

## REVIEW ARTICLE

# Antibiotic residues in milk: Past, present, and future

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### ABSTRACT

Now-a-days, various types of antibiotics are being used worldwide in veterinary sector indiscriminately for promotion of growth and treatment of the livestock. Significant portions of antibiotics are released through milk of dairy animals unaltered and exert serious harmful effects on human health. This review evaluates and compare researches on antibiotic residues in milk in published literatures from Pubmed, CrossRef, CAB direct, DOAJ, JournalTOCs, AGRICOLA, ScientificGate, Electronic Journals Library, CAB abstracts, Global Health Databases, Global Impact Factor, Google Scholar, Park Directory of Open Access Journals, BanglaJOL and ISC E-Journals. Antibiotics residue in milk was first detected in 60s and then with an increasing trend with highest after 2,000 (188). The highest no. of works, 49 (21.87%) were accomplished in China, followed by Spain, 30 (13.39%); Germany, 11 (4.91%); and USA, 10 (4.46%). Continent-wise highest researches are published from Europe, 105 (46.88%), followed by Asia, 77 (34.38%); South America, 18 (8.04%); North America, 16 (7.14%); and Africa, 8 (3.57%). For detection, Bovine milk sample is mostly used, 193 (86.16%), followed by ovine, 19 (8.48%); and caprine, 14 (6.25%). Acetonitrile was used in maximum cases (77) for processing the samples. Chromatographic technique was the highest, 115 (51.34%) for detection. Residue of  $\beta$ -lactam group have been detected mostly 133 (36.54%), followed by tetracyclines, 51 (14.01%); fluoroquinolones, 49 (13.46%); sulfonamides, 46 (12.64%); and aminoglycosides, 38 (10.44%). This review observe that antibiotics residues are more common in milk samples that are being manifested in increasing researches on antibiotic detection and measures should adopt to cease this residue.

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withdrawal time.



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## Introduction

Every year,  $63,151 \pm 1,560$  tons of antibiotics are being used in livestock worldwide [1] In animal husbandries, antibiotics are applied for both therapeutic and prophylactic purposes [2] Due to some positive impacts, multiple veterinary antibiotics (VAs) have been used worldwide recently for promoting growth and treatment of the livestock [3] The global usage of antimicrobials in animals is double compared to humans [4] Many studies have shown that significant portions (30%–70%) of antibiotics are released unaltered, i.e., with potential antimicrobial activity, into the environment [2] Upon release into the environment, most antibiotics are persistent and biologically active [5] Milk is a highly consumed food item in the world which has also a great value for human health [6] Residues of antibiotics are mainly found in milk due to

their injudicious usage in treating infectious diseases of animals [7] Moreover, some antibiotics are being used as feed additives indiscriminately which is another source of antibiotic residues in milk, ultimately responsible for potential public health importance [8].

### Residue

European Union (EU) defines residues as “pharmacologically active substances (whether active principles, recipients, or degradation products) and their metabolites which remain in foodstuffs obtained from animals to which the veterinary medicinal products in question has been administered [9].” After being administered to an animal body, most of the drugs are metabolized for the purpose of detoxification and excretion. In general, most of the parent product and its metabolites are excreted in urine and a

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lesser extent via feces. However, after excretion, portion of the drugs may persist in milk, eggs, and meat for a certain period of time as residues.

### **Antibiotic residue (AR)**

The administered parent antibiotics or their metabolites become deposited in animal tissues and matrix intended to be used for human consumption, where the concentration is beyond the permitted level for a certain period of time, known as antibiotics residues [10].

Among the vital causes of presence of antibiotic residues in milk, dry cow therapy and usage in mastitis treatment are of great importance [11]. The developing countries are in greater risk due to residues in milk than the developed ones. Poor detection facilities as well as lack of proper monitoring system of residues in foods considering the maximum residue limits (MRLs) might be taken as vital causes for higher risk of milk derived antibiotic residues [12].

### **Maximum residue limit (MRL)**

Maximum level or concentration of a drug or chemical thought to be non-hazardous and permitted by the regulatory bodies in or on food or feed intended to be used for animal or human consumption at a specified point of time, known as MRL. The unit used for this maximum allowable concentration is milligrams per kilogram of solid products and milligrams per liter for liquids [12].

Milk and other dairy products, which contain drug residues beyond the MRL, causes serious health problems of the consumers [13]. Though good quality milk and other related products are a prime need for maintaining proper public health [14], presence of antibiotic residues in those food items and subsequent consumption can cause potential health impacts, such as cancer and hypersensitivity reaction along with development of antibiotic resistance [15]. The consequences of such resistance are even more threatening where antibiotics become ineffective clinically. Maintaining proper withdrawal time, established for milk, and other food products can act as a safeguard to resist from hazardous impacts of antibiotic residues.

### **Withdrawal time**

This term is often used more broadly to describe the time needed after drug administration to any food animal where below a determined MRL may be found in marketed meats, eggs, organs, or other edible products. The withdrawal time may vary largely depending on chemical and physical properties of drugs and route of administration [16].

ARs in milk have been one of the major concerns in the recent years. As control policy demands proper detection and quantification approach of ARs in milk, a

good number of research works, have been published worldwide in this context to meet up the feasibilities. Previously, some microbiological tests like Delvotest® SP-NT and Copan® milk tests were used officially [17]. Though these tests are cheap, rapid, and easy to perform but lack of proper selectivity and accuracy level [17]. Chromatographic techniques, in the other hand, are more precise with higher specificity and accuracy, but requires proper sample preparation, sophisticated instrumentations, well trained personnel [11]. As possibilities of residues in milk from multiclass type of antibiotics is increasing day by day, accurate analysis of ARs using a well-developed single technique with minimum cost is always a challenge [11]. Therefore, the present study evaluate and compare the research studies to demonstrate the trends and to assess the works from past to recent decades for analysis of ARs in milk. Various techniques applied for determination of ARs in milk so far, is also a matter to be evaluated, which could ultimately develop a perception on comparative innovation of techniques over the time.

## **Materials and Methods**

### **Article selection**

Published literatures related with antibiotic residue detection in milk were collected from Pubmed, CrossRef, CAB direct, DOAJ, JournalTOCs, AGRICOLA, ScientificGate, Google Scholar, BanglaJOL, and E-Journals of ISI (Institute for scientific information). Original articles, published throughout the period of January 1965 to December 2017, were searched using a bibliographic database called “ISI Web of Science” [18]. The published literatures were searched using the following keywords: (detection and quantification) or only “detection” or only “quantification” (antibiotic/antimicrobial) and (cow/cattle/bovine, sheep/ovine, goat/caprine, mare, and animal). To find out the maximum articles of similar concept, avoiding the risk of missing due to plural word or multiple words, a sign “\*” was used in accordance with the published guidelines [19]. The searched items or publications were thoroughly checked and downloaded for detail and critical reviewing later. Only the original research data containing publications, written in English language, were included for our reviewing. The abstracts of the research articles, which contained data regarding antibiotic residues in milk, were selected for reviewing of the whole content. The research works were thoroughly revised and sorted out to meet up the field of interest. A total of 224 literatures have been finally selected for analysis. The full articles were managed in PDF format using Mendeley—a reference management software.

### Data extraction and analysis

Various data were collected from the literatures and organized in Microsoft excel worksheet-2013 on the basis of splitting those into six decades (i.e., 1960–1969, 1970–1979, 1980–1989, 1990–1999, 2000–2009, and 2010–2017) under various parameters. The parameters were: (1) country-wise or continent-wise distribution of accomplished researches, (2) detected antibiotics of specific type which were further furnished into the following classes: Beta-lactams (penicillins and cephalosporins), tetracyclines, sulfonamides, fluoroquinolones, aminoglycosides, and miscellaneous, (3) types of animals for samples (bovine, ovine, caprine, and mare), (4) type of sample (i.e., solely milk or milk along with other body matrices and tissues), (5) detection categories (i.e., simultaneous detection of several antibiotics within single class, simultaneous detection of several antibiotics within a specific class and multiclass at a time, simultaneous detection but antibiotics from multiple classes and single in each class, and single detection), (6) detection technique (chromatographic, immunological, microbiological, and miscellaneous), (7) chemicals used in chromatographic technique, and (8) chemicals used for sample extraction and mobile phase and. Data from the Excel sheet were furnished in tabular format. The data were statistically analyzed and presented in both Tabular and Bar diagram format.

