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Review

Antibiotic residues in raw and pasteurized milk in Iran: A systematic review and meta-analysis

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Abstract: Improper use of antibiotics to treat or prevent infections, and as a stimulant for livestock growth, can affect public health and the dairy industry due to the spread of antibiotic residues in milk. This systematic review and meta-analysis aimed to investigate antibiotic residues in raw and pasteurized milk in Iran. Data were collected through searching the databases, including Scopus, PubMed, Science Direct, Web of Science, Google Scholar, SID, and Magiran using the following keywords: "pasteurized milk", "raw milk", "milk", "antibiotic residues"," antibiotic", and "Iran". Finally, 40 eligible studies were selected for the systematic review and meta-analysis. According to the reviewed studies, the prevalence of antibiotic residues in raw and pasteurized milk was 26% (95% CI: 20–33%) and 21% (95% CI: 15–27%), respectively. It seems that the control measures are inefficient in dairy industry and milk collection centers for the presence of antibiotic residues and the time of antibiotic withdrawal during milk delivery. Permanent control of milk in the collection centers by the responsible organizations along with implementation of Hazard Analysis Critical Control Point system in milk factories can be very effective in reducing antibiotic residues.

Keywords: antibiotic; veterinary drugs; health risks; milk, food safety

1. Introduction

Milk has a particular place in the diet plan of people in all age groups, especially children, because it provides high quality proteins with all the ten essential amino acids; it also provides fats, in particular essential fatty acids, minerals, vitamins, and energy for the body. Moreover, different bio-functional molecules like peptides, nucleotides, oligosaccharides, immunoglobulins, immune proteins, and metabolites have been found in milk [1–3]. Due to the importance of health issues in society, the quality of food of animal origin, including milk, is very important. Therefore, the milk valve must be free of any physical, biological, or chemical contamination. Since milk is usually consumed in breakfast all around the world, it is very important to check and control the quality of this food [1,4–7].

Antibiotics are antimicrobial substances able to kill or prevent the development and growth of different microorganisms. Today, antibiotics are widely used around the world to treat diseases and improve production efficiency, such as weight gain and livestock growth, in food-producing animals [8–12]. Annually, 63,151 ± 1560 tons of antibiotics are produced in the world for livestock use, which doubles the global use of antimicrobials in animals compared to humans [13,14]. Mastitis, which is the most common and economically important widespread disease in dairy cows, is treated by intra-mammary infusion of antibiotics. The most important groups of antibiotics used to treat infectious diseases in the livestock, especially mastitis and respiratory-digestive infections in dairy animals, include β-lactams, aminoglycosides, tetracycline, sulfonamides, macrolides, and quinolones [5,15,16]. After administration of antibiotics, a period of withdrawal is required; this time is needed for the body of animals to remove the complete antibiotic residue from the treatment outcome. According to the instructions of veterinary medicine, consumption of meat, eggs, and milk is prohibited during this period [17]. Antibiotic residues are defined as chemicals or metabolites of pharmaceutical products that may accumulate in the tissues or oral parts of animals treated with antibiotics. The excessive use of antibiotics can create antibiotic residues in milk. There might be multiple types of antibiotics in milk and the amounts of each of these compounds may be less than the maximum tolerated; however, when these antibiotics are combined, they can be harmful to human health [18,19].

Accordingly, since no comprehensive review study has been conducted on antibiotic residues in milk samples in Iran during the last decade, the current study aimed to investigate antibiotic residues in raw and pasteurized milk in Iran.

2. Materials and methods

2.1. Search strategies

To retrieve the published literature, we searched five English databases, including Scopus, PubMed, Science Direct, Web of Science, and Google Scholar along with two Persian databases, including SID and Magiran from Jan 2010 to May 2022. The references of the retrieved articles were also searched for related studies. The keywords used in the systematic search included "pasteurized milk" OR "raw milk" OR "milk" AND "antibiotic residues" OR "antibiotic" AND "Iran".

2.2. Selection criteria and quality assessment

Searching the databases and data extraction were performed by two independent authors (B. B. and Y. KH.). Also, two different authors (M. A. and M. R.) reviewed the titles, abstracts, and full-texts to determine the articles which met the inclusion criteria, and any discrepancies were resolved by consensus. We considered the articles published in English or Persian languages (abstract in English) indexed in PubMed, Scopus, SID, and Magiran. The criteria for identifying Iranian authors were the authors' names, study location, and affiliations.

Inclusion criteria were as follows: access to full-texts of the articles; studies examining the amount of antibiotic residue in pasteurized, raw, and sterilized milk separately; and studies with a specified sample size and contamination rate.

The exclusion criteria were as follows: lack of access to full-texts of the articles; failure to report the percentage of contamination in pasteurized milk; and failure to examine pasteurized and sterilized milk separately.

2.3. Data extraction

The following details were extracted for each of the included studies: first author's name, study period, publication date, study setting, sample size, source of isolation, and rate of antibiotic residues in raw and pasteurized milk samples.

