Prevalence of Antibiotic Residues in Milk Consumed in Iran: A Systematic Review and Meta-Analysis

Hassan Jolaei[1], PhD; Mostafa Abdollahi[1], DVM; Maryam Safarirad[2], PhD candidate; Enayat Berizi[2], PhD; Mohammad Hashem Yousefi[3], PhD candidate; Seyyed Mohammad Ali Noori[4], PhD

[1]Health Policy Research Center, Institute of Health, Shiraz University of Medical Sciences, Shiraz, Iran
[2]Department of Food Hygiene and Quality Control, Faculty of Nutrition and Food Sciences, Shiraz University of Medical Sciences, Shiraz, Iran
[3]Department of Food Hygiene and Public Health, School of Veterinary Medicine, Shiraz University, Shiraz, Iran
[4]Department of Nutrition, School of Allied Medical Sciences, Ahvaz Jundishapur University of Medical Sciences, Ahvaz, Iran

Correspondence:
Mostafa Abdollahi, PhD;
Health Policy Research Center, Institute of Health, Shiraz University of Medical Sciences, Shiraz, Iran
Tel: +98 9177312420
Email: abdollahi.m227@gmail.com
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Abstract

Background: Improper use of antibiotics and not paying attention to withdrawal time causes antibiotics to enter the milk, which can cause allergies in humans and cause antibiotic-resistant pathogenic bacteria in the long run, so quality and hygienic milk control is essential.

Methods: This study aimed to investigate the prevalence of antibiotic residues in milk as a systematic review and meta-analysis from 2004 to 2021 for 15 years in Iran. The data were collected from four international search databases, including PubMed, Scopus, Science Direct, and Google Scholar, and four Iranian databases, including SID, MagIran, Civilica, and IranDoc.

Results: After reviews of 314 studies, 38 were finally selected, and the information was recorded and analyzed in Stata software. The results of this study show that the residual prevalence of antibiotics in milk using the screening method was 28% (CI: 0.34-0.22). The residual rates of antibiotics using enzyme-linked immunosorbent assay (ELISA) and high-pressure liquid chromatography (HPLC) methods were 43% (CI: 0.26-0.59) and 27% (CI: 0.05-0.49), respectively.

Conclusion: The data obtained from the meta-analysis show that despite various reports of a quantitative amount of antibiotic residue in milk, the average amount in the ELISA method was 16.98 ppm. Although the prevalence of antibiotics in Iran is relatively high, a quantitative amount is optimal. Also, since the use of antibiotics in livestock is almost inevitable, proper withdrawal time of antibiotics can play an important role in preventing the release of antibiotic residues in milk.

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Keywords: Anti-bacterial agents, Iran, Meta-analysis, Milk, Prevalence

