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MICROBIOLOGICAL CONTAMINATION OF MILK AND THE IMPLICATIONS OF BACTERIAL STRAINS IN HUMAN PATHOLOGY

CONTAMINAREA MICROBIOLOGICĂ A LAPTELUI ȘI IMPLICAȚIILE TULPINILOR BACTERIENE ÎN PATOLOGIA UMANĂ

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ABSTRACT | **REZUMAT**

Milk plays a significant role in supplying the essential nutrients for a healthy and balanced existence and is a crucial source of nourishment for millions of people worldwide. Cattle, buffaloes, goats, and sheep are the animals that provide the majority of the world's milk, making the dairy industry one of the most important agricultural industries. Milk has many nutritional advantages, but when it is drunk raw, it poses a risk to the public's health by spreading viruses and germs that are resistant to antibiotics. Pathogens are mostly spread by dairy cows with mastitis. Mastitis has serious zoonotic potential, and milk derived from dairy animals with mammary gland infections may become a great public health concern and a direct human health hazard that may even lead to death. The purpose of this review is to summarise the current knowledge on the main microbial pathogens present in cattle and buffalo milk (large milk ruminants) and describe the potential human health harms associated with milk consumption. The major milk bacteria that we describe in this article as humans' pathogens include *Staphylococcus aureus*, *Escherichia coli, Salmonella* spp., *Campylobacter* spp., *Yersinia enterocolitica*,*Listeria monocytogenes*,*Brucella* spp.,*Coxiella burnetti,* and *Mycobacterium* spp.

Keywords: milk, pathogens, mastitis, public health, antimicrobial resistance

Laptele este o sursă vitală de nutriție pentru milioane de oameni din întreaga lume, având un rol important în furnizarea principalilor nutrienți pentru o viață sănătoasă și echilibrată. Sectorul laptelui este unul dintre cele mai semnificative sectoare agricole, iar speciile care asigură cea mai mare parte a producției mondiale de lapte sunt reprezentate de bovine, bivoli, caprine și ovine. Laptele oferă o multitudine de beneficii nutriționale, dar atunci când este consumat nepasteurizat poate reprezenta un vector în diseminarea agenților patogeni și a bacteriilor rezistente la antibiotice cu risc pentru sănătatea publică. Animalele cu mamită care furnizează lapte pentru consum uman reprezintă principala sursă de agenți patogeni. Mamita are un potențial zoonotic grav, iar laptele animalelor cu infecții mamare poate fi o mare problemă pentru sănătatea publică și, pe cale de consecință, un pericol direct pentru sănătatea omului, care poate duce chiar la deces. Scopul acestei recenzii este de a rezuma cunoștințele actuale cu privire la principalii agenți patogeni microbieni prezenți în laptele de bovine și de bivoliță (rumegătoare mari de lapte) și de a descrie potențialele daune asupra sănătății umane asociate cu consumul de lapte. Principalele bacterii din lapte pe care le descriem în acest articol ca agenți patogeni umani includ *Staphylococcus aureus*, *Escherichia coli*, *Salmonella* spp., *Campylobacter* spp., *Yersinia enterocolitica, Listeria monocytogenes*, *Brucella* spp., *Coxiella burnetti* și *Mycobacterium* spp.

Cuvinte cheie: lapte, agenți patogeni, mamită, sănătate publică, rezistență antimicrobiană

Milk is considered a staple food for humans and which comprises carbohydrates, fatty acids, and high-quality proteins with vitamins, minerals, and trace elements (20, 54). A study in West Sumatra tested the average water content, protein, fat, lactose, total solids, and pH of fresh milk from cows, and buffaloes. The results showed that the average water content in buffalo milk was 78.91% and 80.82% in cow milk. Buffalo milk protein was 6.77%, and the protein content of cow milk was 3.71%. The fat content of buffalo and cow milk was 7.25% and 5.21%, respectively. The lactose content of buffalo and cow milk was 5.28% and 4.34%, respectively. The total solid content of buffalo milk was higher than cow's milk (19.31%), while cow's milk was 13.26%. The pH of milk ranged around 6-7 (61).

In 2022, global milk production reached nearly 927 million tonnes increased by 1.1% from 2021 and is estimated to grow by 1.8% per year until 2031 (32, 33, 67). With a global cattle population amounted to about one billion head, cows produce about 81% of world milk production, followed by buffaloes with a world population of

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approximately 204 million head and 15% of world milk production. The remaining 4% of world milk production is represented by the combined milk of goats, sheep, and camels (Fig. 1) (30-32).

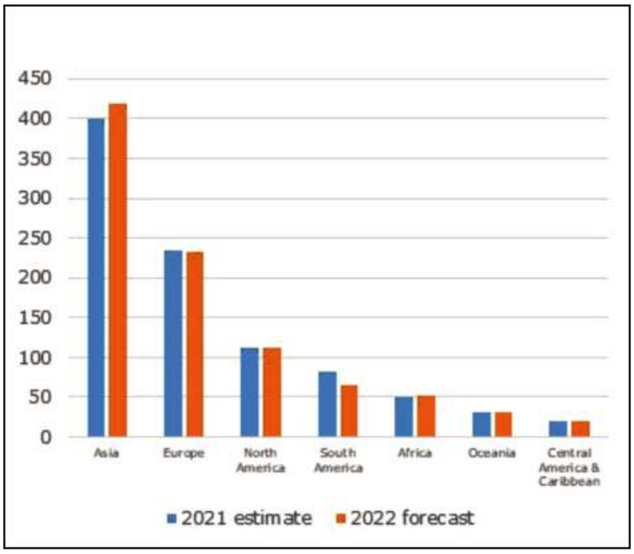

Fig. 1. World milk production (in million tonnes), by region (30)

Different types of microorganisms are found in milk, and they are related to several host and environmental factors (63, 68). These microorganisms that compose the milk microbiota are represented by various species such as *Lactococcus*, *Lactobacillus, Pseudomonas, Micrococcus, Staphylococcus*, yeast, *Leuconostoc, Enterococcus, Streptococcus, Bacillus*, *Clostridium, Listeria*, and *Enterobacteriaceae* (93). Raw milk from various types of mammals, especially buffalo milk, is a major natural source of lactic acid bacteria. These bacteria have antimicrobial properties, roles in organoleptic changes, antioxidant activity, nutrient digestibility, the release of peptides and polysaccharides, amino acid decarboxylation, and biogenic amine production and degradation (3, 64). The amount of lactic acid bacteria indicates the potential of milk as a probiotic (61).