2.4. Statistical analysis

This systematic review and meta-analysis was outlined in accordance with the strategies of the Preferred Reporting Items for Systematic Reviews and Meta-analyses (PRISMA) [20]. The total sample size and number of samples contaminated with antibiotic residues were used to calculate the statistical indices. To estimate the pooled prevalence and the corresponding 95% confidence interval (CI), the random-effects model was applied. In addition, Cochran's Q test and I^2 were used to determine the statistical heterogeneity of the studies, and the meta-regression test was applied to evaluate the possible sources of heterogeneity based on the duration of the studies. The funnel plot, Begg's rank correlation test, and Egger's weighted regression tests were used to evaluate possible publication bias. A $P < 0.05$ was considered as statistically significant for publication bias. In all the statistical analyses, $P < 0.05$ was considered as a significant difference. Sensitivity analysis was applied to determine if exclusion of any study had a significant effect on the estimated pooled prevalence while ignoring each individual study. All statistical analyses were performed using STATA 15.0 statistical software (Stata Corporation, College Station, TX, USA).

3. Results

Figure 1 depicts the selection process of the studies within the PRISMA diagram. In the systematic literature search, 1390 articles were obtained, and the relevant studies were also identified in cross-references. After eliminating the duplicated items, 1343 articles were identified as eligible for title/abstract screening, 45 of which were retrieved for full-text assessment. Finally, 40 eligible studies were selected for the systematic review and meta-analysis. The searching procedure for selection of eligible studies is demonstrated in Figure 1.

Out of 40 included studies, 31 papers investigated the prevalence of antibiotic residues in raw milk. From those studies, the pooled prevalence of antibiotic residues was 26% (95% CI: 20–33%) ranging from 5 to 93% (Figure 2, Table 1). Moreover, there was a significant heterogeneity among these studies ($\chi2$ = 1087.12; P = 0.00; I^2 = 97.33%). The funnel plot for publication bias showed evidence of asymmetry (Figure 3). Additionally, Begg's and Egger's tests were performed to quantitatively evaluate publication bias. According to the results of Begg's test (z = 7.95, P = 0.00) and Egger's test (P = 0.008), a significant publication bias was observed. Raw milk was contaminated with antibiotic groups, such as beta-lactam (penicillin), tetracycline (tetracycline, oxytetracycline, and chlortetracycline), sulfonamides, quinolones (enrofloxacin), aminoglycosides (gentamicin,), macrolides (tylosin), flomocaine, and amphenicol (chloramphenicol) (Table 1).

In 18 studies, the prevalence of antibiotic residues had been investigated in pasteurized milk. The pooled prevalence of antibiotic residues was estimated at 21% (95% CI: 15–27%) ranging from 1 to 63% (Figure 4, Table 2). There was a significant heterogeneity among the 18 studies ($\chi2$ = 471.51; P = 0.00; I^2 = 96.39%). The funnel plot for publication bias showed evidence of asymmetry (Figure 5). Additionally, Begg's and Egger's tests were performed to quantitatively evaluate the publication bias. According to the results of Begg's test (z = 6.79, P = 0.00) and Egger's test (P = 0.014), a significant publication bias was observed. Pasteurized milk was contaminated with antibiotics, including beta-lactam (penicillin), tetracycline (tetracycline, oxytetracycline, chlortetracycline, and doxycycline), aminoglycosides (neomycin), sulfonamides, flomocaine, quinolones (enrofloxacin), macrolides, and florfenicol (Table 2).

The results of sensitivity analysis showed that none of the studies had the ability to substantially change the overall prevalence (Figures 6 and 7).

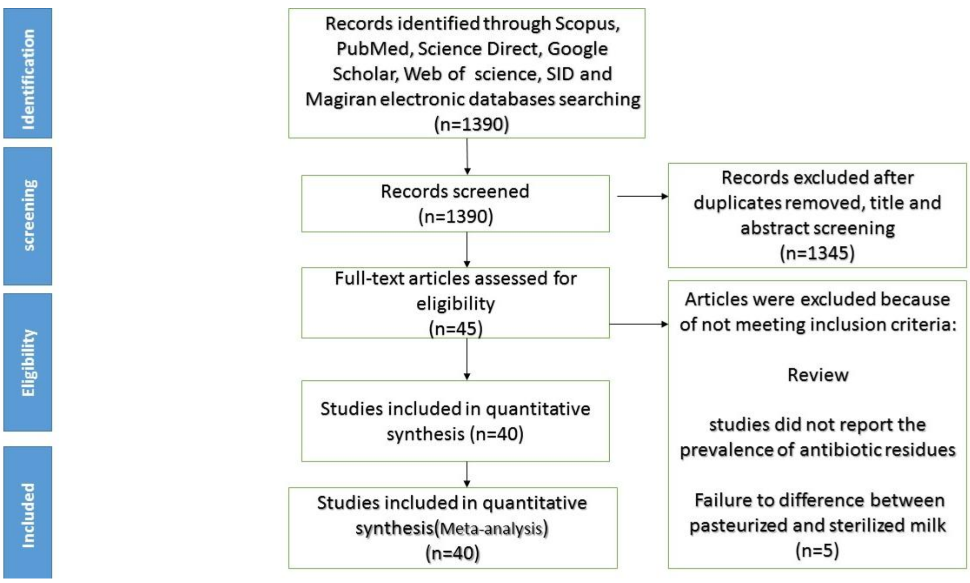

Figure 1. Flow diagram of search process.