Introduction

Iranian milk production reaches about 7 million tons, and per capita milk consumption has reached 82 kg in recent years.[1] Due to the consumption of milk in the daily diet of humans as one of the main food groups, the health and hygiene of this product are of particular importance.[2] Milk is exposed to many chemical contaminants. These substances enter milk through the treatment of cattle, feed, milking environment, and production process in the factory, so it is necessary to minimize the risk of contamination through careful control. Chemical contaminants in milk include antibiotics, hormones, disinfectants, nitrites, nitrates and nitrosamines, insecticides, fungal toxins, toxic metals, and dioxins.[3] The use of antibiotics to control and treat infectious diseases and stimulate growth in livestock is common, and mastitis is the most common use of antibiotics in livestock.[4, 5] Excessive use of antibiotics and not paying attention to withdrawal time in livestock causes antibiotics to enter the milk, which can cause allergies in humans and, in the long run, cause antibiotic-resistant pathogenic bacteria, which has become a major concern today. Therefore, antibiotic residue monitoring in milk seems necessary.[4] Proper use of antibiotics and observance of withdrawal time before milking or slaughtering livestock will prevent the presence of these compounds in milk or meat consumed by humans. This time varies for different drugs and among different animal species, lasting from a few hours to several days and sometimes weeks.[1] Some people, especially children whose diet is milk, are more sensitive to antibiotics. In addition, antibiotics in milk kill the beneficial bacteria used in the production of cheese, yogurt, and other fermented products. Therefore, the presence of antibiotics in milk causes health problems and reduces the quality and quantity of products produced, and due to the economic losses caused by it, these substances must be measured in milk.[3] To evaluate the antibiotic residue, different tests have been proposed. The choice of test method depends on the type of antibiotic, the expected time limits, the sensitivity of the method, and the cost of that method.[4] Most methods used are microbial inhibition tests (screening tests), which are time-consuming. Faster experiments such as radioimmunoassay are now being performed, which make it possible to decide to accept milk in a short time (10-30 minutes). Other methods include quantitative methods such as enzyme-linked immunosorbent assay (ELISA), in which we use antibodies and antibiotics embedded in the wells to determine the presence or absence of the drug. In this method, a unique kit should be used for each antibiotic.[4] Another method is high-pressure liquid chromatography (HPLC), which uses specific chromatographic columns to identify and measure the number of antibiotics.[4] Drug resistance of microorganisms to antibiotics has existed in many parts of the world, and this problem is increasing. Accordingly, it is estimated that we are at the gates of an uncertain future like the era before the discovery of antibiotics. In developed countries, most consumers are aware of the residual risk of antibiotics in livestock products and their effects on their health.[6] Fines based on microbial inhibitor tests have been applied and proved successful in most countries.[3] In Iran, various studies have been performed to evaluate the amount of antibiotic residue in milk. In a study conducted in 2019 on 30 samples taken from farms in Kermanshah province, 23.3% and 8.8% of the samples obtained had tetracycline antibiotic residue, using ELISA and HPLC methods, respectively.[6] In another study conducted in 2011 on 68 milk samples taken from stores in Tabriz, 69.1% of the samples were identified as containing Tylosin residues using the ELISA method.[7] Also, in 2017, a researcher in Isfahan reported 20% antibiotic residue contamination in 80 samples using the ELISA method.[8] In 2016, another researcher reported that 6.6% of the samples taken from 15 milk samples collected from stores in Tehran by the HPLC method contained Chloramphenicol residues.[9]

Consumption of dairy products is increasing today, and ensuring consumer health is vital. Various studies have reported different results of antibiotic residues in milk in Iran. Still, there is no accurate information on the residual levels of these compounds in this product. Hence, the purpose of this study is a systematic review and meta-analysis of the antibiotic residues in milk consumed in Iran.

Methods

Analysis Method

The present study is a systematic review and analysis of the studies on antibiotic residues in milk from 2004 to 2021 in Iran.

Search Strategy

In February 2021, the researchers surveyed four international databases, including PubMed, Scopus, Science Direct, and Google Scholar, and four Iranian databases, including SID, MagIran, Civilica, and IranDoc. Selective keywords for international databases included milk, antibiotics, residues, and MRLs. Persian keywords and similar search strategies were used for internal databases. References of imported articles were also reviewed to add relevant studies. The collected data was entered into EndNote, X8 software, and duplicate articles were automatically deleted.

Screening

Two people (second and third authors) initially searched the studies. Screening of studies, extraction of results, and evaluation of quality control of articles were independently done by two people (second and third authors). If there were no agreement between the two, the team leader (corresponding author) would give the final opinion on the article.

Inclusion and Exclusion Criteria

In the present study, all original cross-sectional studies that examined the amount of antibiotic residues in milk were included. Among the studies, extracted review articles, a summary of articles presented at the congress, studies without abstract and full text, studies that were not original research, studies that were irrelevant to assessing antibiotic residues in milk, and studies that did not explicitly express data were excluded.

Quality Control

A checklist prepared by the Joanna Briggs Institute was used to review and control the quality of articles.[10] This tool contains eight questions answered by yes, no, unspecified, and unused.