In addition to the positive impact of unpasteurized milk consumption on the prevalence of asthma, atopy, rectal cancer, and respiratory illnesses, unpasteurized milk can pose a risk to public health because it contains a large number of bacteria and is an optimal substrate for the multiplication of microorganisms (17, 53, 54, 80). The main health harms associated with milk production and consumption include foodborne hazards, zoonotic diseases, and the emergence of antimicrobial-resistant pathogens and antimicrobial-resistant genes (37). Raw milk can be contaminated in two ways. When milk is contaminated by a direct transfer of pathogens from the blood (systemic infection) or by an infection in the udder, there is occurs endogenous contamination, and when fresh milk is contaminated with animal faeces, the outside of the udder and teats, milking medium, milking staff, milking equipment, milk transport, poor storage conditions, water, soil, dust, the skin of cattle, and other environmental sources, there is exogenous contamination (6,13,69, 89).

Human illnesses that have recently appeared have been linked to meals of animal origin (75). Ingestion of a range of foods contaminated with pathogenic organisms such as bacteria (66%), chemicals (26%), viruses (4%), and parasites (4%) leads to food poisoning syndrome (26). Foodborne illnesses can present with a variety of symptoms, including gastrointestinal ones like nausea, vomiting, diarrhoea, or abdominal cramps, as well as neurological ones like paralysis or paraesthesia, headaches, or problems with the nerve system or the brain (18, 44).

About 4% of the world's foodborne illness burden and 12% of the disease burden from animal sources are attributed to dairy products (44).

In 2021, salmonellosis was confirmed as the most commonly reported foodborne outbreaks, accounting for the largest number of outbreaks and cases. The second zoonoses confirmed in foodborne outbreaks was campylobacteriosis, followed by STEC infections,listeriosis, yersiniosis, and brucellosis. The highest number of deaths from foodborne outbreaks was associated with listeriosis (N = 12), followed by campylobacteriosis (N = 6), and salmonellosis (N = 1) (Fig. 2) (27).

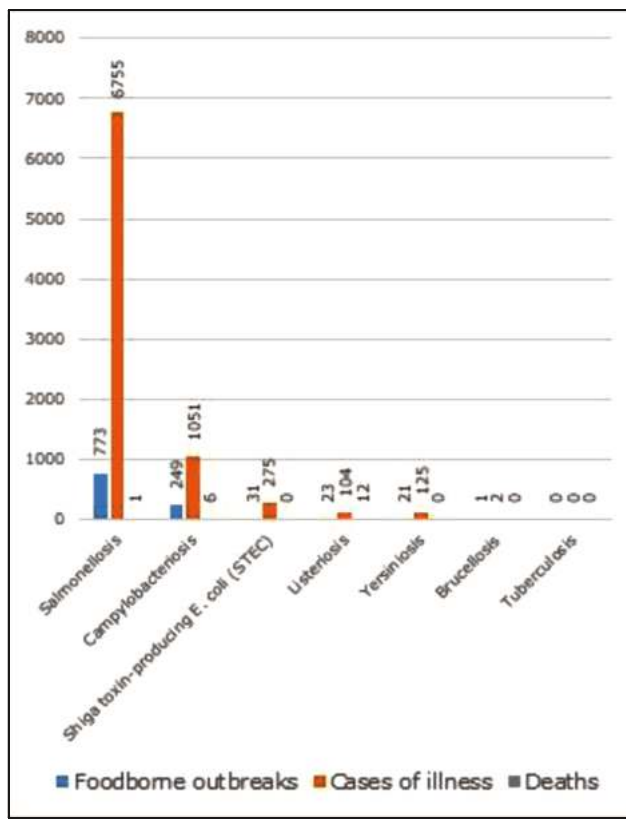

Fig. 2. Reported numbers of foodborne outbreaks, cases of illness and deaths for confirmed human zoonoses in the EU, 2021 (27)

Foodborne pathogens have a zoonotic potential and an ability to produce toxins being associated with various damages and even early death (18, 40). Zoonoses are defined as diseases transmitted between animals and humans as a consequence of a direct contact, indirect envi-

Table 1

The primary pathogenic bacteria that cause foodborne illness linked to consuming milk and milk products, host animal illnesses, mechanisms of transmission to people, key symptoms in humans, and antibiotic resistance