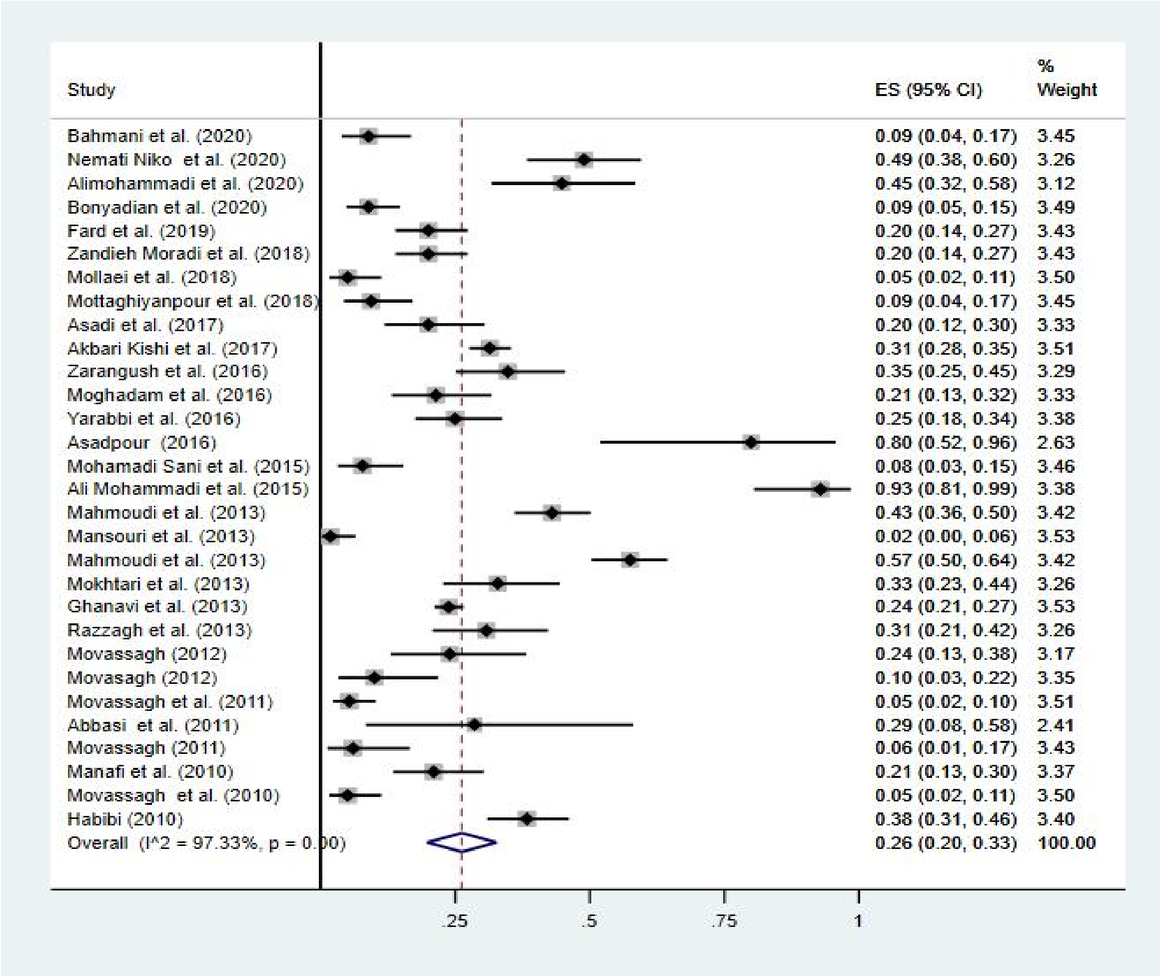

Figure 2. Forest plot presenting effect size (ES) and 95% CI for the prevalence of antibiotic residues in raw milk samples.

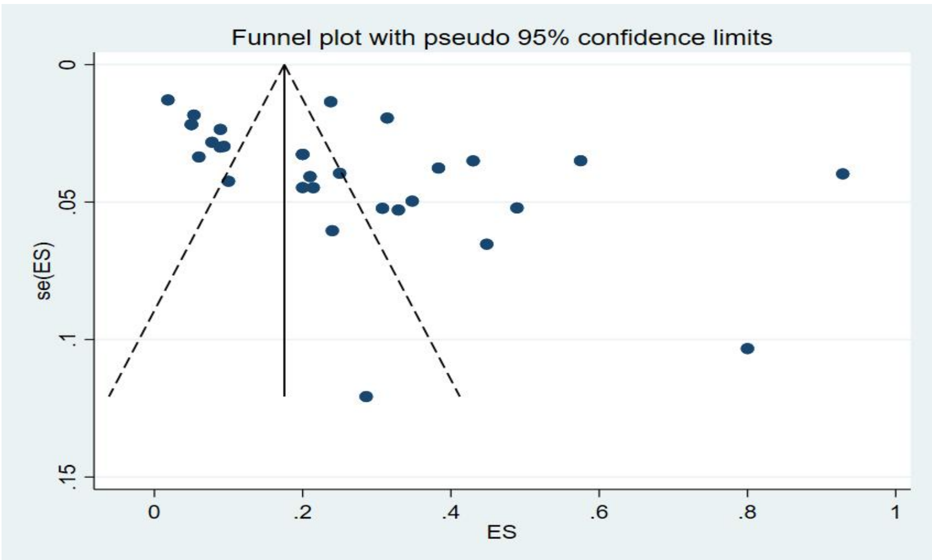

Figure 3. Funnel plot of publication bias based on publication year.

