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A scoping review on the presence of antibiotic residues in milk and the government strategies to control the use of antibiotics in the milk industry in India

SILVY MATHEW[1] AND NAVYA VYAS[1,*]

[1]Department of Health Policy, Prasanna School of Public Health, Manipal Academy of Higher Education, Manipal, India.

* Corresponding author: navya.vyas@manipal.edu

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In dairy farms, antibiotics are administered for therapeutic and prophylactic purposes. After antibiotic administration, lack of adherence to withdrawal periods and irrational use of antibiotics in the feed may lead to antibiotic residues (AR) in milk. The issue is predominantly concerning in India, as it has the most extensive consumer base in the world. It is a matter of grave concern, as numerous studies have identified that consuming milk contaminated with antibiotics may pose a myriad of health hazards. Therefore, this scoping review was conducted to collate all the available information on AR in milk, its associated health risks, and the government initiatives in place to combat inappropriate antibiotic use in the Indian dairy industry. The review was conducted systematically using Joanna Briggs Institute (JBI) guidelines, 2020 as its framework. A comprehensive search was performed using databases such as PubMed, Scopus, Google Scholar, Web of Science, and Google. A total of 19 articles were retrieved for the AR in milk, and 11 grey literature were identified for the government initiatives to control the use of antibiotics. Analysis of the collated information revealed that tetracyclines were the most commonly occurring AR in milk. Additionally, AMR was identified as the most common health hazard that may arise due to AR in milk, followed by allergic reactions. Finally, the review concluded that there is a requirement for more stringent regulations to curb AR in the dairy industry in India.

1. Introduction

Misuse of antibiotics is the driving agent responsible for Antibiotic resistance (AMR) in humans. In 2011, Jaipur Declaration highlighted that antibiotics' irrational use among food animals is another major contributor to AMR along with the human sector (Jadhav, Lata Chauhan, and Garg, 2019a). Some of the animal-derived food products are meat, fish, honey, milk, and eggs. Milk and its derivatives form an integral component of the entire global populace. It is a highly consumed commodity that has proven human health benefits (Sachi et al., 2019). However, it has been established that milk is subjected to adulterants either intentionally or unintentionally, diminishing the health benefits of milk. Generally, milk is adulterated by products such as water, sugar, pond water, detergent, and other synthetic compounds (Singh and Gandhi, 2015). Milk also gets contaminated due to residues from veterinary drugs such as antibiotics following the treatment of infectious diseases in cattle (Sachi et al., 2019. The prevalence of antibiotic residues (AR) in samples of milk has been documented since the 1960s and thus is not a new issue (Sachi et al., 2019). Globally, many studies have reported the presence of AR in milk.

The Food Safety and Standards Act (FSSA), 2006, define veterinary drug residues as “the parent compounds or their metabolites or both in any edible portion of any animal product and include residues of associated impurities of the veterinary drugs concerned” (FSSAI). The most pertinent cause of antibiotic residues in milk is its injudicious use.

1.1. Antibiotic use in the dairy industry

In dairy farms, antimicrobial drugs are used for therapeutic and prophylactic purposes (Panigrahi, Singh Sheoran, and Ganguly, 2017). Antibiotics are administered mostly for clinical mastitis and as “dry cow therapy” to treat any intra-mammary infections (Kumar and Gupta, 2018). Penicillin, tetracyclines, sulphonamides, and aminoglycosides are frequently used medicines among veterinary drugs (Panigrahi et al., 2017). The residues in the milk are mostly found because of extensive use as growth regulators by mixing in their feed, failure to observe the withdrawal period, lack of medical records, injudicious use for treating diseases, and utilization of unapproved drugs (Panigrahi et al., 2017; Pawar N, 2012).

1.2. Global Scenario

The number of antibiotics used in livestock was estimated to be 63,151 ± 1,560 tons worldwide (Van Boeckel et al., 2015). Its indiscriminate use in the dairy industry can have debilitating effects on humans as the global consumption of milk is projected to increase in the coming years due to a surge in demand (Anon, 2020). A review that was done at the global level found that the majority of the work was done in Asia, followed by Europe. In Asia, China accounted for the major proportion of the studies, whereas India had a comparatively lesser number of published works (Sachi et al., 2019). Moreover, the risk of AR in milk is believed to be higher in developing countries antithesis to developed countries. The lack of infrastructure and regulatory authorities for detecting and controlling drug residue levels in food products generated from animals may be one of the reasons. (Jayalakshmi et al., 2017).

1.3. Indian Scenario

India stands among the top five countries with sizable shares of global consumption of antimicrobials in food animals (Sivaraman and Yann, 2018). Consumption of milk infiltrated with AR may steer potential health hazards in consumers. It is a rising issue of prime concern as the milk industry in India has the second-largest consumer market in the world (FICCI, 2020). Additionally, India's dairy industry is the world's major and fastest-growing industry, and antibiotic-contaminated milk can have grave economic consequences. (FAO, 2014). Studies on mastitis have exhibited that milk contaminated with antibiotics causes significant economic losses to the farmers, as the milk infiltrated with such residues must be discarded (FAO, 2014). A loss of 1390 INR per lactation was recorded in a study due to mastitis, in which 48.53% of the loss was incurred because of discarded milk (MK and NN, 2013). Apart from financial losses, inappropriate utilization of antibiotics in cattle can predispose the emergence of resistant bacteria, ultimately leading to antimicrobial resistance in humans along with other long-term health effects (Moudgil, Jasbir Singh Bedi, et al., 2019). WHO posited that Antimicrobial resistance (AMR) develops when bacteria, viruses, fungi, and parasites evolve and become unresponsive to antibiotics, making infections more difficult to treat and raising the chances of disease transmission. With this increased drug resistance, antibiotics are becoming alarmingly ineffective, threatening the ability to treat common infections in humans (WHO, 2020).
Recognizing the gravitas of the situation in India, this scoping review was conducted with the dual objective of mapping the evidence on the occurrence of antibiotics in milk, its public health-associated risks, and the government strategies that have been implemented so far to limit the use of antibiotics in India’s dairy industry.

2. Methodology

The scoping review followed the framework prescribed by Joanna Briggs Institute (JBI) Reviewer's Manual 2020 guidelines (Peters et al., 2020). This framework was primarily used to systematically synthesize the evidence available for AR in milk samples and the health hazards linked with it. A priori protocol was developed before commencing the study. The study systematically followed the six steps mentioned in the JBI framework.

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2.1 Study Location

The geographical context chosen for this study was India, a South-East Asian country as per WHO regions (WHO). India is divided into distinct regions such as North, South, Central India, East, West, and North-east region. India was selected for this study, considering the widespread prevalence of antibiotic use among livestock animals(Sivaraman and Yann, 2018).

2.2. Identifying the research question

For this study, the research questions were set in accordance with the objectives of the study. The research questions identified were: (1) What are the various types of AR found in milk? (2) What is the various health hazards linked with the presence of AR milk? (3) What government policies/ regulations were formulated and implemented to combat the indiscriminate usage of antibiotics in the dairy industry in India?

2.3. Search Strategy

Based on the inclusion criteria, a comprehensive search method was developed to identify relevant studies. Initially, limited searches were conducted in PubMed to identify suitable keywords. Based on the determined keywords, an extensive search was conducted from 25th January 2021 to 12th February 2021 on databases for mapping evidence on AR in milk: (1) PubMed (2) Scopus (3) Web of Science, and (4) Google Scholar. The research articles were limited to those from January 2011 to January 2021 and published in the English language. The articles were restricted to quantitative studies and contained the following terms in their title and abstract: Antibiotic residues, Milk, and India. Various synonyms used for Antibiotics were Oxytetracycline/ Tetracycline/ Penicillin/ Sulfonamide/ Veterinary Antibiotic; Traces was used as a synonym for Residues. Whereas, for milk, milk samples/ dairy milk/ cow milk/ buffalo milk was used. Multiple combinations of keywords were used in conjunction with Boolean operators like AND/ OR/ NOT to form the search string. The terms were also modified in each database to find the maximum number of articles (Appendix 2).

Whereas the preferred type of document to understand the government initiatives to control the use of antibiotics in India was literature in the form of government policies and regulations. A comprehensive search was conducted from 13th February 2021 to 5th March 2021 using the Google search engine. The timeline chosen for the grey literature was also limited to that published from 2011 to 2021 and in English.