Table 1: Information of included articles in systematic review and meta-analysis

Ref	Prevalence (CI*)	Method	Sample size	Year	Antibiotic	Location
2	0.3393 (0.2292-0.47)	Screening test	56	2014	Wide range of antibiotics	Tehran
2	_	HPLC	56	2014	Tetracyclines	Tehran
4	0.2 (0.1438-0.2711)	Screening test	150	2018	Wide range of antibiotics	Lorestan
6	0.255 (0.1768-0.3544)	Screening test	90	2019	Wide range of antibiotics	Kermanshah
6	0.088 (0.0457-0.1657)	HPLC	90	2019	Tetracyclines	Kermanshah
6	0.233 (0.1179-0.4092)	ELISA	30	2019	Tetracyclines	Kermanshah
7	0.691 (0.5737-0.7883)	ELISA	68	2011	Tylosin	East Azarbaijan
8	0.20 (0.127-0.3005)	ELISA	80	2017	β-lactams	Esfahan
9	0.066 (0.0119-0.2982)	HPLC	15	2016	Florfenicol	Tehran
9	0.00 (0.00-0.2039)	HPLC	15	2016	Chloramphenicol	Tehran
11	0.0533 (0.0272-0.1017)	Screening test	150	2011	Wide range of antibiotics	East Azarbaijan
12	0.347 (0.283-0.4183)	Screening test	187	2015	Wide range of antibiotics	Chaharmahal
12	0.1979 (0.1471-0.2608)	HPLC	187	2015	Tetracyclines	Chaharmahal
13	0.408 (0.3418-0.4781)	Screening test	196	2010	Wide range of antibiotics	Khorasan-e-Razavi
14	0.929 (0.8099-0.9754)	ELISA	42	2015	Tetracyclines	Khorasan-e-Razavi
14	0.929 (0.8099-0.9754)	ELISA	42	2015	β-lactams	Khorasan-e-Razavi
15	0.247 (0.1977-0.3039)	Screening test	251	2016	Wide range of antibiotics	Khorasan-e-Razavi
16	0.5244 (0.4177-0.629)	Screening test	82	2020	Wide range of antibiotics	Khorasan-e-Razavi
17	0.0324 (0.0194-0.0536)	HPLC	432	2014	Tetracyclines	Tehran
18	0.3054 (0.2775-0.3348)	Screening test	992	2013	Penicillin G	Whole Of Iran
18	0.029 (0.0204-0.0416)	Screening test	992	2013	Penicillin G	Whole Of Iran
19	0.575 (0.5057-0.6415)	Screening test	200	2013	Wide range of antibiotics	East Azarbaijan
20	0.05 (0.0215-0.1118)	Screening test	100	2018	Wide range of antibiotics	Fars
21	0.05 (0.0215-0.1118)	Screening test	100	2010	Wide range of antibiotics	East Azarbaijan
22	0.851 (0.7741-0.9048)	HPLC	114	2011	Tetracyclines	Ardabil
23	0.181 (0.1293-0.2482)	Screening test	160	2018	Wide range of antibiotics	Zanjan
24	0.2437 (0.1838-0.3158)	Screening test	160	2011	Wide range of antibiotics	East Azarbaijan
25	0.145 (0.1029-0.2005)	Screening test	200	2015	Wide range of antibiotics	East Azarbaijan
25	0.090 (0.0481-0.1623)	ELISA	100	2015	Neomycin	East Azarbaijan
25	0.130 (0.0776-0.2098)	ELISA	100	2015	Neomycin	East Azarbaijan
26	0.291 (0.2102-0.3892)	Screening test	96	2014	Wide range of antibiotics	Ilam
27	0.1 (0.0435-0.2136)	Screening test	50	2013	Wide range of antibiotics	East Azarbaijan
28	0.00 (0.00-0.0876)	Screening test	40	2019	Wide range of antibiotics	North Khorasan
29	0.225 (0.1232-0.375)	ELISA	40	2010	Tetracyclines	Tehran
30	0.118 (0.0608-0.2153)	ELISA	68	2007	Gentamicin	Khorasan-e-Razavi
31	0.083 (0.0459-0.1466)	Screening test	120	2018	Wide range of antibiotics	Esfahan
32	0.073 (0.0414-0.1265)	Screening test	150	2014	Wide range of antibiotics	Sistan and Balouchestan
33	0.3832 (0.3129-0.4588)	Screening test	167	2011	Wide range of antibiotics	Sanandaj
34	0.831 (0.7274-0.8928)	Screening test	80	2018	Tetracyclines	Fars
34	0.917 (0.8302-0.957)	Screening test	80	2018	Penicillin G	Fars
34	0.666 (0.3968-0.8922)	Screening test	10	2018	Tetracyclines	Fars
34	0.256 (0.1078-0.6032)	Screening test	10	2018	Penicillin G	Fars
35	0.455 (0.2692-0.6534)	ELISA	22	2017	Tetracyclines	Semnan
36	0.43 (0.3633-0.4993)	Screening test	200	2014	Wide range of antibiotics	Qazvin
36	0.280 (0.2224-0.3459)	ELISA	200	2014	Gentamicin	Qazvin
36	0.260 (0.2041-0.3249)	ELISA	200	2014	Tylosin	Qazvin
36	0.240 (0.1861-0.3037)	ELISA	200	2014	Enrofloxacin	Qazvin
36	0.20 (0.1505-0.2609)	ELISA	200	2014	Chloramphenicol	Qazvin
36	0.315 (0.2546-0.3823)	ELISA	200	2014	β-lactams	Qazvin
36	0.355 (0.292-0.4235)	ELISA	200	2014	Tetracyclines	Qazvin
37	0.053 (0.0331-0.0848)	Screening test	300	2017	Wide range of antibiotics	Kerman
38	0.2167 (0.1738-0.2667)	Screening test	300	2010	Wide range of antibiotics	Khorasan-e-Razavi
38	0.1167 (0.0851-0.158)	Screening test	300	2010	Wide range of antibiotics	Khorasan-e-Razavi
38	0.18 (0.1407-0.2274)	Screening test	300	2010	Wide range of antibiotics	Khorasan-e-Razavi
38	0.1167 (0.0851-0.158)	Screening test	300	2010	Wide range of antibiotics	Khorasan-e-Razavi
39	0.27 (0.1858-0.3812)	Screening test	77	2009	Wide range of antibiotics	Whole Of Iran
39	0.650 (0.5525-0.7364)	ELISA	100	2009	Chloramphenicol	Whole Of Iran
39	0.980 (0.93-0.9945)	ELISA	100	2009	Streptomycin	Whole Of Iran
39	0.820 (0.7333-0.883)	ELISA	100	2009	Tetracyclines	Whole Of Iran