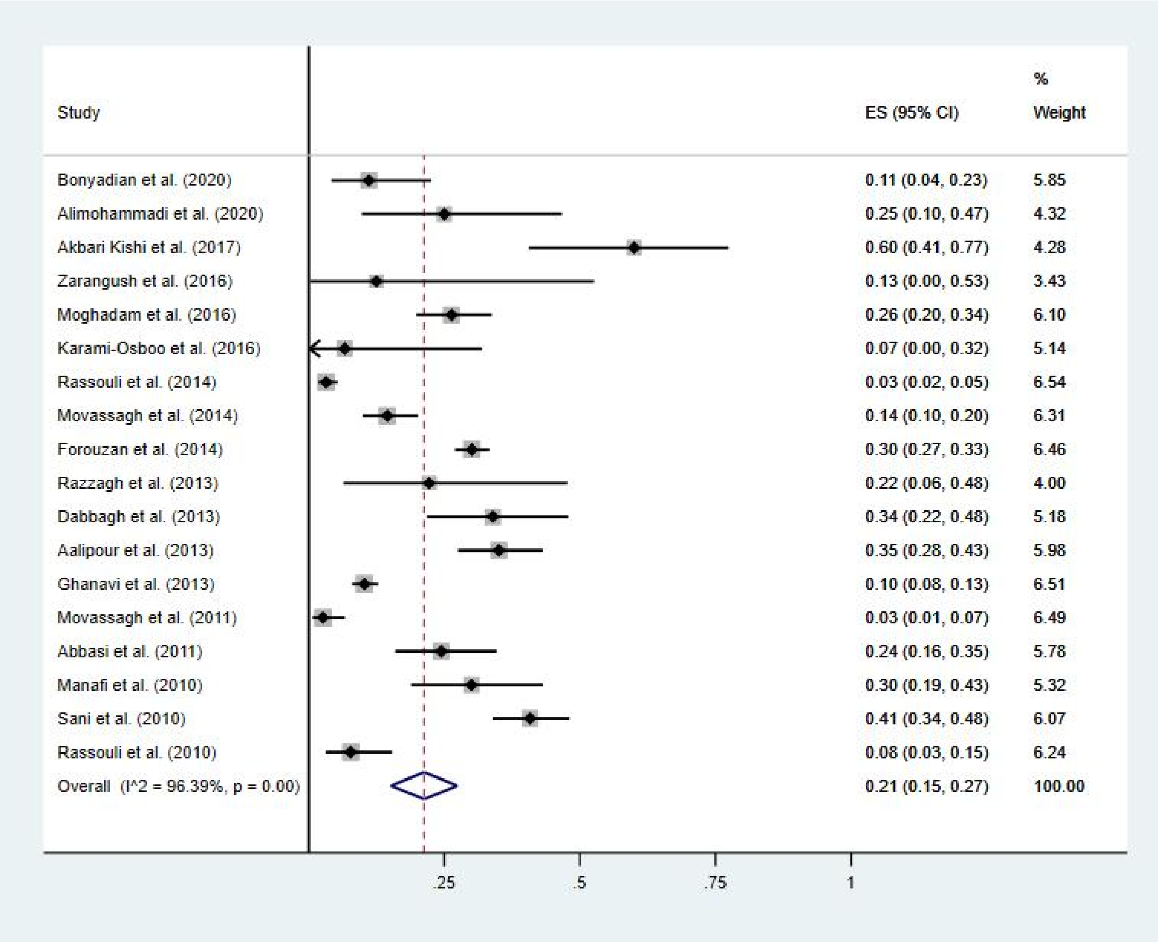

Figure 4. Forest plot presenting effect size (ES) and 95% CI for overall prevalence of antibiotic residues in pasteurized milk samples.