#	Pathogen	Disease in dairy animals	Transmission	Key symptoms in humans	Antimicrobial resistance	Ref.
1	*Staphylococcus aureus*	Clinical, subclinical, and chronic mastitis.	Ingestion of contaminated milk or dairy products	Vomiting, diarrhoea	Methicillin, vancomycin, penicillin, and β-lactam antibiotics	(6, 15, 25)
2	Shiga-toxin producing *E. coli*	Mammary infections	Consuming contaminated food or water, coming into contact with diseased animals up close, eating their food, and person-to-person contact.	Severe haemorrhagic colitis, gastrointestinal disorders.	Streptomycin, ampicillin, amoxicillin, neomycin, and tetracycline	(23, 40, 62, 98)
3	*Salmonella* spp.	Diarrhoea, fever, anorexia, dehydration, reduced milk production, and miscarriages	Ingestion of food or contaminated water, direct contact with infected animals, or consumption of food from infected animals.	Nausea, vomiting, diarrhoea, septicaemia or bacteraemia, and reactive arthritis.	Erythromycin, doxycycline and amoxicillin	(18, 34, 40)
4	*Campylobacter* spp.	Infertility, abortion and foetal death	Intake of tainted food or water, close contact with sick animals, or eating of their food.	Periodontitis, cholecystitis, oesophageal disorders, nausea, vomiting, fever, cramping in the abdomen, and colon cancer.	Tetracycline, β-lactam, aminoglycosides, quinolones, fluoroquinolones, macrolides, tetracycline	(40, 41, 65, 75, 77, 100)
5	*Listeria* spp.	Encephalitis with a high fatality rate of 20 to 100%. Fatal septicaemia in young calves.	Direct contact with diseased animals, eating food from contaminated animals, and person-to-person contact are all examples of ways to get an infection.	Spontaneous abortions, meningitis, encephalitis, gastroenteritis, and septicaemia.	Cefpodoxime, kanamycin, tetracycline, and nalidixic acid	(18, 19, 40, 47, 66, 87, 94)
6	*Brucella* spp.	Abortion, lameness, abscess, reduction in milk production, and decrease in survival chances of newborns	Consumption of raw or unpasteurized *Brucella* contaminate milk and products, and contact with infected tissues or secretions.	Pneumonia, meningitis, endocarditis, septicaemia, serious weakness, pain in muscle and joints, extreme headache, and fever	Ampicillin, erythromycin, and novobiocin	(7, 52, 75)
7	*Coxiella burnetti*	Abortion, infertility, and subclinical mastitis	Milk, birth products, faeces, urine, and other bodily fluids (humans often get the virus by breathing in contaminant aerosols).	Q fever: flu-like syndrom and chronic endocarditis.	Pefloxacin, ciprofloxacin, doxycycline, erythromycin	(8, 11, 29, 50)

ronmental contact, or through food (18).

Zoonoses can be classified into 9 categories: bacterial zoonoses (e.g., Lyme disease, anthrax, salmonellosis, tuberculosis, brucellosis, and plague), viral zoonoses (e.g., rabies, acquired immune deficiency syndrome - AIDS, Ebola, and avian influenza), parasitic zoonoses (e.g., trichinosis, trematodosis, toxoplasmosis, giardiasis, malaria, and echinococcosis), chlamydial zoonoses (e.g., psittacosis), rickettsial zoonoses (e.g., Q-fever), mycoplasma zoonoses (e.g., *Mycoplasma pneumoniae* infection), protozoal zoonoses, diseases produced by prions (e.g., BSE), and fungal zoonoses (e.g., ring worm) (75).

According to List A of Annex I to the Zoonoses Directive 2003/99/EC, *Salmonella, Campylobacter, Listeria monocytogenes, Shiga toxin-producing Escherichia coli (STEC), Mycobacterium bovis, Brucella, Trichinella* and *Echinococcus* are the eight zoonotic agents whose data on animals, food and feed must be reported (27).

Reverse zoonoses are diseases caused by pathogens that are occasionally transmitted to animals from humans and then back from humans to animals. MRSA, *Campylobacter* species, *Salmonella enterica* serovar Typhimurium, influenza A virus, *Cryptosporidium parvum*, *Ascaris lumbricoides*, and *Giardia duodenalis* are a few examples of such infections (74).

Zoonotic infections can negatively impact the cattle industry and public health by increasing morbidity and mortality, lowering agricultural earnings through a reduction in animal production (36, 37).

By releasing bacteria and their toxins into the milk, dairy cows with mastitis have a high zoonotic potential that can result in zoonotic illnesses (38, 60).

Since 1917, bovine mastitis has been closely observed and is currently the costliest illness affecting dairy cows worldwide (48, 54, 58, 59). Mastitis has multiple etiological agents (bacteria, fungi, mycoplasmas, and algae) that are contagious, environmental, or opportunistic, and it results in reproductive losses due to the expense of treating the condition, decreased milk production, changes to the quality of the milk throughout the tank, and unintentional deaths of infected animals (4, 38, 48, 57, 69, 72, 83). Both subclinical and symptomatic types of mastitis have the potential to progress to chronic mastitis. This illness causes a significant reduction in milk supply and quality in all of its forms (60, 73, 88). Coliforms, streptococci, and staphylococci are the most common mastitis pathogens isolated from milk samples (35, 60, 73, 92). According to certain research, milk from cows, sheep, goats, camels, and buffalo may contain Helicobacter pylori. Human disorders, including chronic gastritis, duodenal ulcers, or gastric cancer, are linked to the presence of H. pylori in the gastrointestinal tract (86).

The data linking milk to foodborne infections was reviewed in this research, along with its effects on public health, present state, antibiotic resistance, and susceptibility profile.

BACTERIA WHICH CAN BE RESPONSIBLE FOR MILK-BORNE DISEASES

The main zoonotic bacterial pathogens that cause foodborne illness and death worldwide are represented by *Staphylococcus aureus, Escherichia coli, Salmonella* spp., *Campylobacter* spp., *Yersinia enterocolitica, Listeria monocytogenes, Brucella* spp., *Coxiella burnetti,* and *Mycobacterium* spp. (26, 27, 75).