2.4. Study Selection

Following the search, all identified citations were collected and imported into the reference manager. Duplicate articles were removed, and subsequently, the search results were stepwise screened based on titles and abstracts by the first reviewer. The studies that met the inclusion criteria were retrieved and further screened for full text. Any ambiguity over the inclusion or exclusion of the articles was discussed with the second reviewer and based on the consensus between the two reviewers; the articles were included/ excluded from the review. The study selection process was later charted with the help of the Preferred Reporting Items for Systematic Reviews and Meta-analyses for Scoping Reviews (PRISMA-ScR) flow diagram, and the results of the selection process were elaborated in the results section.

2.5. Charting the data

All the included studies were reviewed and charted using a data extraction tool devised and aligned to the objectives and the research questions of this scoping review. The domains under which the data extraction for AR in milk (Appendix 3) were:

1. Distribution of study as per location in India
2. Type of Antibiotics found
3. Type of risk assessment used for the milk residue, and
4. Public health risks identified.

For the government initiatives, the finalized grey literature articles were categorized into three domains and charted using a table. The three domains were:

1. Initiatives on Quality and Control of Antibiotic Use
2. Initiatives Related to Dairy Animal Health
3. Initiative to Control AMR Arising Due to Food-Animals

2.6. Data Analysis

Following data charting for the retrieved articles and grey literature, all the collated data were exported to Microsoft Excel Spread sheet, and subsequently, data analysis was conducted. The extracted data were subsequently summarised in the form of narrative synthesis.

3. Results

3.1. Identified Studies

The comprehensive search yielded a total of 1027 (PubMed-24, Scopus-20, Web of Science-11, Google Scholar-972) articles for the first objective. After importing the retrieved articles from EndNote, a duplication removal was done from the search results and 287 articles were excluded from the study, resulting in 740 articles. After duplication removal, based on title and abstract screening, 36 articles were selected, and 704 were excluded. Subsequently, full-text screening yielded 17 articles. Additionally, two articles were selected after thoroughly screening the references of the 17 eligible articles, which were later added to the study. The reasons for excluding the articles were:
1) Country setting (other than India)
2) Posters, Conference proceedings, and Review articles
3) Articles that only demonstrate the method of antibiotic residue extraction using spiked milk samples, and
4) Full-text not available.

Ultimately, 19 articles were included in the scoping review. The selection process was later charted in the PRISMA flow diagram (Appendix 1).

3.2. Characteristics of Included studies

3.2.1. Geographical distribution of study

In terms of the geographical distribution of the studies, the gradated map shows that most of the studies were published in Punjab and Haryana, located in Northern India, and Kerala, which is a southern state (Fig. 1). Out of the top 10 major milk-producing states in India (NDDB, 2019), studies have been conducted

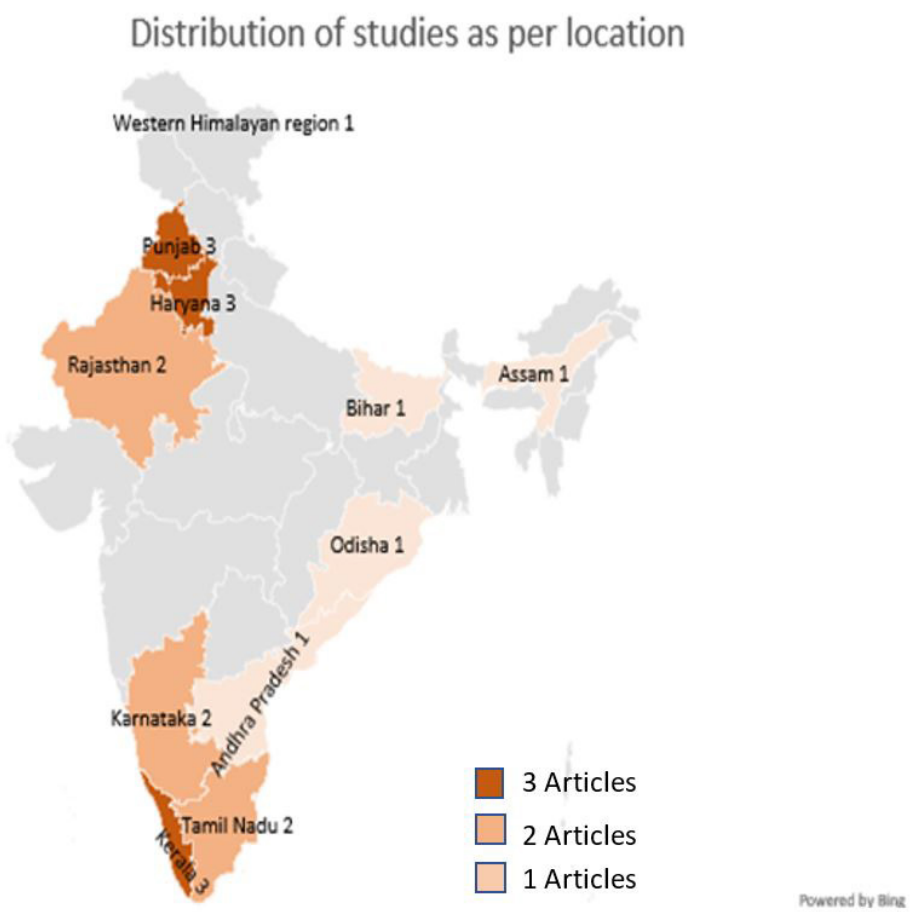

Figure 1. Distribution of studies as per location

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in only 6, that is, Rajasthan (Jaipal et al., 2021; Sharma et al., 2019), Andhra Pradesh (Kalla et al., 2015), Punjab(Gaurav et al., 2014; Moudgil, Jasbir S Bedi, et al., 2019; Moudgil, Jasbir S. Bedi, et al. 2019), Haryana (Chauhan, 2019; Jadhav, Lata Chauhan, and Garg, 2019b, 2019a), Bihar(Nirala et al., 2017), and Tamil Nadu (Moharana et al., 2015; Raosaheb et al., 2020).

3.2.2. Year of Publication

Among the studies selected, predominantly the studies were published in the year 2019 (Chauhan, 2019; Jadhav et al., 2019b, 2019a; M Kurjogi et al., 2019; Moudgil, Jasbir S Bedi, et al., 2019; Moudgil, Jasbir S. Bedi, et al., 2019; Sardar et al., 2019; Sharma et al., 2019) and the no studies were found in the year 2011 and 2012 (Fig.2).

3.3. Type of Antibiotic found

In this review, the detected antibiotics were grouped into 6 classes of antibiotics, namely, Tetracyclines, Beta-Lactam antibiotics, Quinolones, Sulphonamides, Aminoglycosides, and Macrolides (Fig. 3). Out of the 19 selected studies, the Tetracycline group of antibiotics was the most commonly detected residue found across the studies, that is, it was mentioned in 33% of studies Macrolides (Hebbal et al. 2020; Gaurav et al., 2014; Jaipal et al., 2021; Kalla et al., 2015; Kumar, Panda, and Sharma, 2021; Kumarswamy et al., 2018; M Kurjogi et al., 2019; Lejaniya et al., 2017; Moudgil, Jasbir S Bedi, et al., 2019; Moudgil, Jasbir S. Bedi, et al., 2019; Sharma et al., 2019).

Within the Tetracycline group, the identified antibiotics were Tetracycline (18%) and Oxytetracycline (16%). Quinolones were the second most commonly detected antibiotics, that is, in 28% of the studies, followed by Beta-lactams (25%), Sulphonamides (8%), and Aminoglycosides (5%). The least encountered antibiotic in the studies was the Macrolides group of antibiotics (Azithromycin), which was found in only one study (3%). Among Quinolones, Enrofloxacin (18%) was frequently encountered, followed by ciprofloxacin (3%) and Norfloxacin (3%). Table 1 shows the list of antibiotics found in the studies under the six classes of antibiotics.