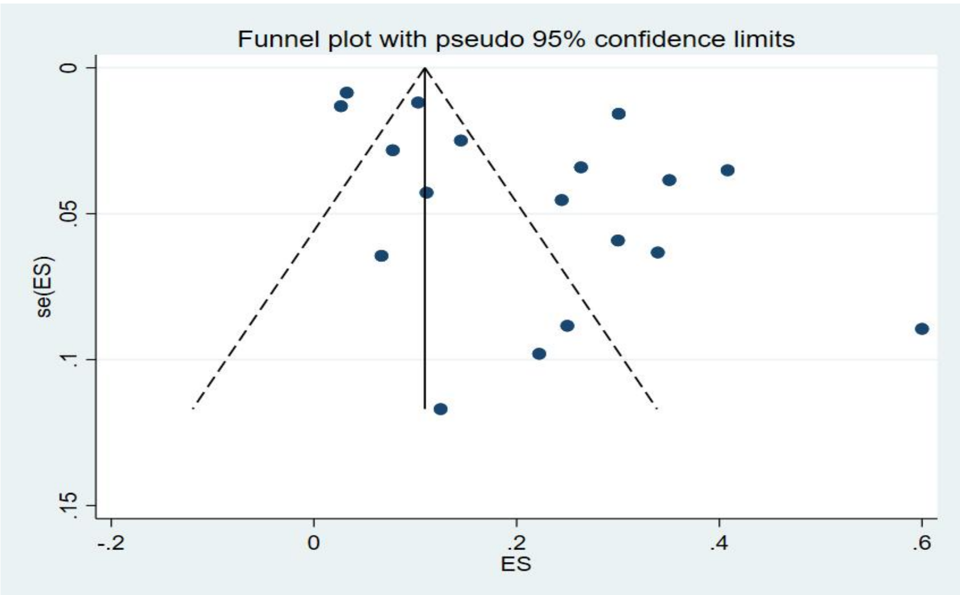

Figure 5. Funnel plot of publication bias based on publication year.

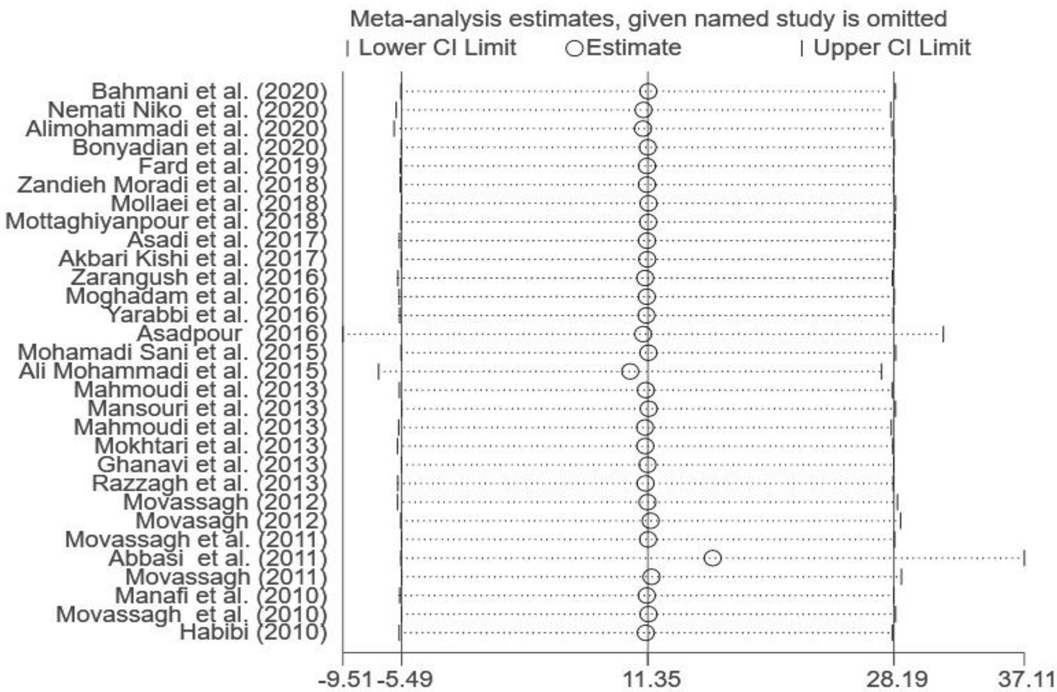

Figure 6. Sensitivity plot of studies included in the systematic review and meta-analysis related to raw milk.

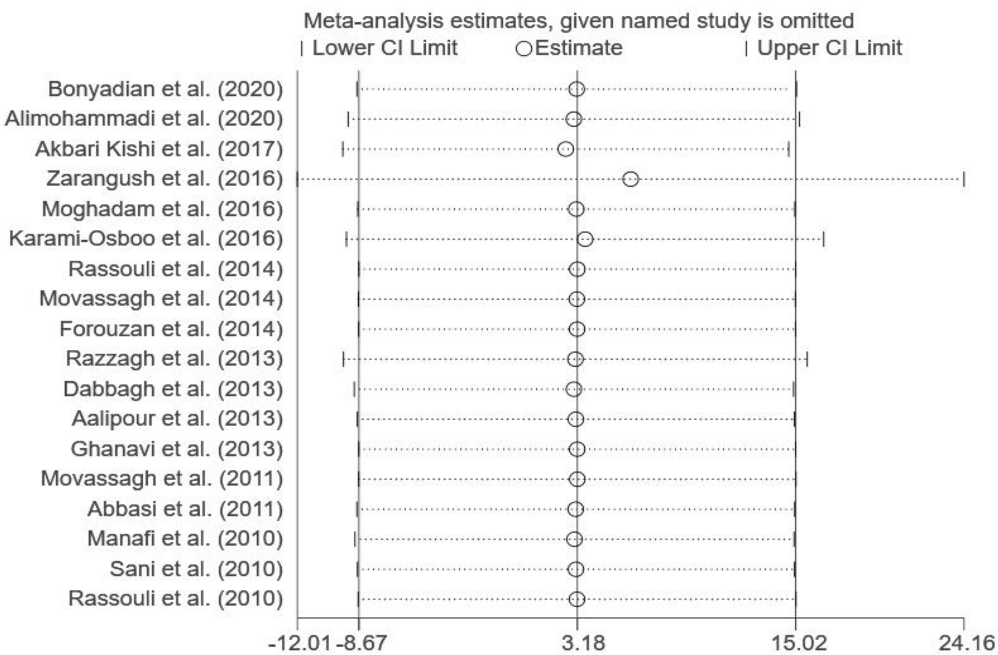

Figure 7. Sensitivity plot of studies included in the systematic review and meta-analysis related to pasteurized milk.

