibiotics in livestock has resulted in negative consequences to both human health and the environment around us. Human exposure to antimicrobial-resistant pathogens occurs throughout various pathways including farm environments, food production chains, consumption of contaminated food, and exposure to contaminated water and soil. However, while meat consumption exposes humans directly through the consumption of meat products or indirect ingestion of resistant bacteria; waste contamination affects humans indirectly through environmental exposure via contaminated water, soil, or crops. For that, waste contamination has broader environmental implications beyond human health, and should be addressed separately from this paper, whose main approach is human infectious diseases.

This literature review examines the current situation of antibiotic usage among the livestock industry; as well as addressing the transmission of antibiotic-resistant microorganisms between animals and humans through direct consumption. Prevalence data may provide some perspective on occurrence and changes in resistance over time; however the reasons are diverse and complex. The current literature surrounding the overview and mechanism of the antibiotic resistance crisis will be presented, followed by the studies focusing on separate regions of the world including South East Asia(Vietnam, Thailand), Chile, Danmark, USA, China, Italy, European Countries (Spain, Germany, France, the Netherlands, the United Kingdom, and Norway), and then suggested solutions. Subsequently, a thorough examination and evaluation of the entire body of literature will culminate in conclusions, offering recommendations for future research endeavors and outlining the subsequent actions to be taken.

Methods.

A thorough review of the literature was undertaken by searching the National Institutes of Health and Google Scholar databases using several keywords "Antibiotic resistance in livestock", “Antimicrobial resistance genes”, “Antibiotic resistance from livestock consumption”, and “Overuse of antibiotics in livestock.” The search aimed to identify pertinent peer-reviewed articles, national and global literature reports, as well as databases related to antimicrobial use and resistance. Understanding these mechanisms of genetic resistance is crucial for developing strategies to combat antibiotic resistance and preserve the efficacy of antimicrobial therapies.

Inclusion criteria were studies that livestock that are treated with antibiotics would have an impact on human health via consumption and farming exposure routes. When humans consume meat from these animals, they can ingest these resistant bacteria or antibiotic residues, which may contribute to the spread of antibiotic resistance.

Exclusion criteria include vegetables, soil, and waste from antibiotic livestock consumers, as this focuses on a different mode of transmission of antibiotic resistance that is not through direct consumption by humans. Animal waste from farms contains antibiotics, resistant bacteria, and antibiotic residues. This waste can contaminate soil, water sources, and crops if not properly managed. When antibiotics enter the environment through waste, they can exert selective pressure on bacteria present in the environment, promoting the development and spread of antibiotic resistance in soil and waterborne bacteria.

Both meat consumption and waste contamination strongly drive antibiotic resistance, with meat products directly exposing humans to resistant bacteria, while waste products affect health indirectly through environmental contamination. With environmental issues being broader than human health and infectious diseases, which is the main focus of this paper, this topic should be addressed separately in another paper.

Background/Literature Review.

Overview of Antibiotic Resistance and the Correlation Between Consumption of livestock

Antibiotic resistance development occurs through two primary pathways: vertical acquisition via de novo mutations and horizontal acquisition through the introduction of antibiotic resistance genes. Understanding these mechanisms is crucial for developing effective strategies to combat antibiotic resistance and preserve the effectiveness of antibiotics for treating bacterial infections in humans and animals.

Vertical acquisition refers to the vertical gain of resistance within a specific population of bacteria through the preservation and transfer of mutations that allow drug resistance. Mutations bring resistance to particular antibiotics or whole groups of drug classes, such as fluoroquinolones. For example, bacterial cells use topoisomerases to code for their genes. When fluoroquinolones are applied to a mutated topoisomerase, binding affinity is reduced as well as effectiveness. Furthermore, mutations give rise to colonies of bacteria that exhibit low growth rates, thereby lessening the impact of antibiotics and leading to the recurrence of infections. De novo mutations can also result in multidrug resistance by causing overexpression of efflux-pump proteins, such as AcrAB-TolC, which expel antibiotics from bacterial cells[1].

On the other hand, bacteria use transposition, conjugation, transformation, and transduction to disperse antibiotic-resistance genes among microbial cells, a process known as horizontal acquisition. Plasmids and conjugative transposons serve as vehicles for the dissemination of resistance genes among bacterial populations. Genes from these classes, with Kluyvera and Shewanella species serving as representatives. Integrons, genetic elements containing integrase genes, recombination sites, and promoters, also play a significant role in horizontal gene transfer. It is noted that integrons can carry numerous resistance gene cassettes and contribute to the spread of antibiotic resistance worldwide.

Both vertical and horizontal acquisition of antibiotic resistance genes are driven by selective evolution, leading to the emergence and spread of resistance to multiple classes of antibiotics. The use of antibiotics in food-producing animals has been linked to the emergence

[1] Vidovic N, Vidovic S. Antimicrobial resistance and food animals: Influence of livestock environment on the emergence and dissemination of antimicrobial resistance. MDPI. January 31, 2020. Accessed July 18, 2024. https://www.mdpi.com/2079-6382/9/2/52.

and spread of antibiotic resistance globally. Regulations prohibiting the use of antibiotics as growth promoters in food animals have been implemented in various regions to address this issue.