## Results and discussion

### Publications

In the preliminary step of selection, we found a total of 1,371 articles which could meet up the area of interest. A total of 519 articles were found to contain original research data and English language was used to write up for 497. Out of 497, we did not consider 273 articles for our study due to lack of detailed information (both quantitative and qualitative) on antibiotic residues detection in milk. Therefore, the remaining 224 were taken as our study materials of interest to be reviewed. The results are shown in Figure 1.

### Antibiotic residue in milk: timeline analysis

Antibiotic residue in milk was first detected in 60s [20] followed by a swelling trend with a stiff increase in detection after 2000 (188) [21–208] The related published literatures from 2000 to 2009 is 81 (36.16%) in number [128–208], which is more than double in comparison with previous four decades collectively, where number was 36 (16.07%) in total [19,20,209–242] The ongoing decade merely comprises 47.77% research studies (107 in number) among the last 57 years [21–127], which clearly indicates the increasing trends with concern about antibiotic

residue in milk and detection accordingly. The results are shown in Figure 2.

### Country-wise analysis

Among the countries of the world, the highest no. of works, 49 (21.88%) were accomplished in China, followed by Spain, 30 (13.39%); Germany, 11 (4.91%); USA, 10 (4.46%); and Italy, 09 (4.01%) (Table 1). It is observed that more research studies on detection of antibiotic residue were performed at the developed countries rather than developing countries.

### Continent-wise analysis

Most of the research studies in related field have been performed in Europe, 105 (46.88%), followed by Asia, 77 (34.38%); South America, 18 (8.04%); North America, 16 (7.14%); and Africa, 8 (3.57%) so far (Table 1). Among the Asian countries, China is at the top in ranking, 63.64%; so

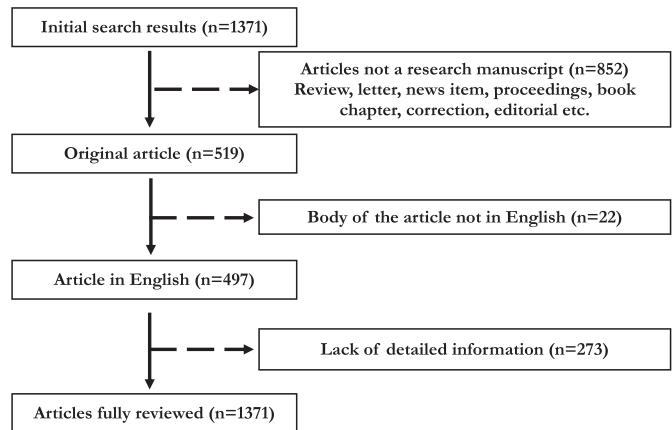


Figure 1. Selection and exclusion criteria for scientific publications on antibiotic residues in milk.

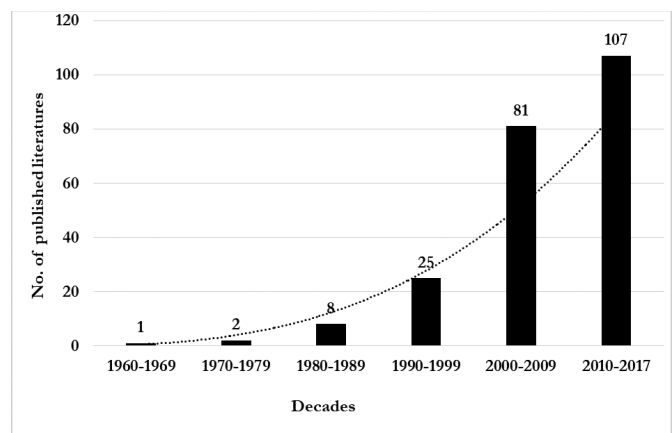


Figure 2. Timeline analysis of published literatures on antibiotic residue detection in milk.

**Table 1.** Continent and country-wise distribution of researches on detection of antibiotic residue in milk.

	Continents				
	Asia	Europe	Africa	South America	North America
No. of researches (%)	77 (34.38%)	105 (46.88%)	8 (3.57%)	18 (8.04%)	16 (7.14%)
References	[21–24,28,30–32, 36, 37,39,42, 43, 45,49,53,55–62, 64,65,67,68,76, 78–81,83,86,89, 90,95,97–99,104, 106,108,109,111, 115,116, 124,127, 140,141, 147–149, 160, 162,164,172, 174, 176–178,182, 199, 212, 225–235]	[25–27,35,40,42,47, 48,50,51,54, 63, 66,69,72,73,75, 82,85,87,88,92, 96,100–103,105,107, 110,111,113,114,118,119, 121–123,125,128–132,134–136, 138,139,142–145,146,150, 151,153–159,161,163,165–167, 169,173,175,180,183, 184,186–189,192,195–198, 200–211,213,214,216,217–224]	[19,29,44,70,181, 236,238,242]	[38,46,62,71,74, 77,93,94,112,120, 137,152,170,171,193, 215,237,240]	[20,34,52,84,91, 117,126,132,179,181, 185,190,191,194, 239,241]
Top ranked countries, No. of researches (%)	China, 49 (63.64%)	Spain, 30 (28.57%)	Nigeria, Tanzania, Bosnia, 3 (37.5%)	Brazil, 8 (44.44%)	USA, 10 (62.5%)
References	[23,24,28,31–33, 36,37,39,42,42, 45,49,53,55–60, 64,65,67,68,76, 78,80,81,83,89, 97,104,106,108,109, 111,116,127,140,141, 147,148,162,164,172, 178,182,218,235]	[41,54,73,82,85, 88,92,100,101,105, 121,128,131,142,143, 146,150,153,154,156–159, 161,169,173,175,186–188]	[29,44,70]	[38,62,71,77,93, 137,152,171]	[34,52,84,91,117,133, 179,185,190]

are Spain, 28.57%; Nigeria, Tanzania, and Bosnia, 37.5%; Brazil, 44.44%; and USA, 62.5% for Europe, Africa, South America, and North America continents, respectively (Table 1).

#### Types of samples used for detection

The highest no. of research studies have been conducted using bovine milk, 193 (86.16%), followed by ovine, 19 (8.48%); caprine, 14 (6.25%); and mare, 1 (0.45%). The production rate, availability of animal and milk, demand, and amount of antibiotic usage might have been considered as important phenomena for selecting bovine milk in most of the cases over others. The majority of the articles, 184 (82.14%) denotes the works on detection of antibiotic residues using milk solely, though a considerable portion of works, 40 (17.86 %) have been accomplished for screening the residues in body tissues and other body matrices along with milk. Results and references are shown in Table 2.

Milk has been found to be categorized as raw or fresh and spiked, raw and non-spiked, pasteurized, unpasteurized, whole milk, skimmed milk, or semi-skimmed milk and various products of milk for detecting the antibiotic residues and innovating the detecting techniques.

#### Types of antibiotics detected

A total of 364 no. of works with different groups of antibiotics has been performed among the studied literatures. A variable no. of published works is found for different groups of antibiotics, so far. The highest number of works, 133 (36.54%) is found for  $\beta$ -lactam group, which comprise only penicillins, 75 (56.39%) and cephalosporins, 58 (43.61%) and the minimum, 38 (10.44%) in case of aminoglycosides (Table 3). The results are shown in Table 3. The data indicates that the usage of  $\beta$ -lactam antibiotics in milking animal is increasing day by day and thereby raising the concern in this regard. A variable number of works were found differentiating the classes of antibiotics during their detection by applying various methods, especially in chromatographic technique to evaluate and establish their respective detection accuracy.