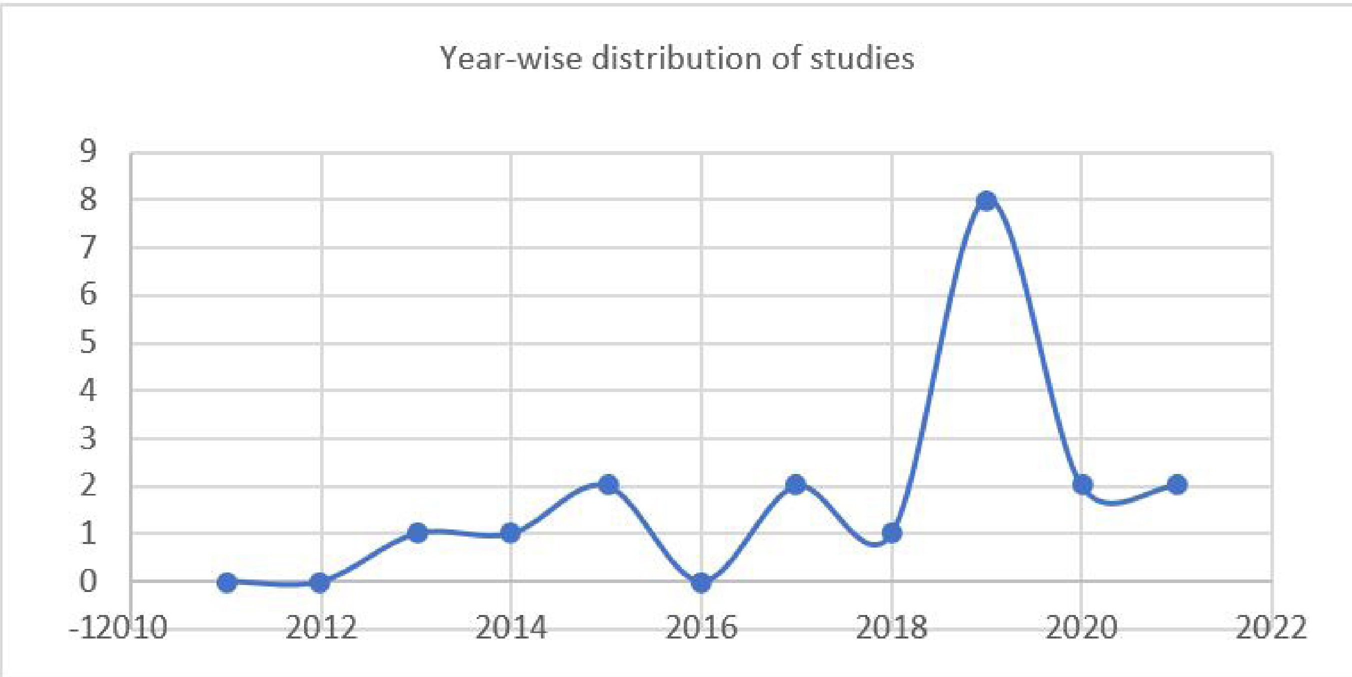

Figure 2. Distribution of studies as per year of publication

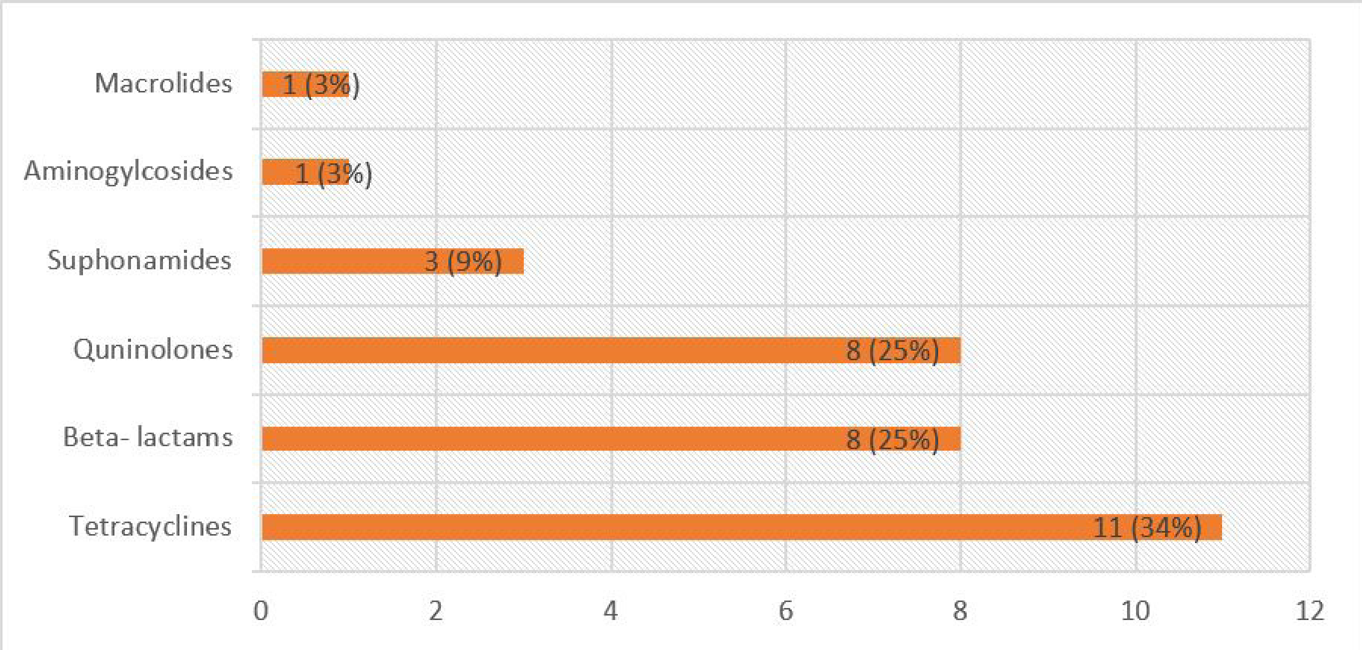

Figure 3. Distribution of studies as per the type of antibiotics

Table 1. The list of antibiotics found in the studies under the different classes of antibiotics

Tetracycline group	Beta-lactam Antibiotics	Quinolones	Sulphonamides	Aminoglycosides	Macrolides
Oxytetracycline	Penicillin G	Enrofloxacin	Sulphamethoxazole	Kanamycin	Azithromycin
Tetracycline	Amoxicillin	Norfloxacin	Sulpha containing drugs	Gentamycin	
	Cloxacillin	Ciprofloxacin			
	Ceftriaxone	Quinolones (broadly found)			
	Beta-lactam (broadly found)				

3.4. Type of Risk Assessment tool used

To understand the risk that may be posed due to the occurrence of ARs in milk samples, the identified studies have used two types of risk assessment measures, Maximum Residual limits (MRL), which are the permissible limits established for safe human consumption, and the Hazard Quotient (HQ), which is a ratio that assesses the adverse health effects based on the exposure to the substance. Out of the 19 studies, Fig. 4 shows that 58% of studies used Maximum residual limits (MRL) (Hebbal et al., 2020; Gaurav et al., 2014; Jadhav et al., 2019a, 2019b; Nirala et al.,, 2017; Kumarswamy et al., 2018; Mahantesh Kurjogi et al., 2019; Moharana et al., 2015; Moudgil, Jasbir S Bedi, et al., 2019; Sardar et al., 2019; Sharma et al., 2019), 16% of studies used both MRL and Hazard Quotient (HQ) (Chauhan, 2019; Kumar et al., 2021; Moudgil, Jasbir S. Bedi, et al., 2019), and 26% of studies did not evaluate any form of risk assessment measure to assess the potential risk that can occur due to the detection of ARs of milk (Dinki and Balcha, 2013; Jaipal et al., 2021; Kalla et al., 2015; Lejaniya et al., 2017; Raosaheb et al., 2020).

3.5. Identified Hazardous Health Effects

The studies mentioned the potential health hazards of consuming milk containing ARs. The risks identified were primarily long-term effects. All the hazardous effects mentioned across the studies were grouped based on five domains for this review, namely (Fig. 5):

1. Gastrointestinal Effects
2. Effects on Vital Organs
3. Sensitive Reactions,
4. Drug Resistance, and
5. Other Pathophysiological Effects

Of the Six domains, 33% of studies mentioned other pathophysiological effects comprising carcinogenicity, teratogenicity, phototoxicity, etc. This was followed by drug resistance (25%) and sensitive reactions (16%). The effect under each domain is summarised in Table 2.

