

ANTIMICROBIAL RESISTANCE: A GLOBAL CHALLENGE AND IMPLICATIONS FOR DAIRY CATTLE PRODUCTION

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Abstract: Antimicrobial resistance (AMR), especially antibiotic resistance, currently is one of the most important public health challenges, with serious consequences for human, animal and environmental health. In the context of dairy cattle production, the frequent and often unnecessary use of antibiotics, especially in the treatment of mastitis, significantly contributes to the development and spread of resistant bacteria. The aim of this review was to analyse the occurrence and mechanisms of AMR development in dairy production, with a special emphasis on mastitis as a main model for understanding the connection between veterinary practice, public health and food safety. Furthermore, the paper also provides an overview of current national and European strategic frameworks for AMR control, including selective therapeutic approaches, rapid diagnostics and preventive measures on dairy farms. In conclusion, the need for an integrated approach based on the *One Health concept*, which includes the collaboration of policy, science, education and practice, is necessary in order to preserve the effectiveness of antimicrobials and ensure sustainable dairy production.

Key words: antimicrobial resistance, mastitis, dairy cows, food safety, responsible antibiotic use

Introduction

Antimicrobial resistance (AMR) refers to the ability of microorganisms, including bacteria, viruses, fungi, and parasites, to survive and proliferate despite the presence of drugs designed to eradicate them or inhibit their growth (WHO, 2024). This phenomenon is not a result of human or animal adaptation but rather a natural evolutionary response seen predominantly in bacterial populations. AMR presents a formidable challenge in effectively treating infectious diseases in both humans and animals. Furthermore, the development of antimicrobial resistance is a naturally occurring process; however, it is significantly accelerated by the misuse and overuse of antibiotics in various sectors. In human healthcare, factors such as the unnecessary prescription of antibiotics for viral infections, patients not completing prescribed courses, and self-medication contribute to the emergence of resistant strains. In veterinary medicine, the routine use of antibiotics for disease prevention and growth promotion in livestock can create environments conducive to resistance development. Furthermore, the application of antibiotics in animal husbandry complicates disease management and impacts food safety. On a global scale, the implications of AMR extend far beyond treatment complexities; it threatens the effectiveness of essential medical procedures, such as surgeries and chemotherapy, which rely on effective antibiotics to prevent infections. In veterinary practice, the challenge is illustrated by conditions such as mastitis in dairy cattle, where resistant infections can lead to significant economic losses, decreased milk production, and deteriorated animal welfare. Addressing AMR necessitates a coordinated effort across healthcare systems, agriculture, and public health to ensure effective management and containment strategies are implemented.

This review aimed to analyse the mechanisms of AMR development in dairy production, with emphasis on mastitis as a model for understanding the connection between veterinary practice, public health and food safety. Furthermore, this paper also provides an overview of current national and European strategic frameworks for AMR control, including selective therapeutic approaches, rapid diagnostics and preventive farm measures.

Materials and Methods

A comprehensive literature search was conducted using electronic databases including Web of Science, Scopus, PubMed, and Google Scholar, as well as relevant websites of international organizations (WHO, WOAH, EFSA, EU). The following keywords and their combinations were applied: “*antimicrobial*

resistance,” “antibiotic resistance,” “dairy cattle,” “mastitis,” “antimicrobial use,” “public health,” and “One Health.”

Publications considered included peer-reviewed articles, review papers, systematic analyses, official reports, and strategic policy documents published between 2000 and 2025, with particular emphasis on recent studies and the European regulatory framework. Literature was selectively included based on its relevance to antimicrobial resistance in dairy production, with mastitis serving as a primary model for exploring the interconnection between veterinary practice, public health, and food safety.

In total, more than 40 references were reviewed, of which those most directly contributing to the understanding of AMR development and spread, its economic and health implications, and potential strategies for prevention and control on dairy farms were cited in this paper.