In descending order, 72 (32.14%) research studies showed the simultaneous detection of a number of antibiotics within a specific class; 71 (31.69%) revealed the technique on detection of a single type of antibiotic at a time, 64 (28.57%) were found to have detected multiclass and simultaneous detection of a number in each class, and the rest of the papers, 16 (7.14%) were on detection of multiclass but single in each class (Table 4).

**Table 2.** Types of samples and animals used for detection of antibiotic residues in milk.

	Animals for samples			
	Bovine (n = 193)	Ovine (n = 19)	Caprine (n = 14)	Mare (n = 1)
References	[19–23,25,26,28–30, 32–42,44–47,49–61, 64–73,75–81,83–87, 89–113,115–122, 124–127,130,132–137, 139–145,147,148, 152–160,162–173,175–186, 190–192,194–217, 219–227,229–242]	[48,63,82,88,114,123,132,138,146, 149–151,161,174,187,188,193,228]	[24,27,31,43,62, 74,88,114,123,128, 131,146,189,218]	[123]
	Type of sample			
	Solely milk (n = 184)		Milk with other body matrices and tissues (n = 40)	
References	[20–29,31–37,39,41–46,49–54,56,57,60–63,65–70,73–77, 81–97,100–103,105,107–115,117,119–124,126,128–148, 150–162,164,166–171,173–175,177, 178, 182,184–189,191, 193–197,199–204,206–220,224–226,228–235,237,239,240–242]		[19,30,38,40,47,48,55,58,59,64,71,72, 78–80,98,99,104,106,116,118,125,127,149,163,165,172,176, 179–181,183,190,192,198,205,221,227,236,238]	

### Techniques for detection of residues

Diversified techniques have been applied for detection of ARs in milk, which are classified broadly as chromatographic, immunological, microbiological, and miscellaneous. The highest no. 115, (51.34%) is based on chromatography, followed by immunological, 58 (25.89%), Microbiological, 38 (16.96%), and miscellaneous, 18 (8.04%) (Table 5). The results are shown in Figure 3. The chromatographic technique is increasingly being used over others, especially the rate is much higher in recent times, due to higher sensitivity and specificity, higher quantification capability. On the other hand, various immunological and microbiological techniques can be applied at a cheaper rate, rapidly with lesser efficiency, though the quantification and detection is not satisfactory.

### Chemicals used in chromatography

Acetonitrile has been used in most of the cases, 77 (66.95%) for processing of milk during extraction, followed by methanol, 36 (31.30%); trichloroacetic acid, 31 (26.96%); n-hexane, 22 (19.13%); disodiummethylenediaminetetraacetate, 21 (18.26%); formic acid, 18 (15.65%); oxalic acid, 14 (12.17%); ethanol, 9 (7.83%); and sodium hydroxide, 7 (6.09%) (Table 6). The results are shown in Figure 4. In most of the cases two or more than two chemicals have been used for extraction. Variable concentrations of the chemicals were used in different research studies. The chemicals have been selected based on their chemical nature for easy extraction, price, availability, specificity, type of column used, and nature of antibiotics being extracted out.

Waters BEH C18 (50 × 2.1 mm, 2.1 μm), Waters BEH C18 (100 × 2.1 mm, 2.1 μm), Phenomenex AQUA C18 (150 × 2.1mm, 3 μm), Waters HSS T3 C18 (100 × 2.1 mm, 1.8

μm), Waters Symmetry C18 (75 × 4.6mm; 3.5μm), Waters Atlantis T3 C18 (100 × 2.1 mm, 3 μm), Thermo Hypersil Gold (100 × 2.1 mm, 2.6 μm), Agilent Zorbax SB-C18 (100 × 2.1 mm, 3.5 μm), Waters YMC-AQ (100 × 2 mm, 3 μm, 120Å), Agilent Zorbax Eclipse XDB-C8 (150 × 4.6 mm, 5 μm) columns have been found to be used frequently in chromatographic separation, especially in the recent years.

In mobile phase, Acetonitrile and formic acid combination for chromatographic separation has been used in most of the cases. Acetonitrile still belongs to the top in ranking, 76 (66.09%), followed by formic acid, 54 (46.96%); methanol, 37 (32.17%); oxalic acid, 24 (20.87%); ammonium acetate, 21 (18.26%); acetic acid, 14 (12.17%); heptafluorobutyric acid, 11 (9.56%); and ammonium formate, 8 (6.95%) (Table 7). The results are shown in Figure 5.

### Main causes of presence of antibiotic residues in milk

1. Therapeutical uses of antibiotics: Vital cause of presence of ARs in milk is the indiscriminate usage of antibiotics in therapy of infectious diseases, such as clinical mastitis and viral diseases [10].
2. Antibiotics as prophylactics: Sometimes, antibiotics are used in therapy of dry cow [10,243] and management of post-surgical risk, which are also responsible for AR in milk [10].
3. Antibiotics in miscellaneous purposes: There may have direct or indirect pathways of contaminating milk by ARs, when used during processing and preservation of milk and related dairy products [10].
4. If the supplied instructions in the label are not followed accordingly, residues of antibiotics may be found in milk. When an antibiotic is approved only

**Table 3.** Number (%) of antibiotics under various groups or classes detected in milk over the decades.

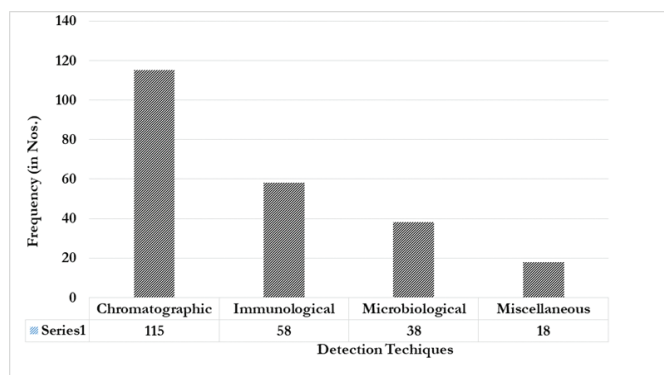
	Name of Groups								Total
	β-lactams		Cephalosporins	Tetracyclines	Fluoroquinolones	Sulfonamides	Aminoglycosides	Miscellaneous	
	Penicillins								
No. of works	75	58	51	49	46	38	47	364	
Percentage (%)	20.60	15.93	14.01	13.46	12.64	10.44	12.91	100	
Recent two decades	2000 to 2009	Nos.	27	24	14	18	18	19	147
	%		18.37	16.33	9.52	12.24	12.24	12.93	100
	2010 to 2017	Nos.	36	28	31	29	15	16	171
	%		21.05	16.37	18.13	16.96	8.77	9.36	100
Total in two decades	2000 to 2017	Nos.	63	52	45	47	43	33	318
	%		19.81	16.35	14.15	14.78	13.52	10.38	100
References	[21,23,26-30, 35,36,39,41, 42,45, 51,52, 60,65,70,73, 74,80, 82,86, 88, 89,98,99, 99,104,105,107, 110,111, 115,117, 120,123-125,129, 131,135, 138,132, 143,150,152,156, 167,180, 184,187, 188,191,193-196, 199-201, 202,203, 214,220,221,223, 224,226,227,229, 230,233,234,239,242]	[32,34,36,39,50, 60,65,66,68,73,7 4,76,80,82,83,84 ,86,88,89,93,96, 98,104,105,113, 115,117,118,123 ,129,131,133,13 4,138,140,148,1 50,152,156,167, 171,174,180,184 ,185,188,190,19 3,194,196,201,2 02,207,218,226, 229,230,234]	[25,26,28,30,32, 36,46,49,51, 57,62,63,66, 71,73-75,77, 86,101,104, 108-110,112,115, 117,120,128,129, 132,139,144, 150-152,160,161, 166,188,201, 206,208,215-217, 222,223,225, 227,232]	[25,28, 30-32, 36,43,49, 51,53-56,67, 71,78,87 91-95, 100,104,105,120, 121,128-130,132, 135,139,141,146,147, 150,153,154,156, 157,162,182,186, 189,200,201, 212,219]	[21,24,26,27,32, 36,49,51,53, 56, 66,71,72,85,90, 93,97,103,106,110, 115,120,121,126, 128-130,132,135, 136,139,145,150, 153,156,158,159, 161,163,164,169, 201,203,210, 232,237]	[27,40,48,51, 61,72,102, 108-110,114, 115,127,128, 130,135,137,144, 150,152,161,165, 166,173,177,179, 183,192,197,201, 203,204,209,213, 223,231,241]	[19,24,37,38, 47,49,58,59, 64,69,72,79, 81,94,104, 107,108,109, 115,116,118, 120-122, 128-130,132, 135,144,153, 161,170,172, 175,176,181, 191,198,201, 203,205,211, 223,228,235, 238]		