The Emergence of Antibiotic Resistance

Antibiotic resistance develops along a trajectory that involves multiple elements: the misuse of antibiotics, poor general public hygiene, and the lack of new drugs (as in the 1990s that began Methicillin-resistant Staphylococcus aureus development). The most concerning outcome of antibiotic resistance is an increasing number of deaths due to multidrug-resistant bacterial infections. In 2020, Kumar et al. showed that microorganisms evolve to develop resistant genes against antibiotic treatments through either vertical or horizontal gene transfer. This, thus, significantly compromises the available drugs to treat infectious diseases. The comprehensive study by Kumar and colleagues demonstrates drug-resistant organisms' routes to the food chain and their consequences for public health and well-being. Large-scale animal farming occurs worldwide, serving as a source of food and various materials as well as a labor transfer for transportation and agricultural activities, particularly in developing countries. Under crowded and unsanitary ground conditions, farmers maximize the growth and health of farm animals, aware that they typically receive low-dose antibiotics in their feed and water to prevent diseases. This massive application of these medicines thus paves the way for their propagation into the environment and fuels the emergence of antibiotic-resistant bacteria. In 2010, the five countries with the largest global antimicrobial consumption in livestock were China (23%), the United States (13%), Brazil (9%), India (3%), and Germany (3%).[2]

Humans develop antimicrobial resistance through consuming contaminated foods and beverages, direct exposure to livestock animals, or environmental exposure, especially from drinking contaminated water. Pathogens affecting both animals and humans can transfer antibiotic resistance genes (ARGs) to human pathogens. For instance, administering fluoroquinolones such as enrofloxacin to meat-producing animals has triggered the occurrence of strains of Salmonella, Campylobacter, and E. coli that are resistant to ciprofloxacin, which is the most common treatment for these infections. Furthermore, the international exchange of animal products carrying ARGs allows for the introduction of antibiotic resistance to previously uninfected regions[2]. The use of Avoparcin, a glycopeptide antibiotic and growth promoter in European livestock, made it easier for Vancomycin-resistant enterococci to spread among human gut flora, meat products, and commensal microbes of animals around the world.

For the past couple decades, the excessive use of antibiotics in medicine and animal and plant husbandry has been drastically escalated to handle the ever-increasing food demand. This intensive use in food production gives rise to the spread of antibiotic-resistant genes (ARGs) and antibiotic-resistant bacteria (ARBs). The movement of resistance bacteria and resistance genes between human-associated, animal-associated, and environmental microbiomes in food production systems across borders only worsens such a problem. The consumption of food

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[2] Kumar, S. B., Arnipalli, S. R., & Ziouzenkova, O. (2020). Antibiotics in food chain: The consequences for antibiotic resistance. Antibiotics, 9(10), 688.

products, particularly raw vegetables and animal-derived foods, serves as a significant route for acquiring ARGs.[3]

Global factors such as overpopulation, international travel, and host movements also contribute to the current dissemination of ARGs on a planetary scale. Within the food production industry, occupational workers notably face health risks from frequent exposure to antibiotic-contaminated environments and pathogens. According to the U.S. FDA's 2021 summary report[3], more than half of medically important antibiotics are being used in animal farming, which poses a significant concern when it negatively affects the food production industry. The antimicrobial agents are only partially metabolized and excreted into the environment through urine and feces, mainly in the form of manure and wastewater. Even in organic farming where antibiotics are not used, these risks remain. With evidence of shared Colistin resistance genes between animals and farmers, there is consideration of potential transmission pathways through direct contact and environmental contamination. A similar concept also highlights ready-to-eat meat products often harbor pathogens with high antibiotic resistance prevalence, increasing human infection risks.

Over time, the communities of undefeated bacteria enter the food supply and infect the consumers, resulting in an increase of allergies in humans and also a lethal phenomenon called " the Superbug", which has resulted in many of the current treatments for bacterial infections in human populations to become ineffective[4]. In reality, we are running out of time and effective antibiotics in our own race against antibiotic-resistant bacteria[5].

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[3] Tiedje, J. M., Fu, Y., Mei, Z., Schäffer, A., Dou, Q., Amelung, W., ... & Wang, F. (2023). Antibiotic resistance genes in food production systems support One Health opinions. Current Opinion in Environmental Science & Health, 100492.

[4] Padhy A, Sahu AR, Ranabijuli S, Ganguly S. (2016) Superbug, an emerging global threat in current scenario: A Review. International Journal of Research Studies in Microbiology and Biotechnology.;2(2). doi:10.20431/2454-9428.0202003

[5] World Health Organization. (2019). Antibacterial agents in clinical development: an analysis of the antibacterial clinical development pipeline.World Health Organization; 2019. Accessed July 23, 2024.

Superbug

The superbug, in essence, is a pathogen resistant to the majority of antibiotic classes. Superbugs, which are members of the gene pool of bacteria responsible for increased morbidities and mortalities due to multiple drug resistances, manifest great difficulties in healthcare. In the last two decades, infections arising from multidrug-resistant organisms have peaked due to the emergences of enzymes like extended-spectrum β-lactamases (ESBLs), carbapenemases, and Metallo-β-lactamases[6]. The consequence is surging of "Superbug" that is resistant to Penicillin, third-generation cephalosporins, and carbapenems, which are the most commonly used antibiotics in the clinical setting. Another example is the case of multidrug-resistant Mycobacterium tuberculosis or different bacterial pathogens, including Klebsiella pneumoniae, S. aureus, Acinetobacter, Burkholderia, and E. coli. At the same time, the Community-Associated Methicillin-Resistant Staphylococcus Aureus (CA-MRSA) strains are the ones that cause the highest risks in terms of the virulence and antibiotic resistance of S. aureus for the general population. Pathogenic bacteria usually contain harmful virulence properties that can enable them to colonize and attack the host tissue.