Table 1. Detection of antibiotic residues in raw milk.

Year	City/Province	Sample size	Type of antibiotic	Total Contamination rate (%)	Maximum residue limit (ISIRI*)	Ref.
2020	Kermanshah	90	Tetracycline	8.88	Penicillin G: 4 µg/kg	[66]
2020	Qazvin	92	Gentamicin, Tylosin, Chloramphenicol, Sulfonamides Tetracycline, Penicillin	48.91	Tetracycline: 100 µg/kg Other antibiotics: Negative	[67]
2020	Neyshabur	58	Flomocaine, Tetracycline, Sulfonamide, and Enrofloxacin groups	44.82		[68]
2020	Chaharmahal and Bakhtiari	146	Penicillin, Tetracycline	8.9		[69]
2019	Bojnurd, North Khorasan	40	0	0		[70]
2019	Borujerd	150	Not reported	20		[71]
2018	Borujerd	150	Not reported	20		[72]
2018	Sepidan and Beyza,	100	Not reported	5		[73]
2018	Zanjan	96	β-lactams, Tetracycline	9.37		[4]
2017	Esfahan	80	Sulfonamides	20		[74]
2017	Gilan	570	Not reported	31.4		[75]
2016	Maragheh and Bonab	92	Penicillin, Macrolides, Enrofloxacin.	34.78		[76]
2016	Gonabad city	84	Not reported	21.42		[23]
2016	Khorasan Razavi	120	Not reported	25		[77]
2016	Gilan	15	Oxytetracycline, Tetracycline	80		[78]
2015	Mashhad	90	Not reported	8		[79]
2015	Mashhad	42	Sulfanamides Tetracycline	93		[80]
2013	Qazvin	200	Enrofloxacin, Gentamicin, Tylosin Tetracycline, Chloramphenicol, Sulfonamides	43		[81]
2013	Kerman	109	Not reported	1.83		[82]
2013	Tabriz	200	Not reported	57.50		[5]
2013	Kazeron, Tabriz, Shiraz, and Sari	79	β-lactams, Tetracycline	32.9		[83]

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Year	City/Province	Sample size	Type of antibiotic	Total Contamination rate (%)	Maximum residue limit (ISIRI*)	Ref.
2013	Zanjan, Tehran, kerman, gilan, mashhad, gorgan	992	β-lactams, Penicillin	23.8	Penicillin G: 4 μg/kg Tetracycline: 100 μg/kg	[84]
2013	Ilam	78	Not reported	30.76	Other antibiotics:	[85]
2012	Bostanabad, East Azerbaijan	50	Not reported	24	Negative	[86]
2012	Eilikhchi (Southwest of Tabriz)	50	Not reported	10		[87]
2011	Tabriz	150	β-lactams	5.33		[88]
2011	Ardabil	14	Oxytetracycline, Tetracycline, Chlortetracycline	28.6		[89]
2011	Ardabil	50	Not reported	6		[90]
2010	East Azerbaijan	100	Not reported	21		[91]
2010	East Azerbaijan	100	Not reported	5		[92]
2010	Sanandaj	167	Not reported	38.32		[93]

Note: *Institute of Standards and Industrial Research of Iran.

Table 2. Detection of antibiotic residues in pasteurized milk.

Year	City/ Province	Sample size	Type of antibiotic	Total Contamination rate (%)	Maximum residue limit (ISIRI*)	Ref.
2020	Chaharmahal and Bakhtiari	54	Penicillin Tetracycline	11	Benzylpenicillin: 4μg/kg	[69]
2020	Neyshabur, Khorasan-e Razavi	24	Flomocaine, Tetracycline, Sulfonamide, and Enrofloxacin groups	25	Chlortetracycline 100 μg/kg Other antibiotics: Negative	[68]
2017	Gilan	30	Not reported	60		[75]
2016	Maragheh and Bonab	8	Penicillin Macrolides Enrofloxacin.	12.5		[76]
2016	Gonabad	167	Not reported	26.34		[23]
2016	Shiraz	15	Florfenicol	6.66		[94]
2014	Tehran	432	Oxytetracycline and Tetracycline	3.24		[95]