**Table 4.** References for detection categories of antibiotic residues in milk.

	Detection categories			
	Simultaneous within single class (n = 72)	Simultaneous and multiclass (n = 64)	Multiclass and single (n = 16)	Single (n = 71)
References	[31,37,38,40,41, 46,48,60,62,67, 70,75,76,77,78, 83,85,92,96,97, 98,100,103,111,112, 118,119,123,125,131, 138,143,145,146,148, 154,163,167,169,173, 175,176,180,182,183, 184,186,187,189, 192–196,198,202,204,206, 209,213,215–217,219, 224–227,229,231,232,234,242]	[21,22,24–27,36,39, 42,44,49,51,53, 56,63,65,66,69, 72–74,79,80,82,86, 87–90,93,94,101,104, 105,107–109,115,118,126, 128,129,130,132, 134–136,139,141,147,149, 150,152,153,155–156,157, 159,161,191,201,203,223]	[28,30,32,47,110, 117,120,121,144, 188,201,230,235,237, 238,20]	[19,23,29,33,34, 35,43,45,50,52, 54,55,57–59,61,64, 68,81,84,91,95, 99,102,106,113,114, 116,122,124,130,133, 137,140,142,151,158, 160,162,165,170–172,174, 177–179,181,185,190,197, 199,200,205,207,208, 210–212,214,218,220–222,228, 233,234,235,238,240,241]

**Table 5.** References for detection techniques of antibiotic residues in milk.

Detection techniques	References
Chromatographic (n = 115)	[19,21,24,25,29,30,33,34,36–41,45,47–50,50,53,55,56,58–60,62,68,69,71–73,75–77,79, 82–87,90,91,93,94,98,100,103–107,111,116,119,122,124–123,129,133,137,141,143,145–147,149, 151–154,157,160,164–166,171,172,175,176,179,181–184,186,189–191,195,196,207,199,205,208,211–215, 218–222,225,227–229,232,235,238,240]
Immunological (n = 58)	[26,27,29,31,32,34,35,37,39,43–45,58,59,64,65,74,77,78,80,81,88,89, 96,102,106, 113–115,107,118,121,127,130,135,136,139,140,144,148,152,156,159,162,163, 177,180,192,197,200,202,204,207, 209, 210,213, 219,239]
Microbiological (n = 38)	[22,30,42,46,51,63,70,101,110,112,128,131,138,142,150,161,167,170,174,187,188,193–195,201,202,206,208, 216–218,223,224,226,230,233,234, 241]
Miscellaneous (n = 18)	[23,61,66,67,92,95,97,99,109,120,123,158,178,193,178,231,242, 20]



**Figure 3.** Frequency of using various detection techniques for screening of antibiotic residues in milk.

for humans become used injudiciously in animals, or usage in different species where it is not approved, or during a condition where it is not approved, or usage beyond the appropriate concentration, may be referred as extra-label use [244].

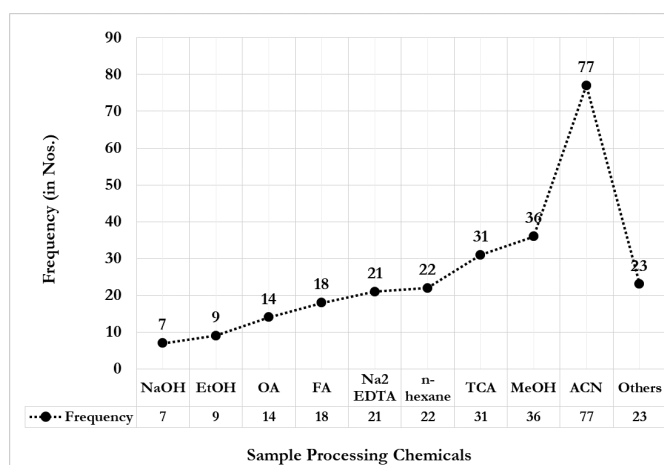
5. Lack of maintenance of proper withdrawal time: Without proper maintenance of withdrawal time of

antibiotics in milking animal, AR appears in milk at higher concentration [12].

6. Limited detection facilities of ARs and improper monitoring system of residues due to the crisis of strong regulatory organization, may be considered as important phenomena in this issue for developing countries [12].
7. Normal metabolic process of antibiotics is hampered in diseased 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 [16].
8. Lack of awareness of farmers about residual effects of AR from milk in human health [16]
9. Improper education of farmers [16].
10. Inadequate literatures supplied by manufacturers [10].
11. Improper cleaning of antibiotics contaminated equipment after using in mixing or administering process.
12. Improper disposal of empty containers of antibiotics in the farm premises which can contaminate feeds of animals. Animals may lick those or even get exposed through contaminated feeds accidentally [245].

**Table 6.** References for various chemicals used in processing of samples during chromatography.

Chemicals used in extraction process	References
Acetonitrile (n = 77)	[19,29,30,33,34,36–41,49,52,53,58–60,62,67,68,71–73,77, 82–87,91,95,98,107,116,122,126,132,145,151–153,164–166,175,181–184,186, 189–191,195,196,198,199,205,208,211–215,218–222,225,227–229,232,235,238,240]
Methanol (n = 36)	[53,58–60,62,67,68,71–73,75,82–87,97,100,107,116,145,148,166,181–184,190,191,208,211–215,238]
Trichloroacetic acid (n = 31)	[25,29,33,34,40,48,50,52,53,55,56,58,77,86, 87,93,98,100,112,129,132,146,147, 151–153,157,165,166,178,209]
n-hexane (n = 22)	[24,33,36–41,49,52,53,67,90,94,98,100,105,143,145,181,189,191]
Disodium ethylenediaminetetraacetate (n = 21)	[49,52,53,67,90,94,81,100,103,111,175,179,182,195,196,199,205,212,214,232,238]
Formic acid (n = 18)	[30,33,36,39–41,50,55,68,71,83,100,122,124,149,153,166,176]
Oxalic acid (n = 14)	[37,53,58,62,67,75,82,87,93,100,104,105,172,199]
Ethanol (n = 9)	[111,175,179,182,199,205,203,213,214]
sodium hydroxide (n = 7)	[73,165,175,195,199,232,238]



**Figure 4.** Frequency of using various chemicals during processing of milk sample prior to chromatography. \*Sodium hydroxide (NaOH), Ethanol (EtOH), Oxalic acid (OA), Formic acid (FA), Disodium ethylenediaminetetraacetate (Na<sub>2</sub>EDTA), Trichloroacetic acid (TCA), Methanol (MeOH), Acetonitrile (ACN).