Mechanisms of resistance development

Bacterial resistance to antibiotics primarily develops through two interconnected mechanisms: genetic mutations and the horizontal transfer of resistance genes (Ferrara et al., 2024). **Horizontal gene transfer** often occurs via mobile genetic elements such as plasmids and transposons, which can move resistance traits between different bacterial species. These genes equip bacteria with various defence strategies, such as breaking down or inactivating the antibiotic, avoiding its effects, or actively expelling it from the cell using specialized proteins known as efflux pumps. In the dairy sector, antibiotic resistance is a particularly pressing issue when it comes to pathogens associated with mastitis, an inflammation of the mammary gland in dairy animals. Mastitis is one of the most common diseases in dairy farming and is frequently treated with antibiotics, which increases selective pressure and contributes to the spread of resistant bacterial strains. Key bacterial causes of mastitis include *Staphylococcus aureus*, a pathogen known for its ability to form biofilms and resist many antibiotics; *Escherichia coli*, which can cause severe infections; *Streptococcus uberis*, frequently associated with environmental mastitis; and *Klebsiella spp.*, which are opportunistic pathogens that can lead to persistent infections. Research has indicated a troubling upward trend in the resistance of these bacteria to critical classes of antibiotics, including β -lactam antibiotics (such as penicillin), tetracyclines, and macrolides. This growing resistance poses a significant challenge for veterinary medicine, highlighting the need for careful antibiotic stewardship in agricultural practices (Alhassan et al., 2025).

The application of antibiotics within dairy cattle farms primarily targets the treatment of both clinical and subclinical mastitis. Additionally, these medications

are often utilized during what is known as "dry cow therapy," a preventative measure administered when cows are nearing the end of their lactation period, aimed at protecting their udders during the non-lactating phase to minimize the risk of infections. Historically, antibiotics have also been employed as growth promoters in livestock, a practice that has contributed to the alarming rise of antibiotic-resistant bacteria within agricultural settings. This misuse has profound implications for both animal health and public safety. In recent years, there has been a concerted effort to promote responsible antibiotic usage within dairy farming to mitigate the risks associated with antimicrobial resistance. However, certain regions continue to rely on blanket therapy, a controversial practice that involves administering antibiotics to all animals without confirming the presence of an infection. This indiscriminate approach fosters an environment conducive to the development of resistant bacterial strains. These resistant pathogens can infiltrate the food supply by contaminating milk and other dairy products, posing a significant public health risk as they can ultimately be transmitted to humans through consumption (WHO, 2024). *Staphylococcus aureus* is a significant pathogen associated with chronic mastitis, a condition that leads to inflammation and infection of the udder tissue. Notably, many strains of *Staphylococcus aureus* demonstrate resistance to commonly used antibiotics, particularly penicillin, and some have developed resistance to methicillin, classifying them as methicillin-resistant *Staphylococcus aureus* (MRSA). This resistance poses a significant challenge in treating infections effectively. On the other hand, *Escherichia coli* is often implicated as the primary pathogen in cases of acute mastitis. This bacterium can possess genes responsible for producing extended-spectrum beta-lactamases (ESBLs), enzymes that confer resistance to many beta-lactam antibiotics. The presence of these resistant strains complicates treatment options, making it critical for clinicians to identify the specific bacteria involved and determine the most effective antibiotic therapy. Effective management of both types of mastitis requires a thorough understanding of these pathogens and their resistance mechanisms.

Additionally, incorporating data on the spread of antibiotic resistance genes (ARGs) through manure and wastewater would provide valuable insights; for example, resistance genes such as blaCTX-M can persist in soil for months and facilitate horizontal transfer to environmental bacteria (Berendsen et al., 2015). Furthermore, related to human health, a study conducted Van Cleef et al. (2010) detected the identical MRSA strains in both humans and livestock, suggesting direct zoonotic transmission, confirming the potential for zoonotic transmission of MRSA and ESBL-producing *E. coli* from farms to humans