Multiple strains of bacteria have developed resistance to antibiotics, demonstrated through various mechanisms, shown in Table 3 from a study by Kumar et el.[2] :

[6] Aslam, B., Wang, W., Arshad, M. I., Khurshid, M., Muzammil, S., Rasool, M. H., ... & Baloch, Z. (2018). Antibiotic resistance: a rundown of a global crisis. Infection and drug resistance, 1645-1658.

Table 3

ARG in animal production settings.

Sl. No.	Bacterial Species	Infection	Antibiotic Resistance Pattern	Sources of Human Infection	Genes
1	*Campylobacter* spp.	Gastrointestinal sequelae: Guillain-Barré syndrome	Fluoroquinolones, erythromycin	Food-producing animals (poultry)	*tetO, gyrA* [39,40]
2	*Enterococcus* spp.	Sepsis, urinary tract	Aminoglycosides ampicillin vancomycin	Food-producing animals (poultry); People exposed to hospital care, food animals	*Tuf, VanC-1, VanC-2-VanC-3, pbp5* [41,42,43,44,45]
3	*E. coli*	Gastrointestinal, urinary tract, diarrhoea	Quinolones sulphonamides trimethoprim	Childcare facilities	*Bla, qnrS, frdD* [46,47,48]
4	*Salmonella* spp. (non-typhoidal)	Gastrointestinal, diarrhoea	Cephalosporins quinolones tetracyclines	Food-producing animals (pigs, cows, poultry)	*IntI1, qnrA* [49,50,51,52]
5	*S. pneumoniae*	Otitis media, pneumonia, sinusitis, meningitis	Penicillin, macrolides, cephalosporins, tetracyclines	Childcare facilities, paediatric populations	*erm(B), mef* [53,54,55,56]
6	*S. pyogenes*	Pharyngitis, impetigo, cellulitis	Macrolides, tetracyclines	Childcare facilities, paediatric Populations, schools	*ermB, ermA and mefA* [57]
7	*S. aureus*				
	Community-associated	Skin, soft tissue, pneumonia, sepsis	Methicillin, cephalosporins, macrolides	Childcare facilities, injections, drug users	*erm(A), erm(C), tetK, tetM, aacA-aphD, vat(A), vat(B) and vat(C)* [58,59]
	Healthcare-associated	Endocarditis, pneumonia, sepsis	Methicillin, cephalosporins, quinolones, aminoglycosides, macrolides	People exposed to healthcare facilities such as nursing homes, dialysis, recent surgery or hospitalization	
8	*N. gonorrhoeae*	Urethritis, pelvic inflammatory disease	Penicillin, cephalosporins, quinolones	Commercial sex workers	*penA, penB, NorM* [60,61]

Common livestock antibiotics are also frequently used in human medicine for their empiric characteristics. Meaning, poor choice of livestock antibiotics could lead to consequences in human health when it comes to treating infection. For example, Tetracyclines, which are poorly absorbed by the animal, and their active residues can concentrate in meat, urine, and feces. A study of broiler farms in Egypt, found higher levels of chlortetracycline and oxytetracycline in chicken litter than other types of antibiotics[7]. The existence of antibiotic residues in the environment creates on-site selection pressure, resulting in the presence of antibiotic-resistant-bacteria, which are often isolated from manure samples.

While antibiotic resistance and bacterial virulence have independently evolved over time, they share common features of horizontal gene transfer in survival and withstanding the effects of antimicrobial agents through Darwinian selection[5]. This is achieved by developmental defenses such as target site alteration, drug entry inhibition, and production of enzymes to

[7] Zalewska M, Błażejewska A, Czapko A, Popowska M. 2021 Mar 29. Antibiotics and Antibiotic Resistance Genes in Animal Manure - Consequences of Its Application in Agriculture. Front Microbiol. ;12:610656. doi: 10.3389/fmicb.2021.610656. PMID: 33854486; PMCID: PMC8039466.

degrade antibiotics. For instance, microbial soil communities harbor immense genetic variety in antibiotic resistance plasmids and possess a unique evolutionary power for acquiring and propagating such genetic material. Bacteria's development of antimicrobial molecules significantly influences microbial physiology and evolution, leading to a complex extent of microbial interactions.

Tackling this planet-wide issue requires identifying the factors responsible for the transmission of antibiotic resistance. Resistance in microbes emerges spontaneously, along with antibiotics targeting sensitivity and selections in the healthcare setting and agriculture. Plasmid transmission occurs at the height of the gene indenture, conveying the horizontal gene instinctively to other organisms. Uncontrollable antibiotic usage accelerates genetic exchange between organisms, which is essential for the spread of antibiotic resistance and exerting resistance gene emergence stimulation.

Global concern

The global concern over antibiotic residues in various environmental mediums points to an obvious issue of food contamination and antibiotic resistance. According to Ghimpețeanu et el., this prompts developed countries to enact stringent laws that restrict antibiotic use in cattle, aiming to control antibiotic resistance[8]. In an attempt to investigate how meat consumption results in antibiotic resistance among humans, various independent studies have been done across the world to examine the close relationship between food contamination habits and antibiotic resistance.