Staphylococcus aureus

S. aureus is a typical component of the skin's and certain animals' mucous membrane microbiota, but it can produce illness when the host's immune system is weakened or when it enters the body after trauma (5, 70). *S. aureus* can spread from one person to another, from one animal to another, and from one human to another (71). Clinical, subclinical, and chronic mastitis in ruminants, from simple abscesses to severe mastitis and toxic shock syndrome, furunculosis, dermatitis, arthritis, omphalitis, urinary tract infections, gastroenteritis, osteomyelitis, meningitis, pneumonia, endocarditis, and wound infections are just a few of the severe animal diseases caused by *S. aureus* (5, 70, 71, 81).

Krishnamoorthy et al. (2021) found that the *Staphylococcus* species is the major mastitis pathogen present in the milk of dairy cattle and buffalo in the world, followed by *Streptococcus* species and *Escherichia coli* (54)

Consumption of preformed *S. aureus* enterotoxins in food forms staphylococcal food poisoning, which is the most prevalent cause of gastroenteritis in the world (22). Foods associated with Staphylococcal food-borne disease include meat and meat products, poultry and poultry products, egg and egg products, milk and dairy products, bakery products, salads, and particularly cream-filled cakes and pastries and sandwich fillings (15, 71).

The food chain's primary sources of *S. aureus* are cattle (73). *S. aureus* contamination of milk is linked to sick cows or milk handlers, particularly those with poor hygiene practises such as coughing or sneezing when milking or handling milk (25). *S. aureus* in milk produces heat-stable enterotoxins that cause invasive infections in people, including septicaemia, osteomyelitis, skin infections, pneumonia, nausea, vomiting, abdominal cramping with or without diarrhoea, and infections of the central nervous system. In rare cases, especially in infants and the elderly, acute illness and death may result. In extreme situations, blood pressure and pulse rate fluctuations, as well as headaches, cramping muscles, and other symptoms, may manifest. Also, one of the main pathogens responsible for nosocomial infection is *S. aureus* (25, 44, 71). The resistance of *S. aureus* to methicillin, vancomycin, penicillin, β-lactam antibiotics, and others mediated by various genetic and enzymatic mechanisms has been a major concern for scientists. Methicillin-resistant *Staphylococcus aureus* (MRSA) is a pathogenic strain of *S. aureus* that has been noted to acquire resistance to different groups of antibiotics and become multi-drug resistant (51, 71, 76). In cattle, methicillin-resistant *Staphylococcus aureus* is associated with mastitis, and in humans, it is responsible for a wide variety of infections, from mild skin infections to life-threatening invasive disease, being a major drug-resistant pathogen (22, 76). During 2021, in Germany, 28 of 366 raw milk samples (7.7%) were positive for MRSA at the farm (27).

Escherichia coli

E. coli is a natural inhabitant of the gastrointestinal tract in both humans and animals. Most strains are harmless, but a few of them cause severe disease due to the production of toxins and/or other virulence factors when the immune system is compromised or as a result of environmental exposure (49, 62, 84).

Ruminants, especially cattle and sheep, are considered to be the major reservoirs for *E. coli* (40, 62). Dairy cattle asymptomatically carry Shiga toxin-producing *E. coli* (STEC) and enterohemorrhagic *E. coli* (EHEC) (84). *E. coli* can grow in milk and is the most common infectious agent involved in mammary infections of environmental origin (23, 98). As a member of the faecal coliform group, *E. coli* is often used as an indicator of faecal contamination of milk, and its presence refers to poor hygiene conditions (25, 44, 56). The milk's low quality can persist for weeks after the eradication of *E. coli* (57). Raw milk could contain *E. coli* derived from animals, the environment, or farm workers and milking equipment (62). Shiga-toxin-producing *E. coli* (STEC) and enterotoxigenic *E. coli* (ETEC) were associated with several food-borne outbreaks worldwide (25, 62). During 2021, the number of confirmed cases of human STEC infection in the EU was 6.084, representing an increase of 36.9% compared with cases in 2020 (27). These pathogens can transmit to humans from farms through contaminated milk, water, and direct contact with animals or their environmental equipment (84). STEC causes serious human illnesses such as haemorrhagic colitis and haemolytic uremic syndrome that usually end up with fatal consequences, and ETEC causes diarrhoea, being the most common cause of endemic diarrhoea in children in developing countries (25).

***Salmonella* spp.**

Dairy cattle serve as a major reservoir for salmonellosis in humans. *Salmonella* spp.is one of the most common organisms in nature. It can spread to people through the environment and the faeces of sick animals (84). *Salmonella* can be carried by cattle asymptomatically, but it can also cause symptoms such as diarrhoea, fever lasting up to 7 days, anorexia, dehydration, decreased milk supply, miscarriages, or the presence of toxins in the blood (18). Most serious disease occurs in new-borns, young calves 2-6 weeks of age, and cows approaching calving (77). *Salmonella* depends on the serovar's ability to adapt to the environment of its hosts. *S. enterica* is widely distributed in the environment and has also been associated with a variety of infections in cattle (45). *Salmonella* can be found in different foods, including milk, eggs, meat, vegetables, fruit juices, and dairy products (34). *S.* Newport, *S.* Typhimurium, and *S.* Newport can be found in the milk or colostrum of infected lactating animals and in bulk tank milk (42). *S.* Typhimurium is the most dominant serovar around the world, and it is associated with food-borne outbreaks in both developing and high-income countries (40). In humans, the range of infections depends on the bacterial virulence factors, immunity, and host-resistant capability. Salmonellosis signs and symptoms could evolve from nausea, vomiting, and diarrhoea to septicaemia or bacteraemia, localised gastroenteritis, and reactive arthritis as a post-infection sequela (40). *Salmonella* is highly resistant to most common antibiotics like ampicillin, chloramphenicol, streptomycin, sulphonamides, and tetracycline (34).