Mastitis as a model for understanding AMR

Mastitis represents a key model for investigating the dynamics of AMR, especially within the dairy sector. Characterized by inflammation of the mammary gland, mastitis is the most common disease affecting dairy cows and stands as the leading cause of antibiotic use in dairy farming. Treatment typically involves the frequent, and often empirical application of antibiotics, making mastitis a central reference point for examining and monitoring the development of antimicrobial resistance (Ruegg, 2017). The widespread occurrence of mastitis, particularly in its subclinical form, has led to an increased dependence on antimicrobial agents, often administered as a preventive measure. This is especially true during the dry-off period, a critical phase when cows transition into the next lactation. However, such preventive use exerts significant selective pressure on bacterial populations, encouraging the emergence and spread of resistant strains. The consequences are serious: not only is the efficacy of existing treatments diminished, but producers face rising costs, and potential risks to public health grow more pronounced (Oliver et al., 2011; WHO, 2024). Mastitis typically presents in two forms: clinical and subclinical. *Clinical mastitis* is characterized by visible symptoms such as changes in milk appearance (e.g., clots, discoloration), swelling or heat in the udder, and elevated body temperature. These clear indicators make clinical cases relatively easier to detect and manage. *Subclinical mastitis*, by contrast, is far more insidious and accounts for up to 90% of mastitis cases on some farms. It lacks obvious external signs, making diagnosis reliant on elevated somatic cell counts (SCC) or specialized laboratory analysis of milk samples (Halasa et al., 2007). This hidden nature poses a major challenge for herd management, allowing undetected infections to persist and spread within the population. Furthermore, chronic subclinical infections can lead to sustained inflammation, reduced milk yield, and a gradual build-up of resistance due to prolonged antibiotic exposure.

The pathogens responsible for mastitis are typically categorized into two major groups: contagious agents, which spread from cow to cow (often during milking), and environmental pathogens, which originate from the cow's surroundings, such as bedding or manure. Among the **contagious agents**, the most notable are *Staphylococcus aureus*, *Streptococcus agalactiae*, and *Mycoplasma spp.*, *Staphylococcus aureus*, in particular, poses a significant challenge due to its multifaceted resistance mechanisms, including its ability to form biofilms and its characteristic intracellular localization. Moreover, the emergence of methicillin-resistant *Staphylococcus aureus* (MRSA) strains complicates treatment, rendering β -lactam antibiotics largely ineffective (Barkema et al., 2009). Turning to **environmental pathogens**, notable examples include *Escherichia coli*, *Klebsiella spp.*, *Streptococcus uberis*, and *Prototheca spp.* While *E. coli* is frequently

associated with acute cases of mastitis, recent developments have raised concerns about its increasing acquisition of extended-spectrum beta-lactamase (ESBL) genes. These genes produce enzymes that can degrade a broad array of β -lactam antibiotics, thus severely limiting the treatment options available for affected herds (Oliver et al., 2011).

Treating mastitis in dairy cows involves numerous challenges that often lead to not optimal outcomes. One of the main complications is subclinical mastitis, a form of the disease that progresses without visible symptoms. Because it often goes unnoticed, affected cows can remain untreated for extended periods, allowing the infection to spread silently within the herd. Even when treatment is initiated, it is frequently based on empirical decisions, without identifying the specific pathogen, which not only reduces the likelihood of success but also contributes to the growing problem of AMR due to inappropriate antibiotic use (Ruegg, 2017). Another significant challenge is the limited efficacy of antibiotics during lactation. Many commonly used drugs fail to reach therapeutic levels in the mammary gland, especially when the infection involves biofilm-forming bacteria such as *Staphylococcus aureus*. Additionally, veterinary regulations often restrict the use of certain antibiotics during lactation, leaving veterinarians and producers with fewer options for effective treatment. The economic implications of treatment also present serious concerns. During the required withdrawal period, milk from treated cows must be discarded, which results in considerable financial loss, especially in high-yielding animals. Faced with these costs, some producers may shorten the duration of therapy or resort to unapproved treatments, actions that not only compromise animal health but also contribute to AMR (Oliver et al., 2011). Furthermore, pathogen identification remains a persistent obstacle. In the absence of detailed microbiological testing, it is difficult to distinguish between contagious and environmental causes of mastitis. As a result, treatment often involves broad-spectrum antibiotics used without precise targeting, which increases the likelihood of resistance development and reduces treatment effectiveness (Halasa et al., 2007).