[8] Ghimpețeanu, O. M., Pogurschi, E. N., Popa, D. C., Dragomir, N., Drăgotoiu, T., Mihai, O. D., & Petcu, C. D. (2022). Antibiotic use in livestock and residues in food—A public health threat: A review. Foods, 11(10), 1430.

Iraq & Iran

The presence of antibiotics in edible crops has been the subject of recent research, primarily due to poor wastewater management in irrigation and manure. High levels of penicillin residues in raw milk and meat samples in Iraq and Iran confirm suspicion of antibiotic contamination in foods's origin. Studies of Al-Mashhadany[9] and Babapour et al.[10], have examined the risks associated with antibiotic residues in food products, particularly meat, milk, eggs, and honey. Their conclusion emphasizes the importance of ensuring that antibiotics are not present in foods intended for human consumption.

Southeast Asia (Vietnam, Thailand, Indonesia)

The transmission of antibiotic-resistant bacteria through the food chain poses a significant threat to public health, particularly in Asia, where antibiotic resistance is a significant hotspot. In the area, casual treatment or easy availability of antibiotics, limited or lack of regulation, and self-medication have led to the rise in antimicrobial products, and so has resistance to these drugs. Sympathetically, the common fermented food in South East Asia(SEA) also becomes a source of antibiotic resistance, as bacterial flora harbor and transmit directly to human digestive systems.

National studies in Myanmar, Indonesia, Vietnam, Thailand, and Malaysia have unveiled antibiotic resistance in human food sources at unacceptable levels, demonstrated

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[9] Babapour, A.; Azami, L.; Fartashmehr, J. (2012). Overview of Antibiotic Residues in Beef and Mutton in Ardebil, North West of Iran. *World Appl. Sci. J.19*, 1417–1422.
[10] Babapour, A.; Azami, L.; Fartashmehr, J. (2012). Overview of Antibiotic Residues in Beef and Mutton in Ardebil, North West of Iran. *World Appl. Sci. J. 19*, 1417–1422.

in Table 3 by Thapa et el.[11]:

Table 3
Summary of the prevalence of antibiotic resistance in food samples of SEA region.

Country	Food/Specimen	Antibiotic Resistant bacteria	Prevalence (%)	References
Thailand	Chicken	ESBL- producing Enterobacteriaceae	45.4	Boonyasiri et al. (2014)
		ESBL- producing *E. coli*	50	
		ESBL-producing *Klebsiella*	40	
	Pork	ESBL- producing Enterobacteriaceae	53.5	
		ESBL- producing *E. coli*	61.5	
		ESBL-producing *Klebsiella*	44.4	
	Fish	ESBL-producing *Klebsiella*	66.7	
	Beef	ESBL-producing *Klebsiella*	36.4	
	Bean sprouts	ESBL-producing *Klebsiella*	30.8	
	Shrimp	ESBL-producing *Klebsiella*	20	
Thailand and Cambodia	Green leaf lettuce	*E. coli*	57.45	Chanseyha et al. (2018)
		Salmonella isolates	46.43	
Thailand	Chicken	MDR- *E. faecalis*	73	Usui et al. (2014)
Vietnam		MDR-*E. coli*	91.5	
		MDR-*E. faecalis*	100	
Indonesia		MDR- *E. coli*	62.8	
		MDR- *E. faecalis*	84.5	
Malaysia	Chicken	ESBL- producing *E. coli*	48.8	Aliyu, Saleha, Jalila, and Zunita (2016)
Thailand and Laos	Pork	MDR- *Salmonella*	98.2	Sinwat et al. (2016)
		ESBL-producing *Salmonella isolates*	2.4	
Philippines	Poultry meat	MDR- *Salmonella enterica*	67.8	Calayag, Paclibare, Santos, Bautista, and Rivera (2017)
Thailand and Cambodia	Broilers, pigs and meat	MDR-*Escherichia coli*	75.3	Trongjit, Angkittitrakul, and Chuanchuen (2016)
		ESBL- producing *E. coli*	2.4	

ESBL, extended spectrum β-lactamase producers.
MDR, Multi-Drug Resistant.

Chicken, Pork, Fish, and Beef show alarming prevalence and resistance toward multi-drug bacteria. Resistance toward several different antibiotics directed at Salmonella and Escherichia coli strains has also been confirmed from meat samples in Vietnam.

Northern Thai pig farms were found to be connected to multiple antibiotic resistances. Despite all the restrictions on some drugs like Fosfomycin, there are still cases of recycled prescriptions, inter-species transmission, or unauthorized sale of drugs for animal use. A whole genome sequence study by Hickman et el. detects a high prevalence of extended-spectrum beta-lactamases (ESBLs) and colistin resistance genes in medium-to-small-scale farms with a dissemination gradient from pigs to handlers to

[11] Thapa, S. P., Shrestha, S., & Anal, A. K. (2020). Addressing the antibiotic resistance and improving the food safety in food supply chain (farm-to-fork) in Southeast Asia. Food Control, 108, 106809.

consumers. This result suggests zoonotic transmission and horizontal gene transfer astwo significant modes of antimicrobial resistance (AMR) dissemination[12].