***Shigella* spp.**

Shigella is a pathogen that causes contamination of animals, humans, the environment, and milk. It is found in water and faeces.Shigellosis is a universal public health concern and one of the main causes of bacillary dysentery, which is associated with high morbidity and mortality, especially in developing countries such as Egypt. Members of the *Shigella* genus are classified into four species: *S. dysenteriae, S. flexneri, S. boydii,* and *S. sonnei*. Raw milk and unpasteurized cheese remain important vehicles for the transmission of *Shigella* to rural and urban populations (24).

***Campylobacter* spp.**

Bacteria belonging to the genus *Campylobacter* were only known to cause animal diseases until the late 1980s. Since that time, the discovery has been made that they also cause health problems in humans, and the incidence of infections has been constantly growing (18). Thermophilic *Campylobacter* is the responsible pathogen for campylobacteriosis, which represents the most frequent foodborne disease in the European Union (100). *C. jejuni* and *C. coli* have the most frequent implications in campylobacteriosis (44). Cases of campylobacteriosis have been linked to cattle, and the prevalence of this bacteria varies greatly from 6% to nearly 90% (40). The number of positive *Campylobacter* spp. units detected during 2021 in the EU showed the highest proportion in pigs (41.3%), followed by cattle (13.5%), cats and dogs (12.3%), and finally broilers (10.5%) (27). Clinical disease in cattle is characterised by infertility, abortion, and foetal death, and animals infected remain asymptomatic and continue to shed bacteria through faeces (77). Contamination of milk with cattle faeces may be an important source of *Campylobacter* contamination (36).

The majority of *Campylobacter* spp. cross-infections in raw milk occur during milking or as a consequence of udder infection (18). According to several studies, milk is the primary cause of human *Campylobacter* outbreaks (41, 90, 99).When unpasteurized milk is tainted, *C. jejuni* enters the human host and colonises the digestive tract to infect and cause illness (15). Watery or bloody diarrhoea, stomach cramps, nausea, light-headedness, malaise, vomiting, and fever are some of the clinical symptoms of campylobacteriosis (44, 90, 100).Reactive arthritis, inflammatory bowel disease, and neurological conditions like Guillain-Barré syndrome are examples of chronic complications (100).

Yersinia enterocolitica

Although *Y. enterocolitica* was found more than 60 years ago, it wasn't expected until the late 1960s that it would be a human or animal pathogen. Since then, food-borne gastrointestinal illnesses have become more common (39). The majority of human yersiniosis were brought on by the *Y. enterocolitica* (98.1%), which is widely distributed in the environment (27, 44). It is transmitted to humans through the consumption of products obtained from infected animals, including fresh milk, pasteurised milk, and other dairy products. Water and nutrients contaminated by infected animals play an important role in the transmission of *Y. enterocolitica* to humans (18, 39, 101). In humans, yersiniosis is associated with clinical and immunological manifestations such as enterocolitis with bloody diarrhoea (in severe cases in infected infants and young children), acute terminal ileitis, pseudoappendicitis and mesenteric lymphadenitis (in older children and young adults). The extraintestinal manifestations are rarely pneumonia, reactive arthritis, erythema, mycotic aneurysm, axillary abscesses, or endocarditis (39). *Y. enterocolitica* is a vector for the transmission of antimicrobial resistance to humans as a result of improper handling and cooking during preparation, resulting in considerable health problems for consumers, particularly the young and new-borns. The antimicrobial-resistant *Y. enterocolitica* strains in animal-origin foods could be a public health concern for consumers (1).

Listeria monocytogenes

The first study about *L. monocytogenes* was in 1975, when Weis confirmed that this bacterium is a causative agent of mastitis in dairy cows, which can lead to contamination of excreted milk. The first report was in 1985, when *L. monocytogenes* was found in 2% of pasteurised milk in Massachusetts (82). *L. monocytogenes* can be found in plant, soil, and surface water samples, in silage, sewage, slaughterhouse waste, milk from normal cows and cows with mastitis, and in human and animal faeces (40). Ruminants can spread germs to the environment through their faeces, milk, uterine discharges, nasal discharges, and urine (18, 47). Ruminants may also be asymptomatic carriers of *L. monocytogenes*. The absence of clinical signs in adult animals' points to a balance between this virus and the gastrointestinal ecology of cattle. However, the mortality rate for animals that show clinical symptoms, such as encephalitis, is severe and ranges from 20 to 100%. Young calves are also vulnerable to deadly septicaemia and may die from it (19).

L. monocytogenes is often isolated from a variety of food products for direct consumption, including raw milk and dairy products, and is the causative organism of several outbreaks of foodborne disease (16, 18, 40, 44, 94). In the EU, during 2021, the prevalence of *L. monocytogenes* in milk products was 0.51% (N = 26,154 tested units for detection), with 0.69% for cheeses (N = 14,985), and 0.30% for milk (N=1,642) (27).Young children,neonates, elderly people, pregnant women, and immunocompromised consumers are more susceptible to foodborne listeriosis than healthy adults (44, 94). Listeriosis is characterised by symptoms such as meningoencephalitis, septicaemia,primary bacteraemia, endocarditis, non-meningitic central nervous system infection, conjunctivitis, influenza-like symptoms, febrile gastroenteritis (self-limited in healthy adults), and may also lead to abortions (28, 40, 47, 94).

***Brucella* spp.**

The two principal zoonotic diseases in nature that are spread by sheep, goats, cattle, and other Bovidae are *B. melitensis and B. abortus* (46, 75). The main hosts of *B. abortus* and *B. melitensis* are ruminants (69). Brucella abortus, which replicates in the mammary gland and supra-mammary lymph nodes in dairy cows, continuously excretes milk (80). Farm animals are thought to be more susceptible to *Brucella* spp. infections, which can result in miscarriage, lameness, abscesses, decreased milk supply, and decreased neonatal survival rates (7, 43, 75). Brucellosis is quite prevalent in cattle and buffalo in several Indian districts (43).