To effectively combat antimicrobial resistance in veterinary medicine, especially regarding mastitis in dairy cows, several focused strategies have been developed. One key approach is *Selective Dry Cow Therapy* (SDCT), which replaces the traditional blanket antibiotic treatment during the dry period with a more targeted method. Instead of treating all cows with antibiotics, SDCT focuses only on those showing signs of infection or with a history of mastitis. This helps preserve antibiotic effectiveness and reduces overall antimicrobial use. *Rapid diagnostic tests* also play a crucial role in guiding treatment decisions. Tools like the California Mastitis Test (CMT) or PCR for identifying pathogens allow veterinarians and farmers to quickly detect the specific cause of mastitis. This

enables treatments to be tailored to the infection rather than relying on broad-spectrum antibiotics. Regular testing of mastitis pathogens and their antibiotic sensitivities through antibiograms provides valuable insight into local resistance patterns. Knowing which antibiotics remain effective against common pathogens helps farmers make informed treatment choices and minimizes inappropriate antibiotic use. *Biological and preventive measures* are equally important. Vaccination programs can boost animal health and resistance to infections. Improving hygiene during milking and maintaining clean living conditions for the cows significantly reduce infection risk by limiting pathogen exposure. Finally, education and training for farmers and veterinary staff are essential. Teaching the principles of responsible antibiotic use, effective mastitis management, and ongoing herd health monitoring encourages adoption of practices that support antimicrobial resistance reduction goals.

Public health and economic aspects of AMR in dairy farming

AMR in dairy farming poses a significant challenge that extends beyond veterinary medicine and animal health, becoming a critical public health issue as well as an economic concern. The close interaction between humans and livestock, coupled with the complexities of a globalized food supply chain, makes dairy cattle farming a key factor in the potential transmission of antibiotic-resistant microorganisms to people (WHO, 2024). Resistant bacterial strains emerging in animals can reach humans through several main pathways. One such route is through contaminated dairy products. Improper management of antibiotic use in dairy cows can result in residues persisting in milk at the time of processing. When antibiotics are given too close to milking or withdrawal periods are not properly observed, residues can contaminate raw milk. Additionally, inadequate pasteurization may fail to eliminate antibiotic residues and resistant pathogenic bacteria, which poses a serious risk when these products enter the human food chain (Oliver et al., 2011). Another pathway is direct contact with animals. People working on dairy farms, such as farmers, and veterinarians often have close and prolonged contact with livestock. This increases their risk of becoming colonized or infected with antibiotic-resistant bacteria, including strains like methicillin-resistant *Staphylococcus aureus* (MRSA). The occupational exposure heightens the chance of zoonotic transmission, where bacteria can jump from animals to humans (Dignard and Leibler, 2019).

Environmental contamination is also a significant concern. Antibiotic-resistant bacteria and antibiotic residues frequently enter the environment via the manure and urine of treated animals. When this waste is applied as fertilizer, it can contaminate soil and water sources, both surface and groundwater. Such

environmental spread facilitates the transmission of AMR to wildlife and human populations alike, broadening the public health threat (WHO, 2024). Furthermore, the presence of antibiotic residues in milk is particularly concerning for consumer safety. These residues may cause adverse health effects, especially in individuals sensitive to certain antibiotics like penicillins, who may suffer severe allergic reactions from contaminated milk. Moreover, antibiotic residues can disrupt the balance of intestinal microbiota, leading to digestive problems and other health issues. Importantly, these residues also play an indirect role in encouraging the development of AMR within human populations. According to the European Food Safety Authority (EFSA, 2024), this contributes to a wider public health problem, making infections harder to treat due to diminished antibiotic effectiveness.

To address these risks, strict regulatory measures have been implemented to monitor antibiotic residues in milk. Dairy processors are required to conduct routine testing using sensitive methods like the Delvotest, a biosensor test that detects antibiotic inhibitors in milk. Effective control of antibiotic residues depends on several critical factors, including strict adherence to withdrawal periods, ensuring sufficient time has passed after antibiotic treatment before milk is collected. Accurate and detailed record-keeping of all medications administered to livestock is essential to prevent mixing milk from treated and untreated animals prematurely. Additionally, ongoing education and training for dairy producers on responsible antibiotic use are vital. These programs foster best practices in medication management and encourage a culture focused on animal welfare and consumer safety.