3.5.1. Gastrointestinal Effects

The gastrointestinal effects indicated in the chosen articles were Gastrointestinal (GI) disturbances and interferences in intestinal microflora. Gastrointestinal disturbances were mentioned in 5% of the studies, whereas Interferences in microflora were indicated in 8% of the articles. Drugs like penicillin may cause gastrointestinal effects (Moudgil, Jasbir S. Bedi, et al., 2019).

3.5.2 Effects on vital organs

The most affected vital organs due to the consumption of milk containing antibiotics, as mentioned in the articles, were the kidney, liver, and neural organs. A total of 13% of articles mentioned effects on vital organs, of which 8% of studies mentioned damage to renal organs in the form of either nephrotoxicity or nephropathy. Whereas 5% of studies mentioned

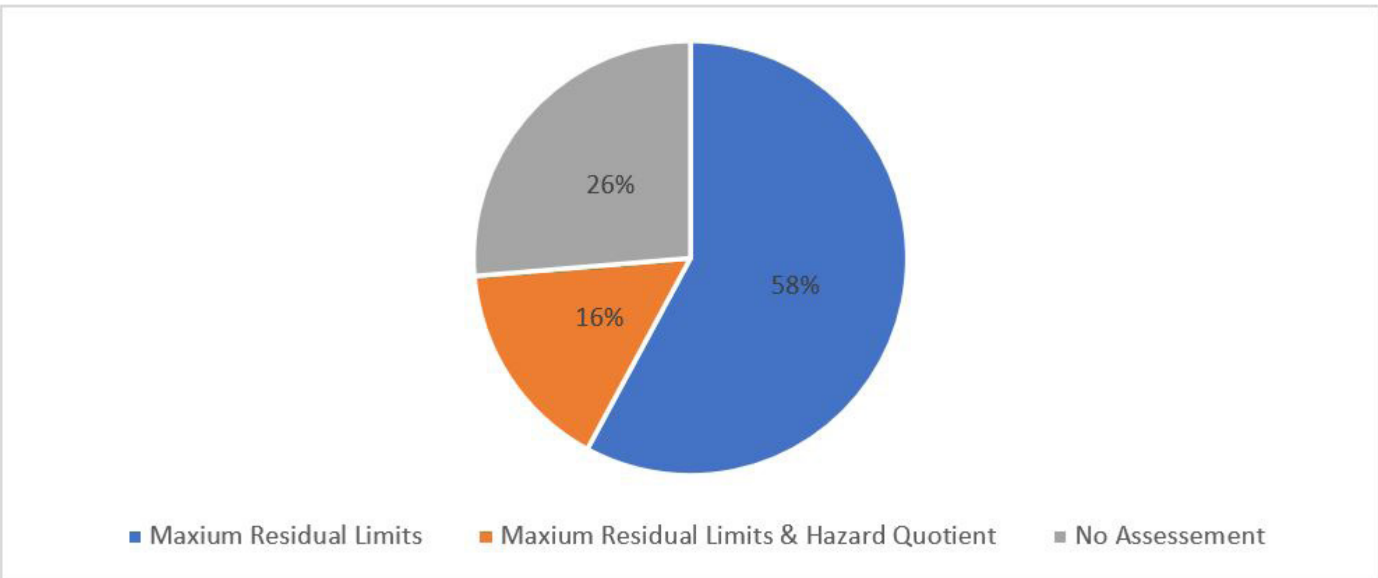

Figure 4. Distribution of studies as per the type of risk assessment tool used

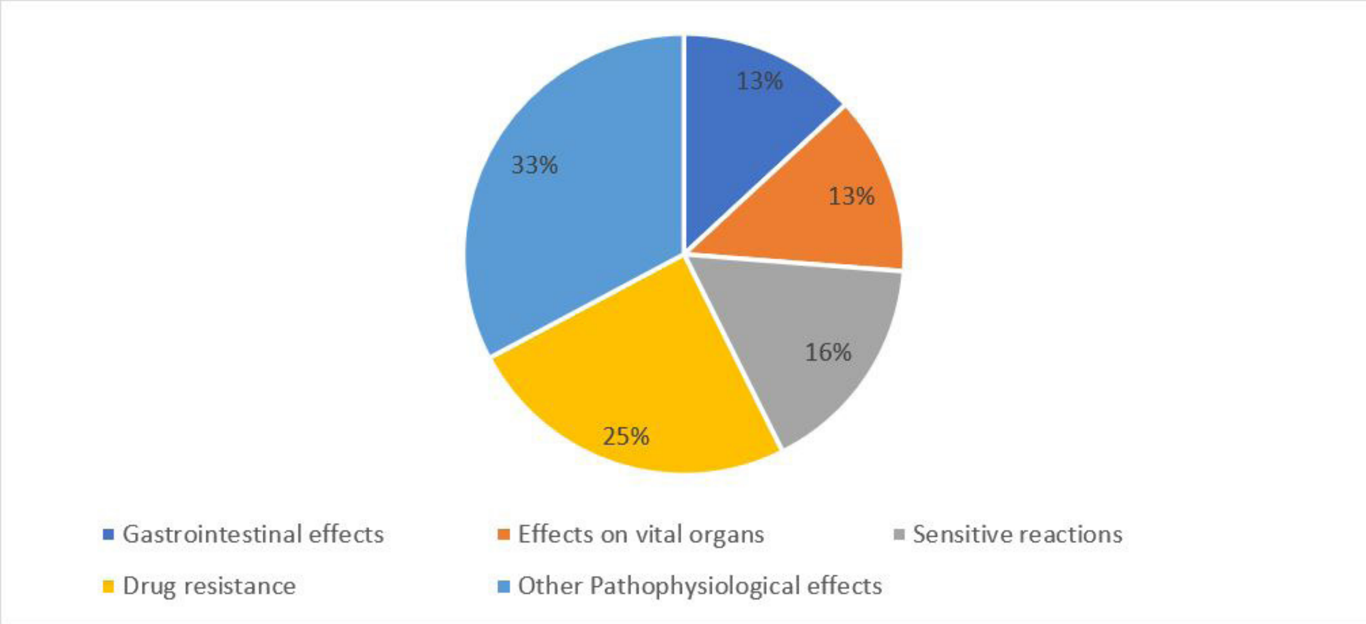

Figure 5. Distribution of studies as per the type of health hazard identified

Table 2. The list of hazardous health effects found in the articles under the domains

GIT Effects	Effects on Vital Organs	Sensitive Reactions	Drug Resistance	Pathophysiological Effects
GI disturbances (n=3)	Nephrotoxicity/ Nephropathy (n=4)	Allergic Reactions (n=9)	AMR (n=15)	Carcinogenicity (n=5)
Interferences of intestinal micro-flora (n=5)	Neurotoxicity (n=1)	Anaphylactic Reactions (n=1)		Teratogenicity (n=1)
	Hepatotoxicity (n=3)			Bone marrow toxicity (n=4)
				Mutagenicity (n=3)
				Toxicological and microbiological (n=1)
				Immunopathological risks (n=2)
				Photosensitivity/ Phototoxicity (n=2)
				Discolouration of teeth/ nails (n=2)

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hepatotoxicity, and 2% mentioned neurotoxicity may arise. Some of the drugs that may lead to effects on vital organs were aminoglycosides, gentamycin, enrofloxacin, oxytetracycline, and Azithromycin (Hebbal et al., 2020; M Kurjogi et al., 2019; Moudgil, Jasbir S Bedi, et al., 2019).

3.5.3 Sensitive Reactions

Two kinds of sensitive reactions were highlighted by the studies. First, allergic reactions were mentioned in 15% of the articles. Second, anaphylactic reactions were highlighted in 2% of studies. Of all the findings, after AMR, the most reported health hazard was allergic reactions to antibiotics by consuming milk contaminated with antibiotics after prolonged exposure. Sensitivity reactions may be caused by antibiotics such as penicillin, sulphamethoxazole, and enrofloxacin (Jadhav et al., 2019a; Moudgil, Jasbir S. Bedi, et al., 2019).

3.5.4 Drug Resistance

AMR was the most highlighted health hazard, which was mentioned in 15 articles, that is, 25% of all the studies. Prolonged exposure to antibiotics may develop drug resistance bacteria, which can further enter the food cycle of humans through milk, was the most common understanding of all the authors that mentioned AMR as a hazard in their study.