40	0.314 (0.2773-0.3532)	Screening test	570	2017	Wide range of antibiotics	Gilan
40	0.6 (0.4232-0.7541)	Screening test	30	2017	Wide range of antibiotics	Gilan
41	0.4 (0.0792-1.0968)	HPLC	15	2015	Tetracyclines	Gilan
41	0.66 (0.3225-1.0968)	HPLC	15	2015	Tetracyclines	Gilan
42	0.33 (0.2456-0.4269)	Screening test	100	2014	Wide range of antibiotics	East Azarbaijan

*Confidence interval

This tool aims to assess the methodological quality of studies and identify potential sources of error in study design, implementation, and data analysis. These questions are as follows:

(1) Were the criteria for inclusion in the sample clearly defined? (2) Were the study subjects and the setting described in detail? (3) Was the exposure measured validly and reliably? (4) Were objective and standard criteria used to measure the condition? (5) Were confounding factors identified? (6) Were strategies to deal with confounding factors stated? (7) Were the outcomes measured validly and reliably? And (8) Was appropriate statistical analysis used?

Extracting the Data

Article information, including the author's name, the number of samples, type of product, the prevalence of antibiotic residue, type of antibiotic residue, measurement method, location, and year, were entered in pre-designed tables (Table 1). Data were categorized and analyzed statistically.

Risk of Bias Between Studies

The Egger test was used to investigate the risk of propagation bias.[43]

Statistical Analysis

A chi-square test with a significance level of 0.05, I2>50% was used to assess the degree of heterogeneity among the included studies. In the case of heterogeneity, the inverse variance method used the random effects model, and in the absence of heterogeneity, the fixed effects model was used. All analyses were performed using STATA statistical software version 13.