From an economic perspective AMR in dairy cattle farming has extensive consequences that reach far beyond individual farms, impacting the entire agricultural value chain. One of the primary challenges for producers is the loss of milk production. Infections caused by resistant bacteria can significantly reduce both the quantity and quality of milk produced by affected cows. As a result, farmers may receive lower prices since buyers tend to prefer higher-quality products. Hogeveen et al. (2011) emphasize that the cumulative financial impact of these production losses can be substantial. Treatment costs also rise as managing antimicrobial resistance often requires more intensive veterinary care. This can involve multiple treatments, longer durations of therapy, and the use of more expensive or less effective antibiotics. Seegers et al. (2003) point out that these factors increase direct veterinary expenses and create logistical difficulties for farmers as they struggle to control resistant infections. Animal losses further exacerbate economic pressures. Chronic infections such as mastitis, particularly when treatments fail, can lead to the culling or euthanasia of affected cows. This not only results in immediate financial loss but also diminishes the herd's genetic diversity, which can negatively affect the long-term productivity and health of the

dairy operation. A serious economic risk arises when milk contains antibiotic residues above the maximum residue limits (MRLs). In such cases, contaminated milk must be discarded, causing significant financial damage to producers. Additionally, farmers may be temporarily excluded from milk purchasing networks, harming their market position and reputation among consumers and industry stakeholders.

Furthermore, it would also be beneficial to highlight the economic impact by quantifying the costs associated with AMR; for instance, the U.S. dairy sector incurs annual losses of approximately \$2 billion, while in the EU, mastitis-related AMR costs dairy farms around €1.7 billion each year due to milk waste and treatment expenses (EFSA, 2022). Additionally, presenting comparative data—such as the resistance rates in Croatia versus EU averages, noting 40% *S. aureus* penicillin resistance in Croatia compared to 25% across the EU—could further enhance the analysis.

Beyond individual farms, the socio-economic impact of AMR is even more far-reaching. The rising costs of human healthcare are a direct consequence of infections caused by resistant pathogens becoming more difficult and expensive to treat. The reduced effectiveness of antibiotics in human medicine due to multidrug-resistant organisms presents major public health challenges, as highlighted by the World Health Organization (WHO, 2024). Moreover, the threat AMR poses to global food security is especially concerning. In regions where agriculture forms the economic backbone, a decline in livestock production caused by AMR could have severe repercussions not only for farmers but also for entire communities dependent on agriculture. The seriousness of resistant pathogens underscores the urgent need for coordinated action to address AMR within agricultural systems, highlighting its critical links to public health and economic stability.

Strategies to mitigate antimicrobial resistance in dairy cattle

Mitigating the spread of antimicrobial resistance requires a multisectoral approach that connects human, animal and environmental health, by the concept of "One Health". Strategies include regulatory measures, changes in veterinary practice and the implementation of recommended hygienic-preventive procedures on farms (WHO, 2024, WOA, 2025).

The Republic of Croatia adopted the "*Nacionalni program za kontrolu otpornosti bakterija na antibiotike 2017. – 2021.*", which establishes priorities and activities in the sectors of public health, veterinary medicine, agriculture and environmental protection (Ministry of health, Republic of Croatia, 2017). Key guidelines include:

- strengthening supervision over the consumption of antibiotics in veterinary medicine,
- encouraging alternative therapies and preventive measures,
- promoting the responsible use of antimicrobials at farm level,
- strengthening the education of veterinarians and producers.

At the European Union level, the new Regulation 2019/6 (EU, 2019) on veterinary medicinal products has been in force since 28 January 2022, which clearly prohibits:

- the prophylactic use of antibiotics without clinical or laboratory evidence of risk (Article 107),
- group medication with antimicrobials except in exceptional situations with the authorisation of a veterinarian,
- the use of antibiotics to promote growth and improve production efficiency, which has been prohibited at EU level since 2006 (Regulation 1831/2003/EC).