In the 22 Member States of the UE, the overall proportion of cattle herds infected with *B. abortus*, *B. melitensis,* or *B. suis* during 2021 remained very low (0.04%; 554 out of 1,719,963 herds). The most contaminated herds were detected in Greece, Italy, and Portugal. No cases of brucellosis in cattle have been reported in the United Kingdom (Northern Ireland) (27). Humans become infected by consuming unpasteurized milk and dairy products, by direct contact with aborted foetuses, afterbirth and parturition fluids, and during slaughter practises (7, 69, 75). Principal signs and symptoms in humans are influenza-like infections, pneumonia, and other complications, including meningitis, endocarditis, septicaemia, serious weakness, pain in muscles and joints, extreme headache, fever, night sweats. Workers on dairy farms, carers, butchers, veterinary professionals, and villagers are most vulnerable to contracting brucellosis (75).

Coxiella burnetii

C. burnetii is an intracellular zoonotic pathogen responsible for Q fever in humans (11). The main reservoirs for *C. burnetii* and the most common sources of human infection include cattle, sheep, and goats (29, 69). *C. burnetii* can be transmitted through urine, faeces, milk, and birth products, and people usually acquire the infection by inhaling contaminated aerosols (29). Consumption of non-pasteurised milk in Nigeria has resulted in the detection of *C. burnetii* in up to 63% of cow milk samples (69) . In cattle, the bacterium is found almost exclusively in milk and is transmitted mainly through inhaling aerosols and dust from contaminated materials shed by infected animals (11, 80). In livestock, the infection can cause significant economic losses due to abortion, infertility and subclinical mastitis (29). In humans, Q fever is associated with a wide clinical spectrum, from asymptomatic to fatal disease, in most cases characterised by severe flu-like symptoms and chronic endocarditis (11, 29, 50). *C. burnetii* can survive for months and even years in the environment, being very resistant to adverse physical conditions and chemical agents. Regarding antibiotic resistance, *C. burnetii* acquired resistance to pefloxacin, ciprofloxacin, doxycycline, and erythromycin, and it is susceptible to oxytetracycline (8).

In Europe, the majority of clinical cases are sporadic, and during 2021, 359 cases (78%) of Q fever (27) were a-cquired (27). In Italy, 2210 cattle were tested for the presence of antibodies against *C. burnetii,* and the prevalence at animal level was 12.0% (11). A similar study found a seroprevalence of 35% at herd level and 13% at animal level in 402 semi-intensive dairy cattle and buffalo herds (herd size ranges from 20 to 50 heads for cattle and 230 to 800 for buffalo) (29).

***Mycobacterium* spp.**

Tuberculosis is the biggest zoonotic disease among bovine zoonoses, with economic and public health importance, being caused by *M. bovis*, *M. tuberculosis*, or *M. caprae* (10, 75, 80). *M. bovis* caused about 5–10% of all

Table 2

The frequency, antimicrobial resistance, and susceptibility profile of bacterial species isolated from milk and milk products