3.5.5 Other Pathophysiological Effects

Cumulatively, 33% of studies mentioned pathophysiological effects, of which, Carcinogenicity was mentioned in 5% of papers. Followed by bone marrow toxicity (7%), mutagenicity (5%), immunopathological effects (3%), and discoloration of teeth (3%). The least commonly identified pathophysiological effects were teratogenicity (2%) and toxicological or microbiological effects (2%). Antibiotics like Oxytetracycline, Tetracycline, Sulphonamides, Chloramphenicol, and Azithromycin may induce pathophysiological effects in humans (Hebbal et al., 2020; Chauhan, 2019; Gaurav et al., 2014; M Kurjogi et al., 2019; Moudgil, Jasbir S. Bedi, et al., 2019).

3.6. Government Initiatives in Dairy Industry

A total of 11 documents were found on the government initiatives in the dairy industry. The initiatives were divided based on three domains:

1. Initiatives on Quality and Control of Antibiotic Use
2. Initiatives Related to Dairy Animal Health
3. Initiative to Control AMR Arising Due to Food-Animals

Of the three domains, most of the documents were found for the first domain (55%), that is, Initiatives on Quality and Control of Antibiotic Use, with a total of six documents (27%). Three documents (18%) were found for Initiatives related to Dairy Animal Health, and two pieces of literature were found for the third domain (Appendix 4).

3.6.1 Initiatives for Quality and Control of Antibiotic Use

The Government of India, the Food Safety and Standards Authority of India (FSSAI), the Department of Animal Husbandry, Dairying & Fisheries, and the Central Drug Standards Control Organisation are some of the governing bodies identified that have been recognised and have worked towards controlling and maintaining standards of milk in India. FSSAI is a safety regulatory body for food that has been established under the Food safety and standard Act, 2006 in India (FSSAI). The Ministry of Health and Family Welfare is the administrative unit responsible for the functioning of FSSAI (FSSAI). It formulates various regulations to ensure the quality and safety of food products in India. Among these is the Food safety standards (Contaminants, Toxins & Residues) Regulations, 2011. Under this regulation, acceptable standards for various toxins and residues are mentioned for various animal-derived food products. This regulation first came in the year 2011 and in the 1st version of the document, antibiotic residual limits were only set for seafood. Even though in 2011, the Jaipur Declaration on antimicrobial resistance (AMR) stated that AMR is caused not only because of irrational use of antimicrobials among humans but also because of its injudicious use in animals (World Health Organization, 2011). It was only in 2018 that residual limits for antibiotics in milk and meat were introduced by FSSAI. These regulations are formulated to limit the quantity of antibiotic residue consumed by humans,

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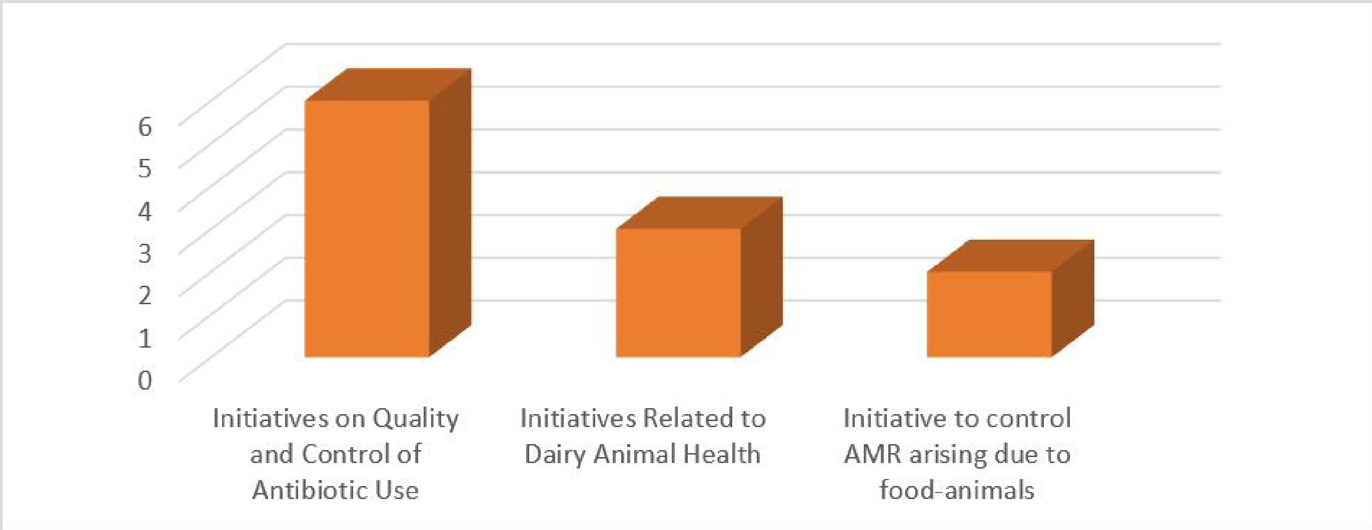

Figure 6. Distribution of reports based on the domains

hence preventing the spread of antibiotic resistance.

In 2013, the National Animal Policy was announced, and one of the major goals was to ensure that quality livestock products met international food safety requirements. The policy highlights the growing concern of excessive residues of antibiotics, fertilizers, pesticides, and other toxins in milk. Thereby, encouraging the states to carefully use antibiotics in livestock (D. & F. Department of Animal Husbandry, 2013). Another organization that identified the public health problem and issued advisories to regulate the use of antibiotics in farm animals is the Central Drugs Standard Control Organization, which also recommends labelling medicine containers with appropriate withdrawal periods to ensure judicious and monitored utilization of antibiotics in food animals (Department of Animal Husbandry, 2013). In 2013, Central Drugs Standard Control Organisation added another category of Schedule H1 drugs under the Drugs and Cosmetics Rule, 1945, along with the existing Schedule H category. The Schedule H1 classification of drugs was predominantly done to control the indiscriminate use of antibiotics both in the human and animal sector (Central Drugs Standard Control Organization, 2017).

Two initiatives concerning the maintenance of the standard quality of milk for consumers were found. First, is the National Programme for Dairy Development, which was implemented by the department of animal husbandry and dairying in 2014. The programme focuses on developing robust dairy infrastructure, quality, and manpower training (Department of Animal Husbandry and Dairying). The second initiative on quality is the Export of Milk and Milk Products (Quality Control, Inspection, and Monitoring) Rules, 2020, which came as a successor to the Export of Milk and Milk Products (Quality Control, Inspection, and Monitoring) Rules, 2000 (Priya, 2020). As per the rule, the standard quality of milk should be maintained and checked before exporting. The rule also mentions that the milk should be free of residues like antibiotics, pesticides, and other harmful substances (Priya, 2020). The milk is to be assessed for residual limits as per national or international standards, and any batch of milk contaminated with such residues is to be discarded as per the rule (Priya, 2020).

3.6.2 Initiatives Related to Dairy Animal Health

To maintain quality milk standards and ensure complete profitability, it is important to maintain proper animal health. To maintain livestock health in India the two regulatory bodies were the Department of Animal Husbandry & Dairying and the National Dairy Development Board were the two regulatory bodies identified to maintain livestock health in India. These institutions have certain initiatives that control and monitor livestock health. In 2011, the National Animal Disease Reporting System (NADRS) was es-

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tablished to collect data on animal health to monitor disease control efforts. (NADRS). Recently, a new version, NADRS 2.0, was released in the year 2021.

Unlike Norway, Australia, and the Netherlands, India does not have a national mastitis control programme (Brightling et al., 2009; Jansen et al., 2010; Østerås, 2013). In one of the states in India a pilot programme called Mastitis Control Popularisation Programme (MCPP) was launched in 2014 to rationalize antibiotic drug usage in infected cattle (National Dairy Development Board). Many other state-run initiatives are there in states like Kerala, Assam, etc. To counter diseases such as Brucellosis and Foot & Mouth Disease, the Department of Animal Husbandry and Dairying launched the National Animal Disease Control Program in 2019, with the goal of eradicating the diseases by vaccinating all livestock animals by 2030 (Department of Animal Husbandry & Dairying, 2019).