Similar findings of antibiotic residues have been reported in chicken samples from Indonesia. Antibiotic residue in milk can be passed on to dairy products and lead to the transmission of antibiotic-resistant bacteria to consumers, especially in regions with low-tech factories and poor milk storage practices[6].

China

Similarly, in China, pig and poultry processing is one of the most important industries of this country, but with little to none regulation for the disposal of antibiotics containing livestock discharge, the amount of wasted antibiotic that enters the environment is dangerously high compared to other parts of the world[13]. Wei and colleagues' study presents a detection of Tetracycline, Cyromazine, and Sulfonamides in animal wastewater and animal farm byproducts from 11 cities and counties in Jiangsu Province. These ecosystems act as reservoirs of antibiotic-resistant microbes, through which, the organisms pass their genes onto other scavenger species, leading to an even wider spread of this trait.

The Tetracyclines and the Sulfonamides show higher detected frequency in swine farms than in poultry and dairy farms.

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[12] Hickman RA, Leangapichart T, Lunha K, et al. March 16, 2021. Exploring the antibiotic resistance burden in livestock, livestock handlers and their Non-Livestock handling contacts: A one health perspective. Frontiers. Accessed July 18, 2024. https://www.frontiersin.org/journals/microbiology/articles/10.3389/fmicb.2021.651461/full.

[13] Wei, R., Ge, F., Huang, S., Chen, M., & Wang, R. (2011). Occurrence of veterinary antibiotics in animal wastewater and surface water around farms in Jiangsu Province, China. Chemosphere,82(10), 1408-1414. doi:10.1016/j.chemosphere.11.067. 2011

Chile

Lateral gene transfer of aquatic bacteria and their genetic elements can share resistance genes with terrestrial animals and humans. There is evidence of this in the presence of antimicrobial-resistant bacteria contamination of aquacultural products intended for human consumption. Salgado-Caxito et al. focus on assessing the risk of antimicrobial resistance in human consumers of salmon fillets from Chilean salmon farming[14]. Their study argues that increasing the use of antibiotics in salmon aquaculture due to the high demand has resulted in contaminated salmon meat, which can be ingested by humans and transmit resistance[15]. However, this study is vastly limited due to the small size sample and lack of a systemic approach in measuring the outcome of antibiotic resistance in aquaculture products.

Denmark

This article is a case study to support the reduction of antibiotics in livestock farming in Denmark. According to the author, while the use of antibiotics constantly magnifies antibiotic resistance in microbes, human health continues to suffer greatly from its consequences. It is recorded that the number of people being infected with strains of bacteria that are resistant to commonly used antibiotics has increased dramatically since the late 1940s. The case study demonstrates that evidently, low doses of antibiotics can

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[14] Salgado-Caxito, M. , Zimin-Veselkoff, N. , Adell, A.D. , Olivares-Pacheco, J. & Mardones, F.O. (2022.) Qualitative risk assessment for antimicrobial resistance among humans from salmon fillet consumption due to the high use of antibiotics against bacterial infections in farmed salmon. *Antibiotics*, 11, 662.

[15] Cabello, F. C., Millanao, A. R., Lozano-Muñoz, I., & Godfrey, H. P. (2023). Misunderstandings and misinterpretations: Antimicrobial use and resistance in salmon aquaculture. Environmental Microbiology Reports.

introduce evolutionary pressure for the resistant strains to survive against antibiotics and reproduce drastically within the environment.[16]

Mild doses of antibiotics have been shown to effectively enhance the growth of animals for non-therapeutic purposes. According to Frank Aarestrup, a Danish veterinarian, almost 90% of industrial antibiotics in Denmark have been used for poultry growth promotion rather than their therapeutic intention. Evidently, low doses of antibiotics can introduce evolutionary pressure for resistant strains to survive against antibiotics and reproduce drastically within the environment. According to a study of Stuart Levy, who analyzed the intestinal flora of an antibiotics-fed chicken farm, bacterial resistance to antibiotics dominated the chicken's gut and took up to 80% of the people living on the farm's intestinal microbes[17]. These bacteria had the ability to create immunity against various antibiotics, including the original drug that was fed to the chickens. This behavior can be explained using Darwin's Theory of Evolution, in which antibiotics will most likely kill off the majority of bacteria within the gut of the animals, but the small percentage of those who survived learns to evolve and begin to produce stronger offspring so that they can fight off the next round of antibiotics.

Italy

In Italy, high levels of antimicrobial resistance in cattle have been observed, especially to antibiotics classified as critically important. A study by Ferroni et al. aims to assess the prevalence of ARM in Central Italy cow-calf beef farms and identify what risk

[16] Aarestrup, F. (2012). Get pigs off antibiotics. *Nature, 486*(7404), 465-466. doi:10.1038/486465a.
[17] Levy, S.(2014). Reduced Antibiotic Use in Livestock: How Denmark Tackled Resistance. *Environmental Health Perspectives, 122*(6). doi:10.1289/ehp.122-a160.

factors increase the transmission to human consumption[18]. Nearly 75% of farms show resistance to at least one class of antibiotic, and at least 50% of farms present with multi-resistant bacteria. Crucial drugs like tetracyclines and sulfonamides were common, while resistance to fluoroquinolones and penicillins, although was observed to a lesser extent, highlighting a potential public health risk as Beta-lactam use was strongly linked to E. coli resistance.