13. Insufficient identification of treated cows [245].
14. Miscellaneous factors those influence the presence of AR in milk [246]:
  - a) Type and concentration of antibiotics
  - b) Excipients used during preparation of medicine
  - c) Frequency of milking and quantity of milk collection
  - d) Absorbance of udder tissues
  - e) Milk yield (AR in milk is inversely related with milk yield) [243]
  - f) Individuals factors

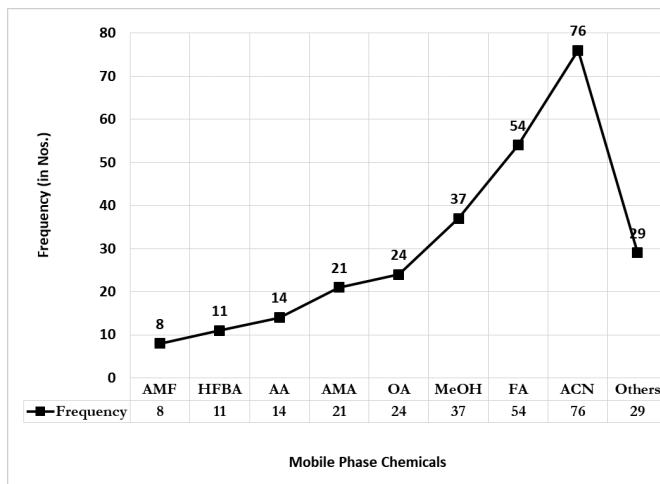
### Potential effects of ARs on public health and in dairy industry

1. **Antibiotic resistance:** Presence of low level of antibiotic residues in milk and other dairy products causes microorganisms to be resistant against antibiotics. The resistant microbes may be transmitted among the individuals via direct contact or indirectly by exchange of resistant genes in the environment [16].
2. **Allergic reactions:** Residues of various antibiotics are associated with multiple types of allergic reactions, including serum sickness and anaphylaxis, especially in case of penicillins [16]
3. **Carcinogenicity:** Residues of antibiotics possess potential carcinogenic impacts by interacting with cellular elements, such as DNA and RNA [16]
4. **Mutagenicity:** Mutagenic effect is another dangerous impact of ARs, which can cause mutation of DNA molecule or damage of chromosomes [66] Infertility of human being may results from this mutation [16]
5. **Teratogenicity:** Various congenital anomalies may be seen in new born child due to long term exposure of ARs during gestation period [16].
6. **Disturbances in the normal intestinal environment:** Normal habitant of the intestine coexists with others and colonizes to prevent the pathogenic microbes from producing diseases. ARs in milk resulting from usage of broad-spectrum antibiotics may kill a wide range of microflora in the intestine including the non-pathogenic organisms, which can make the disease causing microorganisms more prominent and disrupt the normal intestinal environment [16]
7. **Effects in dairy industry:** Existence of ARs in milk, even in very low concentration is of great concern in dairy industries. The residues of antibiotics can



**Table 7.** References for chemicals used in mobile phase during chromatography.

Chemicals used in mobile phase	References
Acetonitrile (n = 76)	[29,30,33,34,36,40,41,48,49,52,54,59,60,62–68,71,72,75,76,79, 82–87,93,95,98,100,107,116,119,122,126,129,133,137,145–147,151–153,154,165,166,175,179, 181–183,198,199,205,208,211–215,218–222,221,227–229,240]
Formic acid (n = 54)	[30,33,34,40,41,36,38,48,50,53,60,68,71,76,79, 82–87,100,103,105,107,111,116,119,122,125,126,129,132,133,143,147,149,152,153,154,157,166,176,198,199,205, 218–222,228,229,240]
Methanol (n = 37)	[47,53,58–60,62,67,68,72,73,75,83,97,100,103,107,111,116,124,141,143,145,147,149,152,166,172, 181–184,190,191,208,211,213]
Oxalic acid (n = 24)	[37,47,53,58–60,72,73,75,82,87,93,97,100,104,105,111,116,145,149,152,172,181,199]
Ammonium acetate (n = 21)	[47,59,111,119,122,126,129,141,146,157,181,198,205,208,212,214,219,222,227–229]
Acetic acid (n = 14)	[38,93,84,95,98,100,103,107,116,122,145,164,172,179]
Heptafluorobutyric acid (n = 11)	[96,98,133,179,196,205,214,219,220,228,235]
Ammonium formate (n = 8)	[50,133,172,179,184,196,199, 208]



**Figure 5.** Frequency of using various chemicals in mobile phase during chromatography. \*Ammonium formate (AMF), Heptafluorobutyric acid (HFBA), Acetic acid (AA), Ammonium acetate (AMA), Oxalic acid (OA), Methanol (MeOH), Formic acid (FA), Acetonitrile (ACN).

interfere with the fermentation process during production of cheese and yogurt by inhibiting the starter cultures [16].

**Control and preventive measures to avoid ARs in milk**

- 1) There are two basic approaches to control ARs in milk: (a) Development of highly sensitive detection tools to avoid the false negative results; (b) Usage of appropriate methods for confirmation and quantification of ARs, where possibility of false positive outcome will be minimum [247] Simple, rapid, sensitive, specific, and economic procedures should be

developed to analyze ARs in milk, followed by discarding if exceeds the MRL [16] The MRLs in milk for some antibiotics, established by European Commission (mentioned in council regulation 2377/90/EC) is given below [248]:

Antibiotics	MRLs in milk (µg/kg)	Antibiotics	MRLs in milk (µg/kg)
Benzyl penicillin	4	Gentamicin	200
Ampicillin	4	Neomycin	1500
Amoxicillin	4	Spiramycin	200
Tetracycline	100	Tylocin	100
Oxytetracycline	100	Erythromycin	40
Chlortetracycline	100	Colistin	50
Streptomycin	200	Ceftiofur	100
Dihydrostreptomycin	200		

- 2) The level or concentration of ARs in milk should be under regular basis monitoring and surveillance policies nationwide [10].
- 3) Following measures can be taken to inactivate some of the antibiotics: (a) Penicillin becomes inactivates following refrigeration. (b) Pasteurization can be used as an important measure to make most of the antibiotics inactive. (c) Some of the antibiotics loss their activity if treated with UV radiation, activated charcoal or resin etc. [10].
- 4) Development of public awareness through arrangement of some effective activities in this field, facilitated by the expert personnel or organizations [10]
- 5) Indiscriminate uses of VAs should be strictly prohibited [10].

- 6) Herbal sources of medicines may be taken in consideration as an alternative option for treating diseases [10]
- 7) Following guidelines for an effective drug use program:
  - a) Paying attention to proper withdrawal times of antibiotics for milking cows [10]
  - b) Label instructions should be read prior to purchasing of antibiotics to understand the consequences of usage [16]
  - c) Drugs used for lactating and non-lactating animals should not be intermixed, rather storing those in separate places [16].
  - d) Maintaining the good hygienic management practices during antibiotic administration [16].
  - e) Proper biosecurity should be maintained in dairy farms to avoid infections. Highest priority should be given in maintaining better health quality of dairy animals, where usage of antibiotics can be avoided in large extent [16].
  - f) Marking of antibiotics treated cows for easy identification, which will help the milkers to recognize them and withheld milk from marketing up to appropriate withdrawal time [16]
  - g) Data regarding treatment of milking cows should be preserved cautiously in written form, where date and cause of treatment, name and dosage of drugs used, withdrawal time must be included [16]
  - h) Antibiotics treated cows should be separated from the rest ones and milking lastly to minimize the risk of ARs contamination [16]
  - i) Milk should be withdrawn and discarded from all of the quarters following intra-mammary infusion of antibiotics, as infused drug can be disseminated through circulation easily [16].
  - j) The dairy producers should be made competent about maintaining proper quality of milk as well as its assurance [16]

## Conclusion

Presently, existence of ARs in milk is one of the burning issues, having great public health interest in many perspectives. According to the research studies, the causal factors of ARs in milk are not very few. A number of causes are also responsible for presence of antibiotic residues in milk. Detection and quantification of residues precisely in cost effective way within the shortest possible time is always a challenge. Few techniques haven been developed recently to detect residues and research studies are ongoing in this field for reaching the feasibilities. From the analysis of literatures in this review, chromatographic technique has

been found to be the most sensitive, specific, reliable, and feasible for this modern era. Hence, various modifications in chromatographic methods are still being applied and need to perform comprehensive research works in future to maximize the feasibilities. The rising trends of work in this regard surely denote the alarmingly increasing usage of antibiotic in livestock and threat of residues as well and increasing concern accordingly. Therefore, the appropriate measures should be implemented to cease the ARs in milk.