3.6.3 Initiative to Control AMR Arising Due to Food-Animals

To control AMR arising due to food animals, the Indian Council of Agriculture Research (ICAR) and the National Centre for Disease Control (NCDC), were the two organizations found. The previous National policy on AMR containment (2012-2017) did not recognize the spread of AMR through the animal sector as well; it was only limited to irrational use by humans. Although in 2017, the National action plan on AMR (NAP-AMR) (2017-2021) was introduced with one of its objectives to optimize antibiotic usage in the human, animal, and food sectors (Sharma and Anuj 2017). The action plan was formulated keeping the Global Action Plan on AMR (GAP-AMR) into consideration (Sharma and Anuj, 2017). A national surveillance network of veterinary laboratories exists in India, which was established in collaboration with the Food and Agriculture Organisation (FAO) and ICAR in 2017 (FAO, 2017). The network is known as the Indian Network for Fishery and Animal Antimicrobial Resistance (INFAAR). The surveillance system was created to capture all AMR-related data from the veterinary industry.

4. Discussions

This scoping review was undertaken to collate all the evidence available on the occurrence of ARs in milk. The findings of the analysed publications demonstrated high evidence of ARs in milk across India's several states. The antibiotics in milk were a considerable cause of concern as most of the antibiotics found in this scoping review belong to the WHO's critically Important Antibiotics List. It is a list that categorizes antibacterial drugs based on their importance in human medicine (WHO, 2011). Of the antibiotics found, Tetracycline and sulphonamides belong to the "Highly Important" group. In the critically important category, Aminoglycosides and Penicillin belong to "High Priority", whereas Cephalosporins (3rd generation), Macrolides, and Quinolones belong to the "Highest Priority" groups (WHO, 2011). The European Medicines Agency (EMA) puts these Critically Important Antibiotics under their "Restricted" category, which recommends limited use of these antibiotics in animals to safeguard public health (European Medicines Agency, 2020). Also, with measures such as banning the preventative use of antibiotics and using certain models, the Netherlands successfully reduced the use of antibiotics in dairy animals by 2015 (Lam, Jansen, and Wessels, 2017; Scherpenzeel et al., 2016). Therefore, urgent attention and similar stringent measures are required to control the use of antibiotics in India as well.

Also, 79% of articles selected for the study indicated AMR as a significant long-term public health hazard, which may arise from consuming milk containing AR. Bhattacharya et al found Vancomycin-resistant strains of bacteria in the milk samples and stated that the irrational use of antibiotics may have contributed to the development of such strains (Bhattacharyya et al., 2016). Some of the enabling factors responsible for the development of AMR through the food-animal industry are lack of antibiotic awareness and information, use of fake and substandard drugs, poor 'one health' integration in developing countries, and lack of alternatives to antibiotics for animal use (Grace, 2015).

In India in terms of government activities, there are some restrictions in place to control the use of antibiotics in the dairy business, but there is a need for more stringent controls. Requirement for appropriate regulations, robust surveillance system, strengthened quality control system, and training programs for farmers were highlighted by several authors included in the review (Hebbal et al., 2020; Gaurav et al., 2014; Kalla et al., 2015; Nirala et al., 2017; Moudgil, Jasbir S Bedi, et al., 2019; Moudgil, Jasbir S. Bedi, et al., 2019; Raosaheb et al., 2020). According to a report, some guidelines to limit the use of antibiotics exist in India, but they have never been implemented into laws or regulations (CDDEP, 2016). Another report on antibiotic usage in food animals stated that India does not have a stringent regulatory framework to limit the utilization of antimicrobials in livestock and food animals (Sivaraman and Yann, 2018).

5. Conclusion

The present scoping review portrayed India's situation in terms of ARs in milk with the help of studies conducted in India. Although there is growing evidence on the subject year by year, there is a paucity of literature concerning public health effects that may arise from consuming milk contaminated with antibiotics. Antibiotics in milk are primarily an issue of prime importance in India as it has the most extensive consumer base for milk. The majority of antibiotics detected in this study were on the WHO's Critically Important Antibiotics list, which is a cause of great concern for humans. AMR was also identified as the most common public health risk associated with antibiotic-contaminated milk. Given that India is one of the world's hotspots for AMR, a more proactive approach involving stricter laws and monitoring systems is the need of the hour to prevent the spread of AMR that can result from the overuse of antibiotics in dairy animals and other food-producing animals in India.

6. Recommendations

The recommendations for this scoping study were based on the information presented in the literature reviewed.

- Regulating WHO recommended critically important antibiotics used in food animals.

- Awareness and training for dairy farmers and veterinarians about the use of antibiotics (public health implications, appropriate withdrawal periods, and residual limits) and about AMR that can arise due to their irrational use in animals.

Conflict of interest

The authors declare no conflict of interest.

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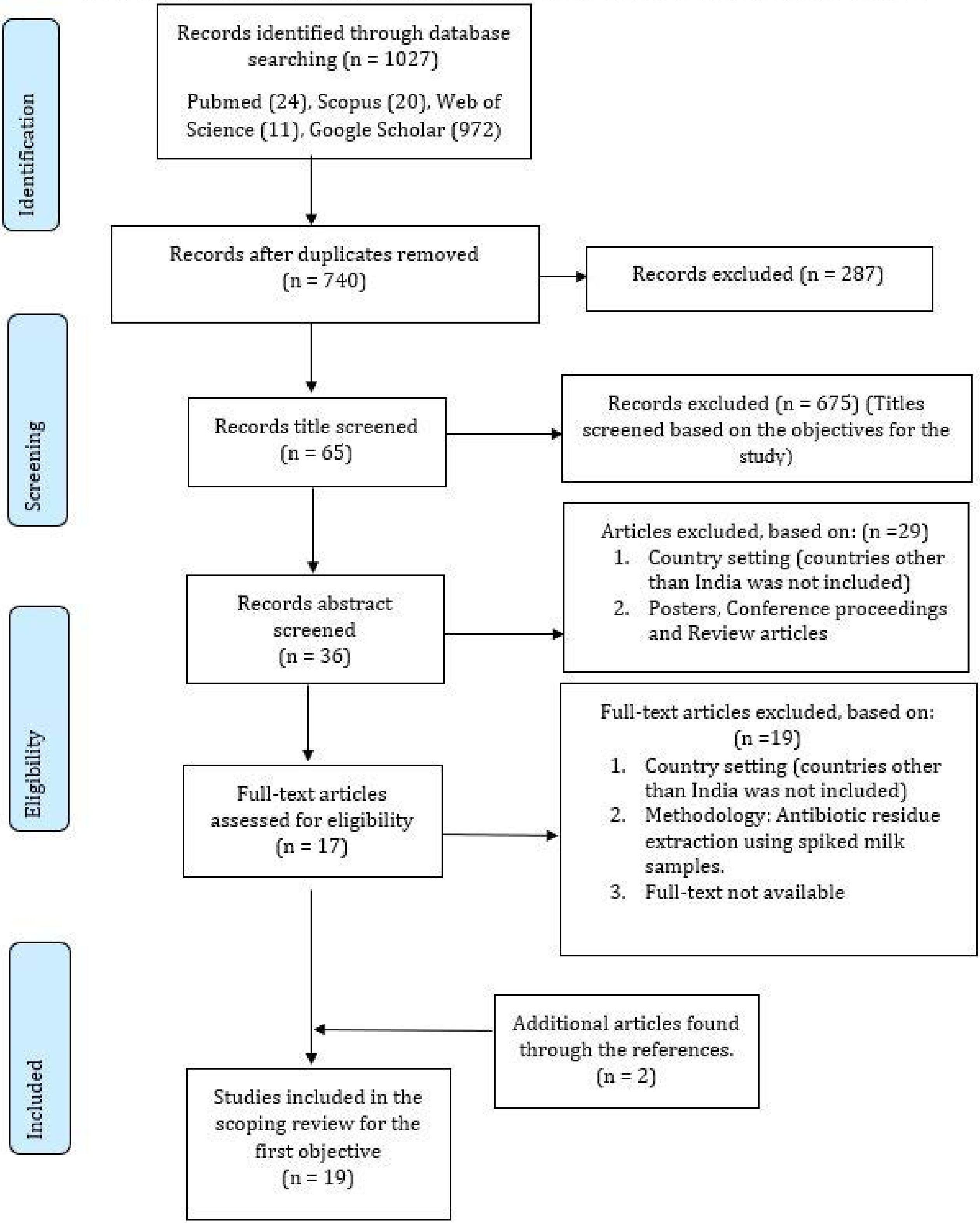
Appendix 1: PRISMA Flow diagram demonstrating the study selection process.