USA

Within the US, nearly 13 million kg of antibiotics are being fed to livestock and poultry, which are four times higher than that of humans. This is proof that farmers use mild doses of antibiotics to effectively enhance the growth of animals for non-therapeutic purposes. In reality, these drugs are prescribed not only to treat infections but mainly to help the animals gain more weight. Due to the economic benefit of using antibiotics and also the lack of legal regulation, many meat producers began integrating antibiotics into the routine diet of their animals. Consequently, the biggest issue that arose from the extensive use of antibiotics is the propagation of antibiotic-resistant bacteria, which disables the function of common antibiotics and contaminates wildlife ecosystems. [19]
While the European Union has defined clear thresholds for antibiotic residues, the United States lacks such regulations, with a deadline set for 2023 to establish these requirements.

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[18] L. F, E. A, C. L, et al. January 19, 2022. Antibiotic consumption is a major driver of antibiotic resistance in calves raised on Italian cow-calf beef farms. Research in Veterinary Science. Accessed July 18, 2024. https://www.sciencedirect.com/science/article/abs/pii/S0034528822000182.

[19] Alcorn, T. (2012). Antibiotic use in livestock production in the USA. *The Lancet Infectious Diseases,12*(4), 273-274. doi:10.1016/s1473-3099(12)70071-3.

Africa

South Africa's agricultural sector heavily relies on antimicrobials to boost livestock health and production, resulting a huge discrepancy of antibiotic dosing in livestock compared to humans. The farming industry serves as a hotspot for the accumulation of AMR as there are multiple species of animal involved[20]. The food-borne pathogens commonly experienced, including Staphylococcus, Salmonella, Clostridium, Campylobacter, Listeria, Vibrio, Bacillus, and Escherichia coli (E. coli), have varied degrees of resistance and are a contributing factor to human health problems.

In Nigeria, five potential human pathogens were isolated from chicken manure, such as Salmonella typhi, E. coli, Shigella dysenteriae, S. aureus, and Aeromonas hydrophila, all of which were resistant to tetracycline[21]. The isolation of five potential pathogens from chicken manure to human highlights several important issues including public health concerns, food Safety and Hygiene, and interspecies health perspective. These pathogens (Salmonella typhi, E. coli, Shigella dysenteriae, S. aureus, and Aeromonas hydrophila) are known to cause serious infections in humans, ranging from gastrointestinal illnesses to systemic infections. Finding them in chicken manure indicates a potential pathway for transmission to humans through contaminated food, water, or direct contact. The fact that these pathogens are resistant to tetracycline is alarming. Tetracycline is a commonly used antibiotic in both human medicine and

[20] Honert M van den, Gouws P, L.C. H. February 2018. (PDF) importance and implications of antibiotic resistance ... South African Journal Of Animal Science . Accessed July 18, 2024. https://www.researchgate.net/publication/323035404_Importance_and_implications_of_antibiotic_resistance_development_in_livestock_and_wildlife_farming_in_South_Africa_A_Review.

[21] Magdalena, Z., Aleksandra, B., Agnieszka, C., Magdalena, P. (2021). Antibiotics and Antibiotic Resistance Genes in Animal Manure – Consequences of Its Application in Agriculture. Frontiers in Microbiology, 12, 1664-302X. DOI=10.3389/fmicb.2021.610656.

agriculture. Resistance to tetracycline suggests widespread antibiotic use in farming practices, which can contribute to the development and spread of antibiotic-resistant bacteria, posing challenges for treating infections in both animals and humans. This incident underscores the interconnectedness of human health, animal health, and the environment, and emphasizes the need for improved hygiene and biosecurity measures in poultry farming to reduce the spread of pathogens and antibiotic resistance. Antibiotic use in agriculture can select for resistant bacteria, which can then spread to humans through various routes, exacerbating the global challenge of antibiotic resistance.

Measures implemented to combat antibiotic resistance

Efforts to control the crisis have been deployed by government and non-government institutions across the globe. The research industry is employed to handle diversified national monitoring and reporting systems to generate and disseminate data on AMR in human and animal populations.

Traditional bio-therapeutics approaches like antibiotics, novel combination remedies, and drug delivery procedures (which are mainly dependent on the production of novel small molecules) have proven themselves to be a failure against this threat, hence the urge for innovative methods[6]. Research has been funded to discover new antibiotics and nonpharmaceutical approaches, as effective treatment methods against bacterial infections pose a real challenge. Antimicrobial peptides, found in animals, microorganisms, and plants, show promise due to their broad spectrum of activity against various microbes. Despite molecules remaining essential, biologics provide potential for fighting MDR bacteria, though their development is still in its early stages. Biological information can aid in the discovery of new and improved solutions during the drug development process. For instance, red sea algae contain furanone, a chemical that prevents bacteria from reproducing[6].

One other potential alternative to antibiotics is the use of essential oils that have antimicrobial properties[22]. These oils can be used during the animal's life to prevent infection, and can also be used in meat processing to cut down on bacterial shedding to humans and the environment. The work shows that this approach has high efficacy against deadly bacteria without affecting the hosts and the environment.

A graduate student at the University of Minnesota lab is researching how using prebiotics and probiotics can increase an animal's natural immune system by boosting the growth of healthy microbiomes[23]. Other governments have begun banning the use of nontherapeutic use of antibiotics; and since then, the amount of resistant microbes has significantly decreased in both animals and meat products**.** It is important to assess the intake amount of antibiotics and their effects on the health of scavengers given its implication in public health and wildlife conservation.