Sample Type	Samples examined	Pathogen	Number of Positive (%)	Antibiotic resistance (%)	Antibiotic sensitive (%)	Ref.
Milk samples of subclinical mastitis	350 (cattle and water buffalo)	*S. aureus* (MRSA)	45(41.4%) - CMT 125 (35.7%) - PCR	Cefoxitin (100%)	Ciprofloxacin, and linezolid (100%), levofloxacin (85%), amikacin and trimethoprim + sulphamethoxazole (80%), tylosine (60%), gentamicin (60%), oxytetracyline (40%).	(81)
Cattle milk	12 *S. aureus* isolated	*S. aureus*	12	Penicillin G (66.7 %), ampicillin (66.7 %), vancomycin (58.3 %), bacitracin (58.3 %).	Ciprofloxacin (91.7 %), gentamicin (66.7 %), chloramphenicol (66.67 %).	(76)
Unpasteurized cow milk	79	*S. aureus*	41 (71%)	-	-	(9)
		Listeria spp.	12 (21%)			
		Campylobacter spp.	5 (9%)			
		Y. enterocolitica	1 (2%)			
		E. coli O 157	1 (2%)			
Raw milk samples from informal markets	121	*E. coli*	16 (13.2%)	Cephalothin (87.5%), ampicillin (68.8%), tetracycline (68.8%)	Gentamicin and chloramphenicol (100%)	(25)
		S. aureus	22 (18.2%)			
		E. coli and *S. aureus* the co-existence of pathogens	3 (2.5%)	Ampicillin (100%), tetracycline and sulfamethoxazole-trimethoprim (90.1%).	Gentamicin (9.1%), methicillin (22.7%).	
Milk samples from cows with clinical mastitis	4,275	*E. coli*	178	**29.8% isolates revealed multidrug resistance,** erythromycin (83%), streptomycin (70%), ampicillin (66%), amoxicillin (62%), neomycin (58%).	-	(23)
Milk	109	*E. coli*	87 (70.16%)	Tetracycline 28.58%, streptomycin (9.52%), aztreonam (4.76%).	-	(98)
Pasteurized and unpasteurized milk	**74 pasteurized**	**-**	**-**	-	-	(14)
	21 unpasteurized	***E. coli***	**14 (66.7%)**	Ampicillin 92.8%, tetracycline 50%.	-	
Cow dung, milk, milker's hand	240	*E. coli*	180 (75%)	Tetracycline (89.44%), erythromycin (88.89%), oxytetracycline (78.89%), ertapenem (66.67%).	Gentamycin, ciprofloxacin, and imipenem.	(84)
		Salmonella spp	136 (56.67%)	Erythromycin (87.5%), tetracycline (86.76%), oxytetracycline (75.73%), ertapenem (50%).	Gentamycin, ciprofloxacin, and imipenem	
Milk	108	*Salmonella spp.*	2 (1.85%)	Erythromycin, doxycycline and amoxycilin (100%).	Gentamicin, neomycin and ciprofloxacin (100%).	(74)
Milk and dairy product samples	131	*Salmonella spp*	**21 (16%)**	Amoxycillin, bacitracin, penicillin G, lincomycin, vancomycin, clindamycin, and cloxacillin (100%).	Evofloxacin, doxycycline, and ciprofloxacin (100%).	(34)
		S. enterica	9/21 (42.8%)			
Marketable milk samples	160	*Yersinia species*	33(20.63%)	-	-	(39)
		Y. enterocolitica	(47.5%)			
		Y. pseudotuberculosis	(7.5%)			
		Y. pestis	(17.5%)			
		Y. intermedia	(10%)			
Cow milk	225	*Y. enterocolitica*	31	Oxacillin (90.3%), tetracycline (80.7%), nalidixic acid (61.3%), cefoxitin (58.1%).	Norfloxacin (83.9%), ciprofloxacin (77.4%), cefotaxime (67.7%), gentamycin (64.5%).	(1)
Milk and milk products	175	*Y. enterocolitica*	19 (10.9%)	Penicillin G. (100.0%), methicillin (89.5%), oxytetracycline (79.0%), amoxicillin, ampicillin and streptomycin (73.7% for each), erythromycin (63.2%).	Meropenem and norfloxacin (79.0% for each), gentamycin (68.4%), ciprofloxacin and cefotaxime (63.2 % for each), florphenicol (52.6%).	(2)
Raw cow milk and milk products	600	*Shigella* spp	42 (7%)	Tetracyclines (100%), ampicillin, amoxicillin-clavulanate (90.5%, each), cefaclor (66.7%).	Imipenem, sulfamethoxazole/ trimethoprim, and azithromycin (100%).	(24)
		S. dysentriae	24 (57.1%)			
		S. flexneri	12 (28.6%)			
		S. sonnei	6 (14.3%)			
Milk and dairy products	174	*Campylobacter spp.*	24 (13.8%)	Tetracycline (50 %)	-	(65)
Milk and milk products	350	*L. monocytogenes*	17 (4.86%)	-	-	(47)
Raw milk from / aborted animals	928	*Brucella spp.*	1.9% (non-aborted) 33% (aborted animals)	Ampicillin, erythromycin, novobiocin.	Rifampicin, doxycycline, kanamycin, gentamicin, streptomycin, tetracycline, and ciprofloxacin.	(7)

human tuberculosis (25% of the patients were children) (75). In the EU, the number of confirmed cases of human tuberculosis during 2021 due to *M. bovis* or *M. caprae* was 111 (103 cases of *M. bovis* and 8 cases of *M. caprae*), corresponding to an increase of 12.4% compared with 2020 (27). The main routes of transmission of tuberculosis to humans are represented by handling or milking contaminated unpasteurized milk or aerosolized milk from the cough of infected animals. Agricultural workers, veterinarians, slaughterhouse workers, or villagers can pose a significant risk of contamination (21, 75). Milk is a good sample for the detection of pathogenic mycobacterium (7). Zoonotic tuberculosis incidence is associated with the number of cattle (the major source of *M. bovis*), people suffering from poverty, and unpasteurized milk and dairy products (21). The overall prevalence of cattle herds infected with MTBC during 2021, in the EU, was very low (9,690 out of 1,726,451 herds; 0.6%), slightly higher than 2020 (0.4%) (27). Huge caseous nodules that grow in the lungs (airborne illness), digestive tract (oral infection), and mammary gland are all signs of TB in cattle. In immunocompromised animals, granulomas, or small nodules, may also arise in these organs (80). In Africa, the consumption of unpasteurized raw milk and dairy products continues to be a major risk for exposure to *M. bovis* (69). A study isolated the organisms of the *M. tuberculosis* complex from bovine milk samples of emaciated animals. From the seventeen milk samples collected, only one isolate was obtained from culture, which was later identified as a non-tuberculous mycobacterium using PCR. Non-tuberculous *Mycobacterium* organisms have been reported to cause disease in both immune-competent and immunocompromised individuals (79).

ANTIMICROBIAL RESISTANCE (AMR) OF MILK BACTERIA

One of the most important achievements of modern medicine was the introduction of antibiotics in the early 20th century. They contribute to the reduction of morbidity and mortality in both humans and animals, but the overuse of antibiotics has created a global public health threat from antibiotic-resistant organisms (35). Antimicrobial resistance (AMR) could be responsible for 700,000 deaths/year worldwide, and it has been estimated that by 2050, AMR will be responsible for more deaths than cancer (102). The rise of antibiotic resistance has been linked to antibiotic use in human medicine, veterinary medicine, and agriculture (91). Tiseo et al. (2020) estimated the global consumption of veterinary antimicrobials from 93,309 tonnes in 2017 to an increase of 11.5% by 2030 to 104,079 tonnes and the antimicrobial use in humans with an increase of 15% between 2015 and 2030 (95).

In 2021, according to estimates, 41% of medically significant antibiotics approved for use in food-producing animals were sold and distributed for use in cattle; 42% were intended for use in swine; 11% were intended for use in turkeys; 3% were intended for use in chickens; and 3% were intended for use in other species (Fig. 3) (31).

Tetracyclines made up 65% of domestic sales and distribution of medically significant antimicrobials authorised for use in food-producing animals in 2021, while penicillins made up 10%, macrolides made up 9%, sulphonamides made up 5%, aminoglycosides made up 6%, lincosamides made up 3%, and cephalosporins made up less than 1% (Fig. 4) (31).