Appendix 2: Search Strategy

Database	Keywords	Number of Articles retrieved
PubMed	(Antibiotics) OR (Oxytetracycline)) OR (tetracycline)) OR (Fluoroquinolones)) OR (Sulfonamides)) AND ((Residues) OR (traces)) AND (((Milk) OR (Milk samples)) OR (Dairy milk)) OR (cow milk)) OR (buffalo milk)) OR (cattle milk))) AND (India) Filter: English, 2011-2021	24 articles
Scopus	TITLE-ABS-KEY (antibiotics OR oxytetracycline OR tetracycline OR penicillin OR sulfonamides OR quinolones) AND TITLE-ABS-KEY (residues OR traces) AND TITLE-ABS-KEY ("milk" OR "milk samples" OR "dairy milk" OR "cow milk" OR "buffalo milk") AND TITLE-ABS-KEY (india) AND (LIMIT-TO (PUBYEAR , 2021) OR LIMIT-TO (PUBYEAR , 2020) OR LIMIT-TO (PUBYEAR , 2019) OR LIMIT-TO (PUBYEAR , 2018) OR LIMIT-TO (PUBYEAR , 2017) OR LIMIT-TO (PUBYEAR , 2016) OR LIMIT-TO (PUBYEAR , 2015) OR LIMIT-TO (PUBYEAR , 2014) OR LIMIT-TO (PUBYEAR , 2012))	20 articles

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Continue Appendix 2: Search Strategy

Database	Keywords	Number of Articles retrieved
Web of science	#4 AND #3 AND #2 AND #1 TS=(antibiotics OR oxytetracycline OR tetracycline OR penicillin OR sulfonamides OR quinolones) AND TS=("milk" OR "milk samples" OR "dairy milk" OR "cow milk" OR "buffalo milk" OR "cattle milk") AND TS=(residues OR traces) AND TS=(india) Refined by: [excluding] PUBLICATION YEARS: (2007 OR 2001 OR 2005 OR 1995)	11 articles
Google Scholar	Antibiotic AND Residue AND Milk AND India AND Oxytetracycline OR tetracycline OR quinolones OR Sulfonamides OR Residues OR traces OR “Milk samples” OR “Dairy milk” OR “cattle milk” -Meat -Pesticides -Toxins -honey -Fish -antibody -poultry	972 articles

Appendix 3: Data Extraction Sheet

S.No.	Author name, Year of publication	Study Location	Study Purpose	Methodology	Key findings			
					No. of samples contaminated with antibiotic residues	Antibiotic(s) found	Type of public health risk assessment used	Public health risks identified in the paper
1.	Dinki & Balcha, 2013	Guwahati	Antibiotic residues were detected and the microbial content of samples taken from six different consumers' collection points were assessed.	120 milk samples were obtained aseptically from milk cans chosen at random.	28 samples	Not mentioned	No Assessment used	-allergic reactions -Drug resistance
2	Gaurav et al, 2014	Punjab	In five areas of Punjab, the study investigated and monitored the presence of Tetracycline in cattle milk.	Tetracycline residual contamination was examined and evaluated in 133 cattle milk specimens collected from dairies in five Punjab districts.	18 samples	Tetracycline	Maximum Residual Limits (MRL) assessed	-Tetracycline can cause Phototoxicity
3.	Kalla et al, 2015	Coastal districts of Andhra Pradesh	Pathogen isolation and identification of antibiotics, aflatoxins, pesticide, and industrial contaminants residues in the milk supply chain.	600 samples were obtained and sent to the laboratory for testing. Antibiotic residues were detected using Delvotest, and fast test kits.	62 samples	Penicillin-G, Tetracycline, and Oxytetracycline	Not assessment used	-allergic reactions -Drug resistance
4.	Moharana et al, 2015	Chennai, Tamil Nadu	The study identified Enrofloxacin residues in samples of cow's milk	125 milk specimens were obtained and analyzed for residues.	21 samples (16.8%)	Enrofloxacin	Maximum Residual Limits (MRL) assessed	-Drug resistance
5.	Nirala et al, 2017	Bihar	The study conducted a sample survey in both organized and unorganized dairy industries to assess the antibiotic presence in milk samples.	The study assessed 250 milk samples from the organized the unorganized sectors in the districts of Bihar, India. High-performance liquid chromatography (HPLC) was used to analyze samples.	8 samples	Enrofloxacin and Ciprofloxacin	Maximum Residual Limits (MRL) assessed	-Allergic reactions and interferences of intestinal micro-flora

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S.No.	Author name, Year of publication	Study Location	Study Purpose	Methodology	Key findings			
					No. of samples contaminated with antibiotic residues	Antibiotic(s) found	Type of public health risk assessment used	Public health risks identified in the paper
6.	Lejaniya et al, 2017	Thrissur, Kerala	The study calculated the amount of antibiotic residue in pooled milk samples.	Pooled morning milk samples were collected from milk cooperatives and organized farms in and around Thrissur district of Kerala. A total number of 50 samples were collected in sterile	7 samples	Beta-lactam and Tetracycline	No assessment	Implicitly stated.
7.	Kumarswamy et al, 2018	Thrissur, Kerala	The goal of this study was to assess the residues of antibiotics in milk.	Morning milk samples were obtained in the Thrissur district of Kerala from milk unions and organized farms. Antibiotic Test Kit (BEIJING YF-MARISGLOBAL CO., LTD, CHINA) was used to check for beta-lactam and tetracycline antibiotic residue in the samples.	14 samples	Tetracycline, ß-lactams, and enrofloxacin	Maximum Residual limits (MRL) assessed	-Carcinogenicity, teratogenicity, allergic reactions, bone marrow toxicity, mutagenicity, and Gastrointestinal disorders. -Antimicrobial Resistance (AMR).
8.	Moudgil et al, 2019	Punjab	The purpose of this study was to examine the prevalence of antibiotic residues in raw and marketed milk, to establish its suitability for human consumption.	Using high-performance liquid chromatography (HPLC), the study examined 524 milk samples, for antibiotic residues, from Punjab, India.	Dairy farms- 78 (16%) samples. Commercial milk samples- 4 (12.5%) samples.	enrofloxacin, oxytetracycline, tetracycline, and Sulphamethoxazole	-Maximum Residual limits (MRL) assessed. -Hazard Quotient (HQ) estimation	Allergic reactions, disorders of intestinal flora, carcinogenicity, and neurotoxicological effects. - Antimicrobial resistance (AMR)

Continue Appendix 3: Data Extraction Sheet

S.No.	Author name, Year of publication	Study Location	Study Purpose	Methodology	Key findings			
					No. of samples contaminated with antibiotic residues	Antibiotic(s) found	Type of public health risk assessment used	Public health risks identified in the paper
9.	Moudgil et al, 2019	Punjab	The study was conducted to detect antibiotics and mycotoxins in raw milk samples obtained from dairy farms in Punjab, India.	The study collected 168 raw milk samples from nine districts of Punjab and analyzed them using competitive Enzyme-linked immunosorbent test kits that are commercially available.	19 samples	enrofloxacin, oxytetracycline, penicillin G, sulphamethoxazole and chloramphenicol	Maximum Residual limits (MRL) assessed.	allergic reactions (Enrofloxacin, Penicillin G), disruption of intestinal flora, carcinogenicity, mutagenicity, nephropathy, hepatotoxicity (Oxytetracycline), and bone marrow toxicity (Oxytetracycline). - Drug resistance
10.	Sharma et al, 2019	Jaipur, Rajasthan	This study assessed the presence of antibiotic (oxytetracycline) residues and withdrawal periods in cattle milk samples from Rajasthan (Jaipur).	The study obtained 90 milk samples from 18 cows that had been treated with the antibiotic oxytetracycline for various clinical indications, for three days. Samples were taken from the day after the administration until the antibiotic residue was no longer detectable.	Day1: 12 samples Day2: 15 samples Day 3: 15 samples Day 4: 13 samples Day 5: 11 samples Day 6: 5 samples Day 7: 2 samples	Oxytetracycline	Maximum Residual limits (MRL) assessed	-pharmacological, toxicological, microbiological, and immunopathological health risks. - Drug resistance