Results

Systematic Review

Search Results and Selection of Study

After searching all international and national databases, 314 articles were obtained, with the removal of 28 duplicate articles and 78 unrelated articles; 208 articles remained for abstract review. After studying the abstracts, 102 articles entered the next stage. At this stage, the full text of the articles was reviewed, and finally, 38 articles were approved and entered into the final analysis. Many studies have been excluded for various reasons, including inaccurate reporting of antibiotic residues and unrelated aspects of the subject, studies that did not fit into our timeline, and duplicate results in screening. Figure 1 shows the flowchart of the included studies.

Characteristics of Studies and Extracted Data

Table 1 presents the results of various studies on antibiotic residues in milk. The data obtained from Table 1 show that in 36 studies, the screening method, in 19 studies, the ELISA method, and in 9 studies, the HPLC method was used to evaluate the antibiotic residue in milk. Numerous studies show different percentages of antibiotic residues in milk. The highest prevalence of antibiotic residues (98%) in milk samples was reported in 2004, and the lowest residual prevalence (0%) was reported in 2016 and 2019, respectively. Most studies have been done in East Azarbaijan and Khorasan Razavi provinces (each with ten replications).

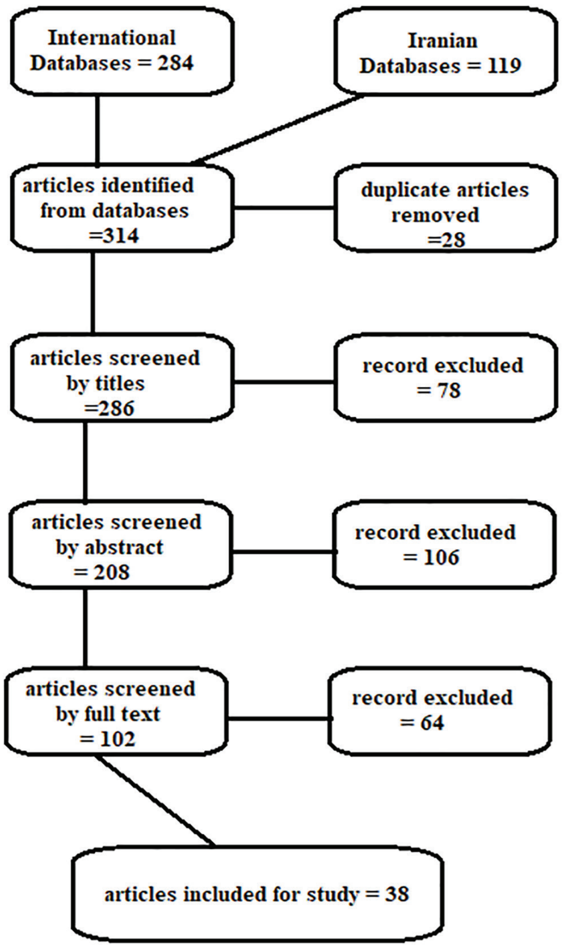

Figure 1: Flowchart of the included eligible studies in systematic review and meta-analysis (Image created by authors).

Meta-analysis Results

The meta-analysis results showed that the pooled prevalence of antibiotic residue in milk using the screening method is 28% (CI 95%: 0.22-0.34) (Figure 2). Also, the prevalence of antibiotics residue using ELISA and HPLC methods is 43% (CI 95%: 0.26-0.59) (Figure 3) and 27% (CI 95%: 0.05-0.49) (Figure 4), respectively. The data from the meta-analysis show that the mean quantitative of antibiotics residue using the ELISA method is 16.98 ppm (CI 95%: 16.17-86) (Figure 5).