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Year	City/ Province	Sample size	Type of antibiotic	Total Contamination rate (%)	Maximum residue limit (ISIRI*)	Ref.
2014	East Azerbaijan	200	Neomycin	14.5	Benzylpenicillin:	[96]
2014	Urmia	848	Not reported	30.14	4μg/kg	[10]
2013	Ilam	18	Not reported	22.22	Chlortetracycline	[85]
2013	Tehran	56	Tetracycline Chlortetracycline Oxytetracycline Doxycycline	33.93	100 μg/kg Other antibiotics: Negative	[97]
2013	Chaharmahal and Bakhtiari	154	Not reported	35.06		[98]
2013	Zanjan, Tehran, kerman, gilan, mashhad, gorgan	652	β-lactams Penicillin G	10.2		[84]
2011	Tabriz	150	β-lactams	2.66		[99]
2011	Ardabil	90	Oxytetracycline, Tetracycline, Chlortetracycline	24.4		[89]
2010	East Azerbaijan	60	Not reported	30		[91]
2010	Khorasan	196	Not reported	40.8		[9]
2010	Tehran	90	Oxytetracycline and Tetracycline	7.77		[100]

Note: *Institute of Standards and Industrial Research of Iran.

4. Discussion

In our study, the outbreak of antibiotic residue in raw and pasteurized milk was 26% and 21%, respectively. The prevalence of antibiotic residues in raw milk in Algeria has been estimated to be 20.51%, which was lower compared to our study [21]. The researchers examined the antibiotic residues in 74 pasteurized milk samples in Kibera, Nairobi, and found that 6.8% of the samples were contaminated with beta-lactam and tetracycline antibiotics, which was lower than our study [22]. This indicates the overuse of antibiotics in animal husbandry in Iran. The high rates in our study show that control measures for raw and pasteurized milk in Iran is not efficient. Almost 12 million kg of antibiotics are used annually worldwide in the livestock industry, of which only almost 9 million kg are used to treat infectious diseases, and the rest are used to prevent diseases or increase the growth of livestock [23]. In 2011, out of 806 tons of antibiotics produced in Iran, 66.4% were used in the livestock industry [23]. The researchers reported that the use of antibiotics in the livestock and poultry in Iran was higher than the rates in developed countries, and tetracycline had the highest consumption rate [24].

Although maximum residue limit (MRL) levels for foods of animal origin help protect the consumers' rights, there is no guarantee that animal products are not over-marketed and eventually consumed by the people. Even if it does not exceed the MRL of antibiotics in foodstuff of animal origin, it can lead to complications and problems in people in the long term [11]. Contamination rate of milk with antibiotic residues varies in different countries, depending on the legislation and effectiveness of the methods [25]. The factors that can cause the presence of antibiotics in milk are as follows: inadequate use of antibiotics in the treatment of infectious diseases such as mastitis [16]; use of antibiotics to prevent diseases and management post-surgical responsible for the presence of antibiotics in milk [26]; use of antibiotics for animal growth and development [27]; normal metabolic process of antibiotics is hampered in illnesses animals, which can cause antibiotics to remain stored for a longer period of time and higher amount in tissues, ultimately impose a higher risk of residues [28]; lack of knowledge of ranchers regarding the impact of antibiotic residual in milk on human health [28]; inappropriate training of ranchers [28]; improper disposal of antibiotic containers that animals can lick [29]; incorrect withdrawal, i.e., lack of attention to withdrawal time of antibiotics in milking the livestock, which causes antibiotics to appear in milk with higher concentrations [16,30]; deliberate addition of antibiotics to milk to delay spoilage in milk [4]; and failure to identify treated cows and send the milk to the factory [29].

4.1. Effects of antibiotic residues in milk on health

The effects that antibiotic residues can have on humans include carcinogenicity (sulfamazone and oxytetracycline), mutagenicity, nephropathy (gentamicin), hepatotoxicity, reproductive disorders, bone toxicity (chloramphenicol), and allergy (penicillin). These residual risks of antibiotics in foods are direct (short-term) and indirect (long-term). The risks that directly affect human health include excretion of the drug in milk. For example, if beta-lactam is present in milk, regardless of its low concentration, it can cause an allergic reaction in a sensitive individual. Also, the long-term effects of beta-lactams occurring in low levels of antibiotics include carcinogenicity, teratogenicity, reproductive effects, drug resistance of treated animals, and disruption of the normal human flora in the gut [11,31–33]. Chronic effects of long-term exposure to low levels of oxytetracycline include leucocytosis, atypical lymphocytes, lung congestion, toxic granulation of granulocytes and thrombocytopenia purpura, and brown discoloration of the teeth [31]. Furthermore, the residual complications of tetracycline include reduced fetal growth, gastrointestinal disorders, pro-inflammatory, cytotoxic, rash, phototoxic dermatitis, allergy, and immune-pathological effects on the human health [32]. Residues of sulfonamides in foodstuff can cause allergies, drug resistance, cancer, injury to the urinary system, prevention of leukocyte production, lack of treatment efficacy in humans, and negative effects on the hypothalamic-pituitary- thyroid interactions [4,16,34–38]. Other harmful effects of antibiotics on the human diet include disruption of the normal human flora in the gut. Many of these bacteria are beneficial in the gut that help maintain a healthy gastrointestinal tract and act as a barrier to prevent pathogenic bacteria and disease. Antibiotics may decrease the total number of these beneficial bacteria in the gut or kill some of them [39]. Many studies have claimed that exposure to antibiotics early in life, from foodstuff and vertical transmission from mother to child, can increase obesity in children [40–43].