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Continue Appendix 3: Data Extraction Sheet

S.No.	Author name, Year of publication	Study Location	Study Purpose	Methodology	Key findings			
					No. of samples contaminated with antibiotic residues	Antibiotic(s) found	Type of public health risk assessment used	Public health risks identified in the paper
11.	Chauhan et al, 2019	Hisar, Haryana	The purpose of this study was to detect aminoglycoside residues in milk from the local market and to quantify the risk of dietary exposure.	this study assessed the presence of aminoglycoside residues in milk accessible on the local market and quantified the risk of dietary exposure to aminoglycoside residues.	15 samples	Aminoglycosides (Kanamycin and Gentamycin)	-Maximum Residual limits (MRL) assessed -Hazard Quotient (HQ) assessed	-Chronic exposure to aminoglycosides can cause nephrotoxicity leading to renal failure, neuromuscular blockage, and irreversible ototoxicity. -Drug resistance
12.	Kurjogi et al, 2019	Dharwad, Karnataka	In this study, a microbiological technique was used to identify antibiotic residues in cow milk specimens.	the study obtained 13 raw cow milk samples from the dairy farms in the Dharwad area of Karnataka, India.	2 samples	Azithromycin and Tetracycline	Maximum Residual limits (MRL) assessed.	-Allergic reaction, intestinal alterations, photosensitivity reaction with nail discoloration, and discoloration of teeth in children -Drug resistance
13.	Priyanka et al, 2019	Hisar, Haryana	The study detected and quantified residues of penicillin in milk.	For the study, 100 milk samples were obtained from Hisar's local market, Samples of raw milk and pasteurized milk of various brands were randomly collected.	14 samples	Penicillin (Amoxicillin and Cloxacillin)	Maximum Residual limits (MRL) assessed	-Penicillin residues can cause health risks such as allergic reactions -Drug resistance
14.	Jadhav et al, 2019	Hisar, Haryana	The goal of this study was to standardize the use of high-performance liquid chromatography (HPLC) for the identification and quantification of quinolone residues.	The study randomly obtained 100 milk samples from Hisar's local market, Both pasteurized and raw milk samples were collected.	8 samples	Quinolones (Norfloxacin and Enrofloxacin)	Maximum Residual limits (MRL) assessed	-bone marrow apla-sia and can alter the normal gastroin-testinal microflora resulting in GI dis-turbances - Drug resistance

Continue Appendix 3: Data Extraction Sheet

S.No.	Author name, Year of publication	Study Location	Study Purpose	Methodology	Key findings			
					No. of samples contaminated with antibiotic residues	Antibiotic(s) found	Type of public health risk assessment used	Public health risks identified in the paper
15.	Hebbal et al, 2020	Palakkad, Kerala	The study was conducted to detect antibiotic residues in samples of milk.	Raw milk specimens were taken from three of Kerala's Palakkad districts. For screening, 215 samples were collected and screened using. Microbial inhibition assay (MIA). The analyzed positive samples were further processed by enzyme-linked immunosorbent assay (ELISA) to assess oxytetracycline residues and validated using high-performance liquid chromatography (HPLC).	22 samples (5 for oxytetracycline)	Oxytetracycline and other antibiotics (not mentioned)	Maximum Residual limits (MRL) as-sessed	-These residues can cause toxic effects such as anaphylactic reactions, carcinogenicity (oxytetracycline, sulfamethazine, and furazolidone), nephropathy (gentamicin), mutagenicity, reproductive disorders, bone marrow toxicity (chloramphenicol), hepatotoxicity, and immunopathological effects in humans. -AMR
16.	Das et al, 2019	Bhubaneswar, Odisha	The goal of this investigation was to detect antibiotic residues in mastitic cow milk after therapy.	The samples of milk were obtained from cured mastitic cows that underwent antibiotic therapy. The cows were divided in six groups and different doses of ceftriaxone and enrofloxacin were administered to each group.	Not specific	Ceftriaxone and Enrofloxacin	Maximum Residual limits assessed	-Intestinal flora interferences -Drug resistance

Continue Appendix 3: Data Extraction Sheet

S.No.	Author name, Year of publication	Study Location	Study Purpose	Methodology	Key findings			
					No. of samples contaminated with antibiotic residues	Antibiotic(s) found	Type of public health risk assessment used	Public health risks identified in the paper
17.	Raoshaeb,2020	Tamil Nadu and Karnataka	Across chosen districts of Tamil Nadu and Karnataka, the study was conducted to estimate antimicrobial utilization for multiple clinical diseases within organized and unorganized dairy sectors.	The information was gathered through surveys from 104 working veterinarians and treatment records on farms were obtained. To quantitatively analyze antibiotic residues in milk, 100 samples were collected from those farms.	13 samples	Not mentioned	No assessment	-AMR
18.	Kumar et al, 2021	The North-western Himalayan state of India.	The study determined the health risks posed by the presence of antibiotics in milk.	For analysis of residues, 173 raw and pasteurized samples were collected in India's northern. Himalayan state.	16 samples	Oxytetracycline and amoxicillin	-Maximum Residual limits (MRL) assessed. - Hazard Quotient	-Allergic reactions, GIT disruption, carcinogenicity, nephropathy, hepatotoxicity. -Drug resistance
19.	Jaipal et al, 2021	Bikaner, Rajasthan	The study describes relationships between the prevalence of antibiotic residues in cattle milk and various farm management strategies used by farmers.	For the study, 200 milk samples were gathered from dairy farms. Samples were retrieved from both indigenous and cross-breed cattle.	28 samples	Beta-lactam antibiotics, Tetracycline, Quinolones, and sulpha drugs	No assessment	Implicitly stated.

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Appendix 4: List of all government issues under the three domains

S. No.	Government initiative domains	Government Initiative	Year	Brief
1.	**Initiatives Quality and Control Antibiotic Use**	• Version 1: FSSAI Food safety standards (Contaminants, toxins & Residues) Regulations, 2011 (Anon) introduced	2011	Antibiotic residues permissible limits only for seafood
		• Version 2		
		• Version 3		changes were made and antibiotic residues permissible limits only for seafood and honey.
			2017	
		• Version 4 (Anon)		changes were made and antibiotic residues permissible limits for animal food products such as meat, milk etc. were added.
			2018	updated version
		• Version 5	2019	updated version.
			2020	
		National livestock Policy (Anon)	2013	encouraged states for careful use of antibiotics. Also highlighted the growing concern of excessive residues of antibiotics, fertilizers, pesticides, and other toxins in milk and milk products.
		Schedule H1 Drugs (Anon)	2013	to control the indiscriminate use of antibiotics both in human and animal
		National programme for dairy development (2013-2017) (2018-2022) (Department of Animal Husbandry and Dairying)	2013	To build dairy infrastructure, ensure milk quality, and manpower training.
		Central Drugs Standard Control Organisation (Rational use of antibiotics for limiting antimicrobial Resistance) (Anon)	2017	Recommends putting labels on antibiotics with appropriate withdrawal periods meant for animal use.
		Export of Milk and Milk Products (Quality Control, Inspection, and Monitoring) Rules, 2020 (Anon)	2020	standard quality of milk should be maintained and checked before exporting and ilk should be free of any residues like antibiotics, pesticides, and other harmful substances.

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Continue Appendix 4: List of all government issues under the three domains

S. No.	Government initiative domains	Government Initiative	Year	Brief
2.	**Initiatives Related to Dairy Animal Health**	National Animal Disease Reporting System (NADRS) (Anon)	2011	Primary objectives of the Animal Disease Reporting System is the collection and collation of animal health information.
		NADRS 2.0	2021	Updated version
		Animal disease control project by National dairy development board (Anon)	2014	Mastitis Control Popularisation Programme (MCPP) was launched in Gujarat
		National animal disease control programme (Anon)	2019	Disease control programmes for foot and mouth disease and Brucellosis.
3.	**Initiative to control AMR arising due to food-animals**	National Action Plan on AMR (NAP-AMR) (Sharma and Anuj, 2017)	2017	optimise the use of antibiotics in humans, animals and food sector
		Indian Network for Fishery and Animals Antimicrobial Resistance (INFAAR) (Anon)	2017	National network of veterinary laboratory for antimicrobial resistance.