Furthermore, the European Commission has introduced an ambitious target: to reduce the total sales of antimicrobials in the EU livestock sector by 50% by 2030 (EU Farm to Fork Strategy, 2020).

Mitigating AMR on dairy farms relies heavily on disease prevention, minimizing unnecessary antibiotic use, and adopting sustainable health practices. One effective approach is **Selective Dry Cow Therapy (SDCT)**, which replaces the routine use of antibiotics at the end of lactation, known as blanket dry cow therapy, with treatment only for cows that have confirmed infections based on indicators such as somatic cell count (SCC), the California Mastitis Test (CMT), or microbiological cultures. Research by Kabera et al. (2021) and Ruegg (2017) demonstrates that SDCT significantly reduces antibiotic use without compromising udder health or milk production. Improving milking hygiene is another crucial practice. This involves thorough udder preparation, disinfecting teats before and after milking (pre- and post-dipping), and ensuring proper maintenance of milking equipment. These measures help decrease the incidence of new intramammary infections, particularly those caused by environmental pathogens like *Escherichia coli* and *Streptococcus uberis*. Vaccination against key mastitis pathogens such as *Staphylococcus aureus*, *E. coli*, and *Mycoplasma bovis* also plays an important role. The use of commercial vaccines can reduce the occurrence of clinical mastitis and lessen the need for antibiotic treatments, especially in herds with a history of recurrent infections (Rainard et al., 2018). The application of rapid diagnostic tests directly on the farm further supports targeted therapy. Tools such as the California Mastitis Test, on-farm bacterial cultures, and PCR diagnostics enable quick

identification of causative agents, improving treatment effectiveness and minimizing unnecessary antibiotic use. Finally, educating farmers and veterinarians about responsible antibiotic use is essential. Training on antimicrobial stewardship fosters informed decision-making, reduces empirical antibiotic prescriptions, and encourages prevention through improved herd health management (Skjølstrup et al., 2020). All of these practices contribute to a comprehensive strategy for controlling AMR in dairy farming.

In addition to preventive measures and targeted therapeutic approaches, there is a growing focus on non-antibiotic strategies for managing bovine mastitis and mitigating antimicrobial resistance. These promising alternatives encompass the use of probiotics, bacteriophage therapy, and plant-derived bioactive compounds. For instance, non-antibiotic options such as probiotics, phage therapy, and herbal extracts like oregano or tea tree oil, along with immunomodulatory plant compounds like curcumin, may help decrease reliance on antibiotics in mastitis control (El-Sayed and Kamel, 2021).

Conclusion

Antimicrobial resistance (AMR) in dairy production constitutes a complex and multidimensional challenge with significant implications for animal health, public health, food safety, and the long-term sustainability of the dairy sector. The frequent and largely empirical use of antibiotics in mastitis therapy accelerates the development and dissemination of resistant strains, reduces treatment efficacy, and jeopardises the safety and quality of milk. Additional concerns arise from the persistence of antimicrobial residues and the emergence of multidrug-resistant pathogens, which increase production losses, elevate veterinary costs, and restrict access to both domestic and international markets.

Addressing this issue requires a comprehensive, evidence-based strategy embedded within the **One Health** framework, which recognises the interdependence of human, animal, and environmental health. Priority measures include limiting non-essential antimicrobial use, advancing rapid and reliable diagnostic methods, strengthening biosecurity protocols at farm level, and implementing targeted interventions such as selective dry cow therapy and immunoprophylaxis against major mastitis pathogens. Equally important are continuous education and awareness-raising activities among farmers and veterinary practitioners to promote prudent antimicrobial use.

Given the limited prospects for the development of novel antimicrobial agents, preserving the effectiveness of existing drugs depends on coordinated collaboration between the scientific community, policymakers, veterinary professionals, and industry stakeholders. Such synergy is essential to mitigate

AMR effectively, safeguard animal and human health, and maintain the resilience and competitiveness of the dairy sector.

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