## Conflict of interests

There is no conflict of interest as declared by the authors.

## Authors' contribution

SS was involved in designing the study, interpretation of data, and drafting the write up of article. JF contributed in manuscript preparation. MHS took part in preparing and critical checking of this manuscript.

## References

- [1] Van Boeckel TP, Brower C, Gilbert M, Grenfell BT, Levin SA, Robinson TP, et al. Global trends in antimicrobial use in food animals. *Proc Natl Acad Sci USA* 2015; 112(18):5649–54; <https://doi.org/10.1073/pnas.1503141112>
- [2] Kümmerer HTK. Pharmaceuticals in the environment – sources, fate, effects and risks. *Aquat Toxicol* 2001; 71:391–2.
- [3] Arikan OA. The fate of chlortetracycline during the anaerobic digestion of manure from medicated calves. *J Hazard Mater* 2008;158(2–3):485–90; <https://doi.org/10.1016/j.jhazmat.2008.01.096>
- [4] Aarestrup F. Sustainable farming: get pigs off antibiotics. *Nature* 2012; 486(7404):465–6; <https://doi.org/10.1038/486465a>.
- [5] Sarmah AK, Meyer MT, Boxall AB. A global perspective on the use, sales, exposure pathways, occurrence, fate and effects of veterinary antibiotics (VAs) in the environment. *Chemosphere* 2006; 65(5):725–59.
- [6] Ventola CL. The antibiotic resistance crisis: part 1: causes and threats. *P T* 2015; 40:277–83.
- [7] Zhang H, Ren Y, Bao X. Simultaneous determination of (fluoro) quinolones antibacterials residues in bovine milk using ultra performance liquid chromatography–tandem mass spectrometry. *J Pharm Biomed Anal* 2009; 49(2):367–74; <https://doi.org/10.1016/j.jpba.2008.10.043>
- [8] Na lampang K, Chongsuvivatwong V, Kitikoon V. Pattern and determinant of antibiotics used on dairy farms in Songkhla province, Southern Thailand. *Trop Anim Health Prod* 2007; 39(5):355–61.
- [9] Commission staff working document on the implementation of national residue monitoring plans in the member states in 2009 (2010) European Commission (EC) Council Directive.
- [10] Nisha AR. Antibiotic residues—a global health hazard. *Vet World* 2008; 1(12):375–7.
- [11] Rossi R, Saluti G, Moretti S, Diamanti I, Giusepponi D, Galarini R.. Multiclass methods for the analysis of antibiotic residues in milk by liquid chromatography coupled to mass spectrometry: a review. *Food additives and contaminants. Food Addit Contam Part A Chem Anal Control Expo Risk Assess* 2018; 35(2):242–57; <https://doi.org/10.1080/19440049.2017.1393107>