Discussion

Various health problems, such as allergic reactions, the possibility of cancer or mutations, the development of antibiotic-resistant microorganisms, and reduced sensitivity to antibiotic treatment, have raised concerns about drug residues in food.[2] This study is the first systematic and meta-analysis study in this field that states the percentage of antibiotic residues in milk from 2004 to 2021 for 16 years in Iran. This study showed that the percentage of antibiotic residue prevalence was measured by screening methods (inhibitory tests, rapid kits), ELISA, and HPLC. In some studies, a combination of different methods was used. These studies have also measured and reported the amount of antibiotic residue in milk samples taken from farms, milk collection centers, dairy industries, and sales centers. The results of the present study showed that the prevalence of antibiotic residues in milk in Iran using screening methods ELISA and HPLC were 28, 43, and 27%, respectively, and the mean antibiotic residue using the ELISA method was 16.98 ppm. Different results have been obtained in different tests due to differences in the sensitivity of each test and the type of test (quantitative or qualitative). Various studies worldwide also show that antibiotic residues' prevalence varies in different ways. The study's results obtained through three methods show a high percentage of antibiotic residue prevalence in milk in Iran. This could be due to the indiscriminate, arbitrary, and unregulated use of antibiotics in livestock farms and the lack of concern for hygiene and veterinary advice in this field. Mastitis prevalence in cows is high due to the type of cattle breeding system in Iran (which is mainly

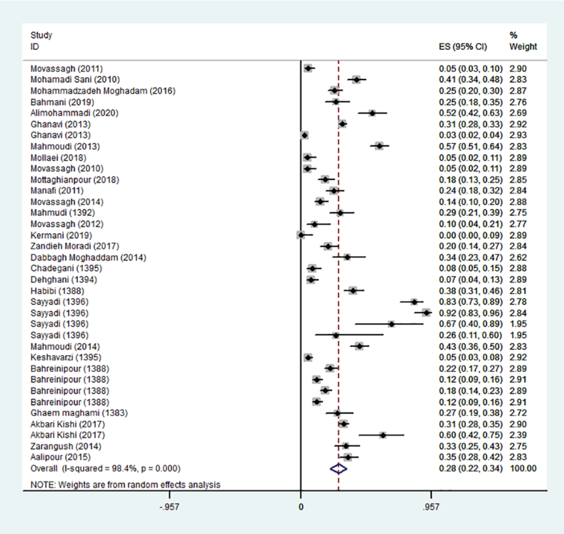

Figure 2: Prevalence of antibiotics residue in milk using screening method (Image created by authors).

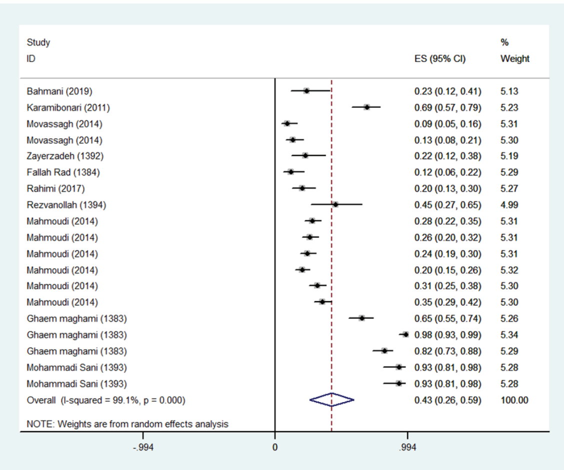

Figure 3: Prevalence of antibiotics residue in milk using ELISA method (Image created by authors).

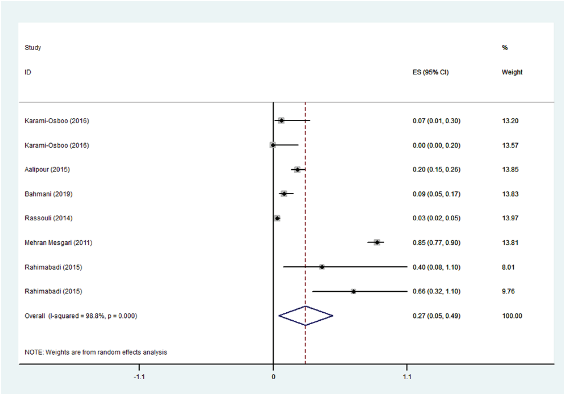

Figure 4: Prevalence of antibiotics residue in milk using HPLC method (Image created by authors).