The final alternative to this problem is bacterial vaccines that can prevent infection by exposing animals to weakened forms of common bacterial invaders. Currently, work is being done to develop a bacterial vaccine to Ornithobacterium rhinotracheale (ORT), a bacterium that causes the avian form of bronchitis[24]. The US turkey industry is excited about this idea and has funneled investment money into the development of a safe and cost-effective vaccine, so this area shows promise in actually being implemented.

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[22] Dewei, G. (2018). Unpublished Thesis. Johny Lab. Department of Veterinary and Biomedical Sciences. College of Veterinary Medicine. University of Minnesota- Twin Cities. Minneapolis, MN.
[23] Johnson, A. (2018). Unpublished Thesis. Johnson Lab.Department of Veterinary and Biomedical Sciences. University of Minnesota- Twin Cities. Minneapolis, MN.
[24] Smith, E. (2018). Unpublished Work. Johnson Lab. Department of Veterinary and Biomedical Sciences. University of Minnesota- Twin Cities. Minneapolis, MN.

Discussion/Analysis

The literature review highlights the impact of consuming food with antibiotic residues on consumer health is a growing concern globally. Stress and prolonged antibiotic use in animal farming led to the formation of resistance against antibiotics. Antibiotic residues negatively impact human health and pose a significant global problem by reducing the number of treatment options, while increasing the death rate from human infections[7]. Antibiotic residues in animal-derived food products can survive high-heat treatment, leading to harmful incidents such as gastrointestinal problems, ever-growing allergies, and the creation of antibiotic-resistant superbugs in humans.

It is beneficial to consider interventions to reduce resistance in use of antibiotics in livestock, which should strictly be therapeutic and dependent on the evaluation of a veterinarian, who assesses the animals thoroughly before prescribing the appropriate type and dosage. Studies have shown a positive correlation between reducing antibiotic use in food animals and a subsequent decrease in antibiotic resistance in both animals and humans in contact with these animals[25]. In addition, instead of using antibiotics, farmers should increase their usage of pre-and-probiotics, vaccines, and essential oils to protect livestock against common diseases. Other alternatives to antibiotics may be more cost-efficient and may not be therapeutically effective as a lifelong course of antibiotics in farm livestock.

Given the costs associated with antibiotic use in livestock, alternatives to antibiotics that could still protect animals should be taken into consideration. Although, it is worth noting that recently developed approaches to this global crisis are mostly unpublished work from university researchers.

Published studies have also agreed that efforts to mitigate AMR include improving farm hygiene, implementing good herd management practices, reducing the use of mass medication, and educating stakeholders about the correct use of antibiotics[25]. Additionally, enhancing surveillance and control strategies, developing effective wild game traceability systems, and promoting good hygiene practices throughout the food production chain are essential measures to address AMR and preserve the effectiveness of antibiotics. Minimizing the transmission of food-borne pathogens via the food chain and adopting good hygiene practices at all stages of food production are crucial steps in combating AMR and safeguarding public health.

Even though it is said that antibiotics should not be banned, the production of antibiotic-free meat should always be encouraged and supported, especially by the government. This is because when the use of antibiotics in livestock is reduced, the cost of producing and maintaining healthy livestock increases rapidly. Also, the fewer antibiotics used, the better it is for the consumer's health, therefore the industry should cover the cost differences if it does not want to lose business as consumer preferences change. For example, Willmar Poultry Company (WPC) has requirements to raise antibiotic-free turkeys, and one of the most expensive changes they implemented is going from basic feed to premium feed. WPC has a plan in place to pay the difference in cost between the standard and premium food to encourage more farmers to go antibiotic-free[26].

There are several limitations to the search that need to be acknowledged, including Data Comparability, Temporal Limitations, Economic and Cultural Factors, and Focus on Specific Antibiotics. Variations in methodologies, definitions, and reporting standards across studies can

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[25] Khurana MP, Essack S, Zoubiane G, et al. Mitigating antimicrobial resistance (AMR) using implementation research: A development funder's approach. JAC-antimicrobial resistance. March 27, 2023. Accessed August 5, 2024. https://www.ncbi.nlm.nih.gov/pmc/articles/PMC10041058/.

[26] Willmar Poultry Company. (2018). Antibiotic-Free Turkeys. Lecture. Willmar Poultry Company.

make it difficult to compare and synthesize findings; along with the the possibility of outdated data, especially in rapidly evolving fields like antibiotic resistance, where new strains and resistance patterns can emerge quickly. Finally, Variations in economic resources and cultural practices can affect antibiotic use and resistance patterns but might not be adequately addressed in the literature. Some studies might focus on a limited range of antibiotics, missing broader trends in resistance.

Conclusions

With the increasing incidents of livestock antibiotic resistance, this literature review examines the current situation on antibiotic usage among the livestock industry; is there a transmission of antibiotic-resistant microorganisms between animals and humans through meat consumption, how does that contribute to the emergence of antibiotic resistance, and what are some solutions to this global crisis?

The author of this paper hypothesized that there is a strong connection between the usage of antibiotics in livestock and the transfer of antibiotic resistance to humans through consumption and exposure, and a review of multiple sources and studies supported the said hypothesis. Countries across the globe have reported the consequences of down-regulated antibiotic use among livestock and the rise of clinal antibiotic resistance incidents. There should be better regulation to handle antibiotics in livestock in order to prevent this disastrous outcome that was foreseen centuries ago.