- [12] Kebede G, Zenebe T, Disassa H, Tolosa T. Review on detection of antimicrobial residues in raw bulk milk in dairy farms. *Afr J Basic Appl Sci* 2014; 6(4):87–97.
- [13] Van den Meersche T, Van Pamel E, Van Poucke C, Herman L, Heyndrickx M, Rasschaert G, et al. Development, validation and application of an ultra-high performance liquid chromatographic-tandem mass spectrometric method for the simultaneous detection and quantification of five different classes of veterinary antibiotics in goat milk. *J Chromatogr A* 2016; 1429:248–57; <https://doi.org/10.1016/j.chroma.2015.12.046>
- [14] Shamsuddin M, Alam MM, Hossein MS, Goodger WJ, Bari FY, Ahmed TU, et al. Challenges and prospects of dairy industry in Bangladesh. *Trop Anim Health Prod* 2007; 39(8):567–81.
- [15] Hassan MM, Amin KB, Ahaduzzaman M, Alam M, Faruk SA, Uddin I. Antimicrobial resistance pattern against *E. coli* and *Salmonella* in layer poultry. *Res J Vet Pract* 2014; 2(2):30–5; <https://doi.org/10.14737/journal.rjvp/2014/2.2.30.35>
- [16] Beyene T. Veterinary drug residues in food-animal products: its risk factors and potential effects on public health. *J Vet Sci Technol* 2016; 7(1):1–7; <http://dx.doi.org/10.4172/2157-7579.1000285>
- [17] Fei Xu, Kang Ren, Yu-ze Yang, Jiang-peng Guo, Guang-peng Ma, Yi-ming Liu, et al. Immunoassay of chemical contaminants in milk: a review. *J Integr Agric* 2015; 14(11):2282–95; [https://doi.org/10.1016/S2095-3119\(15\)61121](https://doi.org/10.1016/S2095-3119(15)61121)
- [18] Clarivate Analytics ISI Web of Knowledge. (Search engine). Available via [www.webofknowledge.com](http://www.webofknowledge.com) (accessed 24 May 2017).
- [19] Hollstein E, Laue W, Zapff G. Gas-chromatographic determination of chloramphenicol residues in animal material. *Nahrung* 1981; 25(2):143–9.
- [20] Siddique IH, Loken KI, Hoyt HH. Antibiotic residues in milk transferred from treated to untreated quarters in dairy cattle. *J Am Vet Med Assoc* 1965; 146:589–93.
- [21] Khanal BKS, Sadiq MB, Singh M, Anal AK. Screening of antibiotic residues in fresh milk of Kathmandu Valley, Nepal. *J Environ Sci Health B* 2018; 53(1):57–86; <https://doi.org/10.1080/03601234.2017.1375832>
- [22] Moghadam MM, Amiri M, Riabi HR, Riabi HR. Evaluation of antibiotic residues in pasteurized and raw milk distributed in the South of Khorasan-e Razavi Province, Iran. *J Clin Diagn Res* 2016; 10(12):FC31–5; <https://doi.org/10.7860/JCDR/2016/21034.9034>
- [23] Chen Y, Li X, Yang M, Yang L, Han X, Jiang X, et al. High sensitive detection of penicillin G residues in milk by surface-enhanced Raman scattering. *Talanta* 2017; 167:236–41; <https://doi.org/10.1016/j.talanta.2017.02.022>
- [24] Qin Y, Jatamunua F, Zhang J, Li Y, Han Y, Zou N, et al. Analysis of sulfonamides, tilmicosin and avermectins residues in typical animal matrices with multi-plug filtration cleanup by liquid chromatography-tandem mass spectrometry detection. *J Chromatogr B Analyt Technol Biomed Life Sci* 2017; 1053:27–33 <https://doi.org/10.1016/j.jchromb.2017.04.006>
- [25] Moreno-González D, Hamed AM, Gilbert-López B, Gámiz-Gracia L, García-Campaña AM. Evaluation of a multiresidue capillary electrophoresis-quadrupole-time-of-flight mass spectrometry method for the determination of antibiotics in milk samples. *J Chromatogr A* 2017; 1510:100–7; <https://doi.org/10.1016/j.chroma.2017.06.055>
- [26] Rama A, Lucatello L, Benetti C, Galina G, Bajraktari D. Assessment of antibacterial drug residues in milk for consumption in Kosovo. *J Food Drug Anal* 2017; 25(3):525–32; <https://doi.org/10.1016/j.jfda.2016.07.007>
- [27] Meyer VK, Meloni D, Olivo F, Märtilbauer E, Dietrich R, Niessner R, et al. Validation procedure for multiplex antibiotic immunoassays using flow-based chemiluminescence microarrays methods. *Mol Biol* 2017; 1518:195–212; [https://doi.org/10.1007/978-1-4939-6584-7\\_13](https://doi.org/10.1007/978-1-4939-6584-7_13)
- [28] Long C, Deng B, Sun S, Meng S. Simultaneous determination of chlortetracycline, ampicillin and sarafloxacin in milk using capillary electrophoresis with electrochemiluminescence detection. *Food Addit Contam Part A Chem Anal Control Expo Risk Assess* 2017; 34(1):24–31; <https://doi.org/10.1080/19440049.2016.1254820>
- [29] Olatoye IO, Daniel OF, Ishola SA. Screening of antibiotics and chemical analysis of penicillin residue in fresh milk and traditional dairy products in Oyo state, Nigeria. *Vet World* 2016; 9(9):948–54; <https://doi.org/10.14202/vetworld.2016.948-954>
- [30] Chowdhury S, Hassan MM, Alam M, Sattar S, Bari MS, Saifuddin AK, et al. Antibiotic residues in milk and eggs of commercial and local farms at Chittagong, Bangladesh. *Vet World* 2015; 8(4):467–71; <https://doi.org/10.14202/vetworld.2015.467-471>
- [31] Chowdhury S, Hassan MM, Alam M, Sattar S, Bari MS, Saifuddin AK, et al. Broad-specific chemiluminescence enzyme immunoassay for (Fluoro)quinolones: Hapten design and molecular modeling study of antibody recognition. *Vet World* 2015; 8(4):467–71 <https://doi.org/10.14202/vetworld.2015.467-471>
- [32] Chen Y, Chen Q, Han M, Liu J, Zhao P, He L, et al. Near-infrared fluorescence-based multiplex lateral flow immunoassay for the simultaneous detection of four antibiotic residue families in milk. *Biosens Bioelectron* 2016; 79:430–4; <https://doi.org/10.1016/j.bios.2015.12.062>
- [33] Wang Y, Li X, Zhang Z, Ding S, Jiang H, Li J, et al. Simultaneous determination of nitroimidazoles, benzimidazoles, and chloramphenicol components in bovine milk by ultra-high performance liquid chromatography-tandem mass spectrometry. *Food Chem* 2016; 192:280–7; <https://doi.org/10.1016/j.foodchem.2015.07.033>
- [34] Grooms DL, Norby B, Grooms KE, Jagodzinski EN, Erskine RJ, Halbert LW, et al. Use of the BetaStar Plus assay for detection of ceftiofur antimicrobial residues in milk from individual cows following intramammary treatment for mastitis. *J Dairy Sci* 2015; 98(9):6270–7; <https://doi.org/10.3168/jds.2014-8802>
- [35] Pennacchio A, Varriale A, Esposito MG, Scala A, Marzullo VM, Staiano M, et al. A rapid and sensitive assay for the detection of benzylpenicillin (PenG) in milk. *PLoS One* 2015; 10(7):e0132396; <https://doi.org/10.1371/journal.pone.0132396>
- [36] Zhang Y, Li X, Liu X, Zhang J, Cao Y, Shi Z, et al. Multi-class, multi-residue analysis of trace veterinary drugs in milk by rapid screening and quantification using ultra-performance liquid chromatography-quadrupole time-of-flight mass spectrometry. *J Dairy Sci* 2015; 98(12):8433–44; <https://doi.org/10.3168/jds.2015-9826>
- [37] Li X, Shen J, Wang Q, Gao S, Pei X, Jiang H, et al. Multi-residue fluorescent microspheres immunochromatographic assay for simultaneous determination of macrolides in raw milk. *Anal Bioanal Chem* 2015; 407(30):9125–33; <https://doi.org/10.1007/s00216-015-9078-3>
- [38] Jank L, Martins MT, Arsand JB, Campos Motta TM, Hoff RB, Barreto F, et al. High-throughput method for macrolides and lincosamides antibiotics residues analysis in milk and muscle using a simple liquid-liquid extraction technique and liquid chromatography-electrospray-tandem mass spectrometry analysis (LC-MS/MS). *Talanta* 2015; 144:686–95; <https://doi.org/10.1016/j.talanta.2015.06.078>
- [39] Chen Y, Wang Y, Liu L, Wu X, Xu L, Kuang H, et al. Gold immunochromatographic assay for rapid and simultaneous detection of fifteen  $\beta$ -lactams. *Nanoscale* 2015; 7(39):16381–8; <https://doi.org/10.1039/c5nr04987c>
- [40] Farouk F, Azzazy HM, Niessen WM. Challenges in the determination of aminoglycoside antibiotics, a review. *Anal Chim Acta* 2015; 890:21–43; <https://doi.org/10.1016/j.aca.2015.06.038>
- [41] Urraca JL, Chamorro-Mendiluce R, Orellana G, Moreno-Bondi MC. Molecularly imprinted polymer beads for clean-up and pre-concentration of  $\beta$ -lactamase-resistant penicillins in milk. *Anal Bioanal Chem* 2016; 408(7):1843–54; <https://doi.org/10.1007/s00216-015-8941-6>