4.2. Effects of the presence of antibiotic residues in milk for the dairy industry

Contamination of food with chemical residues, including antibiotics in milk and meat products has become a public health topic. These chemical residues are resistant to pasteurization operations (72 ℃ for milk). Therefore, these technologies have no effects on the elimination of these drugs [44–46]. The researchers showed that 30% and 17.5% of powdered milk in Iran contain antibiotics beta-lactam and tetracycline, respectively [47]. This study justifies the inefficiency of thermal processes in eliminating antibiotics, which is a serious risk in children constantly being fed by milk powder. Our study also showed that the pasteurization temperature is not sufficient to inactivate antibiotics. The researchers showed that only 1% of beta-lactam antibiotics were degraded in milk at 72 ℃ for 15 minutes, but at 120 ℃ for 20 minutes, beta-lactam antibiotics, including cefoperazone and cefuroxime, were degraded [48]. Due to the heat in pasteurization process, the watery portion of milk is evaporated so that the milk becomes, and thereby the antibiotic residue, becomes concentrated in the boiled milk [45]. Therefore, antibiotic residues or their metabolites and/or their compounds are more concentrated in boiled milk than in raw milk, which can be a risk to dairy products and people's health. Antibiotics in milk can affect the food industry because the bacteria used in the fermentation process are sensitive to antibiotics, leading to the loss of organoleptic properties of the final products and the failure of coagulation or ripening of dairy products. Studies have shown that beta-lactam antibiotic residues near or under MRL level can delay coagulation in sheep's milk yogurt for more than 40 minutes [49–51]. A study on the antimicrobial susceptibility of starter culture bacteria used in dairy products showed that antibiotics at concentrations under MRL decrease the activity of microorganisms, such as lactobacilli and streptococci [52]. This low activity of the initial culture medium in the presence of antibiotics makes the cheese a more favorable environment for the growth of undesirable bacteria such as coliforms and reduces the microbiological safety of the cheese. Therefore, antibiotic residues in raw milk should be controlled, because it can disrupt dairy production and cause the growth of some pathogens such as *Salmonella* and *Staphylococcus aureus* in milk [53]. Lipolytic bacteria in cheese are affected by the antibiotic beta-lactam, which can affect the flavor and texture [54–56]. These starter cultures manufacture part of the enzymes that are responsible for the ripening of the cheese involved [57]. Beta-lactam antibiotic residues can delay the pH of pressed cheeses for 5-300 minutes [58]. According to the World Health Organization (WHO), fat-soluble antibiotics can reach much higher levels of milk fat and cheese than the primary milk content, so it may pose a hazard to consumers [59]. Depending on their physicochemical attributes and ability to interact with the fat and protein components, antibiotics can be present in milk curd to a greater or lesser extent [60,61].

4.3. Control and preventive measures to avoid antibiotic residues in milk

There are some measures to avoid antibiotic residues in milk as follows:

1. Timely use of animal vaccinations and planning to adopt strict health standards and animal husbandry skills can reduce need for antibiotics [39];
2. The timing of antibiotic withdrawal for dairy animals should be considered [26];
3. Hygienic principles should be observed in the livestock to reduce infection [28];
4. Cows treated with antibiotics should be identified and the date and time of treatment, the name and dose of the drugs used, and the time of withdrawal should be noted [28];

5. A comprehensive and trustworthy program for the use and distribution of antibiotics should be implemented [4];
6. Using herbal antimicrobial substances, organic acids, amino acids, enzymes, and probiotics instead of chemical antibiotics can be a promising choice. Other substances that can be used as an alternative to antibiotics in livestock farms due to their antimicrobial properties include organic acids such as acetic acid, formic acid, butyric acid, and propionic acid. The use of probiotics in livestock has had antimicrobial activity and a positive effect on the growth and quality of meat; therefore, it can be substituted for antibiotics for the growth of livestock [32, 39, 62, 63];
7. The use of phytogenic food additives (such as black seed, cinnamon, and their extracts) instead of antibiotics to reduce stress, improve the immune system, and ultimately increase the growth rate of animals are known to be effective [32];
8. Dairy producers must be qualified to maintain and ensure the proper quality of milk [28];
9. Strict international rules on the use of antibiotics are needed to prevent the overuse of antibiotics [39];
10. Implementation of the HACCP system in dairy farms may decrease the use of veterinary drugs [64];
11. Implementation of HACCP in the dairy industry is very helpful [65];
12. The use of antibiotics to enhance the growth of animals should be stopped [39];
13. Prohibiting the use of antibiotics without a veterinarian's prescription can be effective [39]; and
14. Educational programs for the proper use of veterinary drugs, especially antibiotics for dairy farmers should be hold [4].

5. Conclusions

In our study, the prevalence of antibiotic residues in raw and pasteurized milk was 26% and 21%, respectively. According to our results, the control measures are inefficient in dairy industry and milk collection centers for the presence of antibiotic residues and the time of antibiotic withdrawal during milk delivery. Permanent control of milk in the collection centers by the responsible organizations along with implementation of HACCP system in milk factories can be effective in reducing antibiotic residues.

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Conflicts of interest

The authors declare that there is no conflict of interest.

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