Studies also proposed methods to deal with said global crisis, including improving farm hygiene, implementing good herd management practices, reducing the use of mass medication, and educating stakeholders about the correct use of antibiotics. Addressing these issues requires coordinated efforts across sectors (human health, animal health, agriculture, environment) to monitor antibiotic use, enhance surveillance of antibiotic resistance, improve sanitation practices, and promote prudent use of antibiotics in both medical and agricultural settings. This multidisciplinary approach is essential for mitigating the risks associated with antibiotic-resistant pathogens in food production and safeguarding public health and can be widely implemented by the government to encourage the adaptation instead of other costly, potential antibiotic alternatives.

Lastly, unless we take significant actions to improve efforts on changing the way we’re using antibiotics, the world will eventually run out of these valuable health goods and the implications will be much more devastating than we can handle.

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Appendix

(Source #2) Table 3 by Kumar et el.:

Table 3

ARG in animal production settings.

Sl. No.	Bacterial Species	Infection	Antibiotic Resistance Pattern	Sources of Human Infection	Genes
1	*Campylobacter* spp.	Gastrointestinal sequelae: Guillain-Barré syndrome	Fluoroquinolones, erythromycin	Food-producing animals (poultry)	*tetO, gyrA* [39,40]
2	*Enterococcus* spp.	Sepsis, urinary tract	Aminoglycosides ampicillin vancomycin	Food-producing animals (poultry); People exposed to hospital care, food animals	*Tuf, VanC-1, VanC-2-VanC-3, pbp5* [41,42,43,44,45]
3	*E. coli*	Gastrointestinal, urinary tract, diarrhoea	Quinolones sulphonamides trimethoprim	Childcare facilities	*Bla, qnrS, frdD* [46,47,48]
4	*Salmonella* spp. (non-typhoidal)	Gastrointestinal, diarrhoea	Cephalosporins quinolones tetracyclines	Food-producing animals (pigs, cows, poultry)	*IntI1, qnrA* [49,50,51,52]
5	*S. pneumoniae*	Otitis media, pneumonia, sinusitis, meningitis	Penicillin, macrolides, cephalosporins, tetracyclines	Childcare facilities, paediatric populations	*erm(B), mef* [53,54,55,56]
6	*S. pyogenes*	Pharyngitis, impetigo, cellulitis	Macrolides, tetracyclines	Childcare facilities, paediatric Populations, schools	*ermB, ermA and mefA* [57]
7	*S. aureus*				
	Community-associated	Skin, soft tissue, pneumonia, sepsis	Methicillin, cephalosporins, macrolides	Childcare facilities, injections, drug users	*erm(A), erm(C), tetK, tetM, aacA-aphD, vat(A), vat(B) and vat(C)* [58,59]
	Healthcare-associated	Endocarditis, pneumonia, sepsis	Methicillin, cephalosporins, quinolones, aminoglycosides, macrolides	People exposed to healthcare facilities such as nursing homes, dialysis, recent surgery or hospitalization	
8	*N. gonorrhoeae*	Urethritis, pelvic inflammatory disease	Penicillin, cephalosporins, quinolones	Commercial sex workers	*penA, penB, NorM* [60,61]

(Source #11) Table 3 by Thapa et el.:

Table 3
Summary of the prevalence of antibiotic resistance in food samples of SEA region.

Country	Food/Specimen	Antibiotic Resistant bacteria	Prevalence (%)	References
Thailand	Chicken	ESBL- producing Enterobacteriaceae	45.4	Boonyasiri et al. (2014)
		ESBL- producing *E. coli*	50	
		ESBL-producing *Klebsiella*	40	
	Pork	ESBL- producing Enterobacteriaceae	53.5	
		ESBL- producing *E. coli*	61.5	
		ESBL-producing *Klebsiella*	44.4	
	Fish	ESBL-producing *Klebsiella*	66.7	
	Beef	ESBL-producing *Klebsiella*	36.4	
	Bean sprouts	ESBL-producing *Klebsiella*	30.8	
	Shrimp	ESBL-producing *Klebsiella*	20	
Thailand and Cambodia	Green leaf lettuce	*E. coli*	57.45	Chanseyha et al. (2018)
		Salmonella isolates	46.43	
Thailand	Chicken	MDR- *E. faecalis*	73	Usui et al. (2014)
Vietnam		MDR-*E. coli*	91.5	
		MDR-*E. faecalis*	100	
Indonesia		MDR- *E. coli*	62.8	
		MDR- *E. faecalis*	84.5	
Malaysia	Chicken	ESBL- producing *E. coli*	48.8	Aliyu, Saleha, Jalila, and Zunita (2016)
Thailand and Laos	Pork	MDR- *Salmonella*	98.2	Sinwat et al. (2016)
		ESBL-producing *Salmonella isolates*	2.4	
Philippines	Poultry meat	MDR- *Salmonella enterica*	67.8	Calayag, Paclibare, Santos, Bautista, and Rivera (2017)
Thailand and Cambodia	Broilers, pigs and meat	MDR-*Escherichia coli*	75.3	Trongjit, Angkittitrakul, and Chuanchuen (2016)
		ESBL- producing *E. coli*	2.4	

ESBL, extended spectrum β-lactamase producers.
MDR, Multi-Drug Resistant.