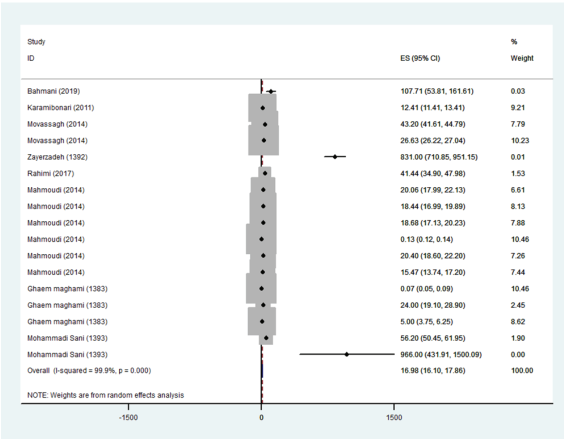

Figure 5: Mean quantitative of antibiotics residue using ELISA method (Image created by authors).

open), the high rate of traditional farms, and the lack of proper observance of health recommendations in farms. The incidence of mastitis has increased, leading to the widespread use of antibiotics. These reasons have led to high levels of antibiotic residues in milk.[44, 45] different rates of antibiotic residues in milk have been reported in different countries. In Sudan, among the 72 raw milk samples obtained from livestock, 38.8% tested positive for antibiotic residues.[44] and in Pakistan, among the 137 raw milk samples, 36.5% tested positive for beta-lactam antibiotics.[45] Also, in a previous study, the amount of antibiotics was investigated in 854 raw milk and 110 pasteurized milk samples by rapid microbial screening. The results showed that approximately 16% of the milk samples were contaminated.[46]

Another study in 1973 reported that more than 5% of raw and 2.5% of pasteurized milk samples were contaminated with antibiotics. In another study, among the 1,000 raw milk samples, more than 53% of them were contaminated with antibiotics. In 1993, researchers announced that out of 606 milk samples collected from livestock farms around Tehran, 27% and 4% of cases were contaminated with penicillin and sulfonamides. A study in 1997 investigated 620 samples of raw milk received from the pasteurized milk factory in Tehran and reported 36.4% antibiotic contamination. In another study conducted on 576 raw milk samples between May and February 1993, the overall contamination rate with antibiotics was reported to be 32.5%.[2] According to the findings of the current study, while various prevalence rates of antibiotic residues have been reported in different studies, most studies that have quantified these residues have found levels to be below the maximum allowable limits (MRL) (the range of acceptable MRL: 0.15-1500 ppb). For example, among the 14 ELISA studies identifying quantitative antibiotic residues, only 3 reported antibiotic residues above the MRL. Therefore, according to the results of this study, it seems that there is no antibiotic residue in milk in Iran at a worrying level. However, management and monitoring programs should be planned to decrease the prevalence of antibiotic residues. Meanwhile, the Iran Veterinary Organization's role is vital and undeniable.

One of the limitations of this study is that not all included studies used the same types of products; for example, some studies included raw and pasteurized milk. In most of these studies, the quantitative measurement of antibiotic residues in milk was not reported. Only in studies that utilized the ELISA method was the quantitative amount of antibiotic residue evaluated. Furthermore, in most of these studies, there was no comparison of the antibiotic residue levels to the Maximum Residue Limits (MRL), and specific information on this matter was lacking.

Conclusion

The results indicate that the prevalence of antibiotic residues in milk produced and consumed in Iran is between 27% and 43% based on different methods, which, at first glance, can be worrying. However, in studies that measured the quantitative amount of antibiotic residue in milk, the average of this parameter was not more than 16.98 ppm. Only in 3 cases determined by the ELISA method was the amount of antibiotic residue higher than the MRL. Therefore, it can be concluded that the quantitative amount of unauthorized antibiotic residues in Iran is not a concern. Also, since the use of antibiotics in livestock is almost inevitable, proper withdrawal time of antibiotics can play an important role in preventing the release of antibiotic residues in milk. The use of licensed veterinary drugs under the supervision of a veterinarian and the avoidance of arbitrary use of antibiotics in cattle can be used as control agents to prevent the release of antibiotic residues into milk. Educating farmers in this field to raise their awareness and train them on the side effects and risks of the overuse of drugs and antibiotic residues in livestock products can play a very important role in improving the current trend.

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Conflict of Interest: None declared.

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