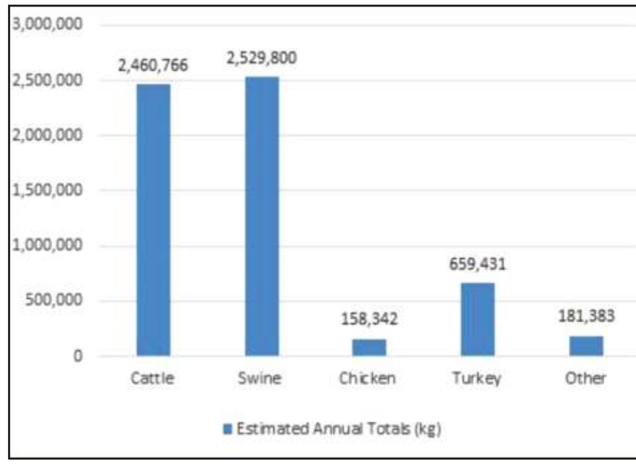

Fig. 3. Medically important antimicrobial drugs approved for use in food-producing animals – Specific estimated sales reported by species in 2021 (31)

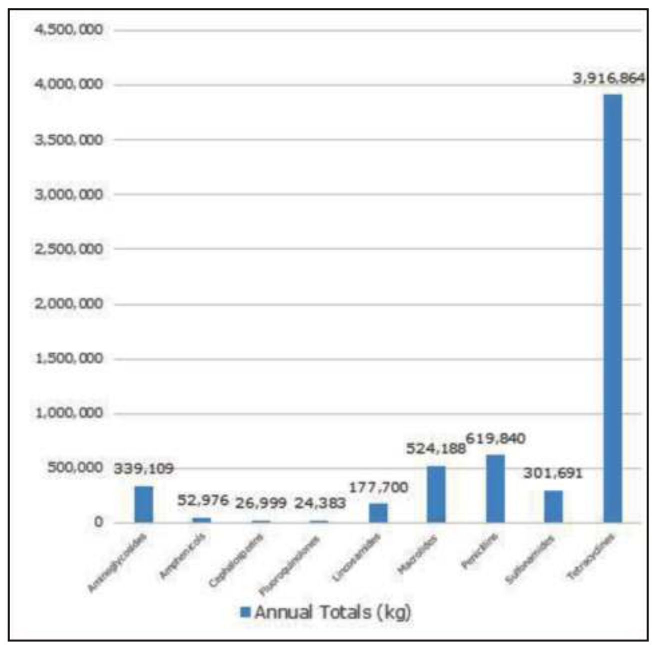

Fig. 4. Domestic sales and distribution data reported by medical importance and drug class (31)

Drug-resistant bacteria can affect human health through contaminated food and the environment as a result of antimicrobial use on farms (95). Transmission of bacterial resistance to antimicrobials from food-producing animals to humans can occur through food routes (in the case of zoonotic bacteria such as *Campylobacter*, *Salmonella*, and *E. coli*), by routes such as water or other environmental contamination, as well as through direct contact with animals (27).

In animal husbandry, antibiotics are applied for therapeutic and prophylactic purposes, as well as to promote growth due to their positive effects (78).

The majority of antibiotic use on dairy farms focuses on mastitis management (85). Residues of antibiotics are mainly found in milk due to their unwise usage in treating infectious diseases in animals, and their concentration can be influenced by the characteristics and health of the animal, the amount and type of antibiotic administered, and the way antibiotics are administered, the amount of milk produced (78, 97). The presence of antibiotic residues in milk affects its quality and constitutes a significant danger to the health of consumers (55).

Milk which contain drug residues may cause serious health problems on public health like: the development of antibiotic resistance and the transmission of resistant microorganisms present in milk and milk products among the humans, allergic such as serum sickness and anaphylaxis (especially in case of penicillins), potential carcinogenic (in case of sulfamethazine, oxytetracycline, furazolidone), reproductive disorders, mutagenic effect who can lead to infertility in humans, congenital anomalies in new born child due to long term exposure of ARs during gestation period, nephropathy (gentamicin), hepatotoxicity, bone marrow toxicity (chloramphenicol), blood dyscrasias, gastrointestinal disorder, neurological disorder (14, 78, 96, 97). The presence of ARs in milk can also have negative effects on the dairy industry due to the fact that antibiotics can interfere with the fermentation process during the production of cheese and yoghurt by inhibiting the starter cultures (78). The consequences of infections with antibiotic-resistant bacteria are increased mortality, morbidity, and social and economic costs (91).

PREVENTION AND CONTROL MEASURES

Some basic measures from dairy farms that contribute to maintaining milk quality and preventing foodborne illness and antimicrobial resistance in humans by regular screening of dairy cattle and buffalo for subclinical mastitis, proper therapeutic interventions based on antibiotic susceptibility testing, good hygiene practises in animal sheds and the environment, and separating sick animals from healthy ones (26, 40, 54, 89). Avoiding the consumption of raw milk is the main effective method for the control and prevention of milk-borne pathogens (40).

CONCLUSIONS

From this study, we conclude that some pathogens from dairy farms are still an animal health concern with public health relevance, and despite all the measures that have been taken to prevent milk contamination, when milk is consumed unpasteurized, it continues to represent a serious threat to people's health. In addition, the alarmingly increasing usage of antibiotics in dairy animals increases the chance of transmission of antibiotic-resistant bacteria to humans through the food chain or through direct and indirect contact. Therefore, appropriate strategies should be implemented to minimise the transmission of pathogenic bacteria from dairy animals to humans and to control the development of antimicrobial resistance in humans and animals.

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