- [42] Bion C, Beck Henzelin A, Qu Y, Pizzocri G, Bolzoni G, Buffoli E. Analysis of 27 antibiotic residues in raw cow's milk and milk-based products—validation of Delvotest®T. *Food Addit Contam Part A Chem Anal Control Expo Risk Assess* 2016; 33(1):54–9; <https://doi.org/10.1080/19440049.2015.1104731>
- [43] Chen J, Shanin IA, Lv S, Wang Q, Mao C, Xu Z, et al. Heterologous strategy enhancing the sensitivity of the fluorescence polarization immunoassay of clinafloxacin in goat milk. *J Sci Food Agric* 2016; 96(4):1341–6; <https://doi.org/10.1002/jsfa.7228>
- [44] Ngasala JU, Nonga HE, Mtambo MM. Assessment of raw milk quality and stakeholders' awareness on milk-borne health risks in Arusha City and Meru District, Tanzania. *Trop Anim Health Prod* 2015; 47(5):927–32; <https://doi.org/10.1007/s11250-015-0810-y>
- [45] Li H, Xu B, Wang D, Zhou Y, Zhang H, Xia W, et al. Immunosensor for trace penicillin G detection in milk based on supported bilayer lipid membrane modified with gold nanoparticles. *J Biotechnol* 2015; 203:97–103; <https://doi.org/10.1016/j.jbiotec.2015.03.013>
- [46] Tumini M, Nagel OG, Althaus RL. Microbiological bioassay using *Bacillus pumilus* to detect tetracycline in milk. *J Dairy Res* 2015; 82(2):248–55; <https://doi.org/10.1017/S0022029915000138>
- [47] Kaufmann A, Butcher P, Maden K, Walker S, Widmer M. Determination of nitrofurans and chloramphenicol residues by high resolution mass spectrometry versus tandem quadrupole mass spectrometry. *Anal Chim Acta* 2015; 862:41–52; <https://doi.org/10.1016/j.aca.2014.12.036>
- [48] Diez C, Guillard D, Staub Spörri A, Cognard E, Ortelli D, Edder P, et al. Aminoglycoside analysis in food of animal origin with a zwitterionic stationary phase and liquid chromatography–tandem mass spectrometry. *Anal Chim Acta* 2015; 882:127–39; <https://doi.org/10.1016/j.aca.2015.03.050>
- [49] Cao Y, Kang J, Chang Q, Hu X, Wang Z, Fan C, et al. Multi-residue determination of veterinary drugs in cheese by QuEChERS and liquid chromatography–tandem mass spectrometry. *Se Pu* 2015; 33(2):132–9.
- [50] Horton RA, Randall LP, Bailey-Horne V, Heinrich K, Sharman M, Brunton LA, et al. Degradation of cefquinome in spiked milk as a model for bioremediation of dairy farm waste milk containing cephalosporin residues. *J Appl Microbiol* 2015; 118(4):901–10; <https://doi.org/10.1111/jam.12765>
- [51] Appicciafuoco B, Dragone R, Frazzoli C, Bolzoni G, Mantovani A, Ferrini AM. Microbial screening for quinolones residues in cow milk by bio-optical method. *J Pharm Biomed Anal* 2015; 106:179–85; <https://doi.org/10.1016/j.jpba.2014.11.037>
- [52] Lindquist DA, Baynes RE, Smith GW. Short communication: pharmacokinetics of intramammary hetacillin in dairy cattle milked 3 times per day. *J Dairy Sci* 2015; 98(3):1856–61; <https://doi.org/10.3168/jds.2014-8715>
- [53] Meng Z, Shi Z, Liang S, Dong X, Li H, Sun H. Residues investigation of fluoroquinolones and sulfonamides and their metabolites in bovine milk by quantification and confirmation using ultra-performance liquid chromatography–tandem mass spectrometry. *Food Chem* 2015; 174:597–605; <https://doi.org/10.1016/j.foodchem.2014.11.067>
- [54] Otero JA, Barrera B, de la Fuente A, Prieto JG, Marqués M, Álvarez AI, et al. The gain-of-function Y581S polymorphism of the ABCG2 transporter increases secretion into milk of danofloxacin at the therapeutic dose for mastitis treatment. *J Dairy Sci* 2015; 98(1):312–7; <https://doi.org/10.3168/jds.2014-8288>
- [55] Cheng G, Dong X, Wang Y, Peng D, Wang X, Hao H, et al. Development of a novel genetically modified bioluminescent-bacteria-based assay for detection of fluoroquinolones in animal-derived foods. *Anal Bioanal Chem* 2014; 406(30):7899–910; <https://doi.org/10.1007/s00216-014-8228-3>
- [56] Chen M, Wen K, Tao X, Ding S, Xie J, Yu X, et al. A novel multiplexed fluorescence polarization immunoassay based on a recombinant bi-specific single-chain diabody for simultaneous detection of fluoroquinolones and sulfonamides in milk. *Food Addit Contam Part A Chem Anal Control Expo Risk Assess* 2014; 31(12):1959–67; <https://doi.org/10.1080/19440049.2014.976279>
- [57] Qin J, Xie L, Ying Y. Determination of tetracycline hydrochloride by terahertz spectroscopy with PLSR model. *Food Chem* 2015; 170:415–22; <https://doi.org/10.1016/j.foodchem.2014.08.050>
- [58] Urine Zhou J, Zhu K, Xu F, Wang W, Jiang H, Wang Z, et al. Development of a microsphere-based fluorescence immunochromatographic assay for monitoring lincomycin in milk, honey, beef, and swine. *J Agric Food Chem* 2014; 62(49):12061–6; <https://doi.org/10.1021/jf5029416>
- [59] Wang Q, Wang G, Xi C, Li X, Chen D, Tang B, et al. Simultaneous determination of zeranols and chloramphenicol in foodstuffs of animal origin by combination immunoaffinity column clean-up and liquid chromatography–tandem mass spectrometry. *Se Pu* 2014; 32(6):640–6.
- [60] Zhang X, Cai X. Rapid simultaneous determination of 53 beta-lactam antibiotics and their metabolites in milk by ultra-performance liquid chromatography coupled with triple quadrupole mass spectrometry. *Se Pu* 2014; 32(7):693–701.
- [61] Mishra GK, Sharma A, Bhand S. Ultrasensitive detection of streptomycin using flow injection analysis–electrochemical quartz crystal nanobalance (FIA–EQCN) biosensor. *Biosens Bioelectron* 2015; 67:532–9; <https://doi.org/10.1016/j.bios.2014.09.033>
- [62] Prado CK, Ferreira FD, Bando E, Machinski M. Oxytetracycline, tetracycline, chlortetracycline and doxycycline in pasteurized cow's milk commercialized in Brazil. *J Food Addit Contam Part B Surveill* 2015; 8(2):81–4; <https://doi.org/10.1080/19393210.2014.968881>
- [63] Raspor Lainšček P1, Biasizzo M, Henigman U, Dolenc J, Kirbiš A. Implementation of the *Bacillus cereus* microbiological plate used for the screening of tetracyclines in raw milk samples with STAR protocol – the problem with false-negative results solved. *Food Addit Contam Part A Chem Anal Control Expo Risk Assess* 2014; 31(11):1840–9; <https://doi.org/10.1080/19440049.2014.966157>
- [64] Que X, Tang D, Xia B, Lu M, Tang D. Gold nanocatalyst-based immunosensing strategy accompanying catalytic reduction of 4-nitrophenol for sensitive monitoring of chloramphenicol residue. *Anal Chim Acta* 2014; 830:42–8; <https://doi.org/10.1016/j.aca.2014.04.051>
- [65] Zheng N, Wang J, Han R, Xu X, Zhen Y, Qu X, et al. Occurrence of several main antibiotic residues in raw milk in 10 provinces of China. *Food Addit Contam Part B Surveill* 2013; 6(2):84–9; <https://doi.org/10.1080/19393210.2012.727189>
- [66] Conzuelo F, Ruiz-Valdepeñas Montiel V, Campuzano S, Gamella M, Torrente-Rodríguez RM, Reviejo AJ, et al. Rapid screening of multiple antibiotic residues in milk using disposable amperometric magnetosensors. *Anal Chim Acta* 2014; 820:32–8; <https://doi.org/10.1016/j.aca.2014.03.005>
- [67] Meng HL, Chen GH, Guo X, Chen P, Cai QH, Tian YF. Determination of five quinolone antibiotic residues in foods by micellar electrokinetic capillary chromatography with quantum dot indirect laser-induced fluorescence. *Anal Bioanal Chem* 2014; 406(13):3201–8; <https://doi.org/10.1007/s00216-014-7730-y>
- [68] Li S, Guo C, Meng L, Huang X. Determination of cefalonium residue in milk by high performance liquid chromatography–tandem mass spectrometry. *Se Pu* 2014; 32(5):519–23.
- [69] Avci T, Elmas M. Milk and blood pharmacokinetics of tylosin and tilmicosin following parenteral administrations to cows. *Sci World J* 2014; 2014:869096; <https://doi.org/10.1155/2014/869096>
- [70] Fejzic N, Begagic M, Šerić-Haračić S, Smajlović M. Beta lactam antibiotics residues in cow's milk: comparison of efficacy of three screening tests used in Bosnia and Herzegovina. *J Basic Med Sci* 2014; 14(3):155–9; <https://doi.org/10.17305/bjbm.2014.3.109>

- [71] Martins MT, Melo J, Barreto F, Hoff RB, Jank L, Bittencourt MS, et al. A simple, fast and cheap non-SPE screening method for antibacterial residue analysis in milk and liver using liquid chromatography-tandem mass spectrometry. *Talanta* 2014; 129:374–83; <https://doi.org/10.1016/j.talanta.2014.04.049>
- [72] Chen Y, Schwack W. High-performance thin-layer chromatography screening of multiclass antibiotics in animal food by bio-luminescent bioautography and electrospray ionization mass spectrometry. *J Chromatogr A* 2014; 1356:249–57; <https://doi.org/10.1016/j.chroma.2014.06.043>
- [73] Junza A, Dorival-García N, Zafra-Gómez A, Barrón D, Ballesteros O, Barbosa J, et al. Multiclass method for the determination of quinolones and lactams, in raw cow milk using dispersive liquid-liquid microextraction and ultra high performance liquid chromatography-tandem mass spectrometry. *J Chromatogr A* 2014; 1356:10–22; <https://doi.org/10.1016/j.chroma.2014.06.034>
- [74] Beltrán MC, Borràs M, Nagel O, Althaus RL, Molina MP. Validation of receptor-binding assays to detect antibiotics in goat's milk. *J Food Prot* 2014; 77(2):308–13; <https://doi.org/10.4315/0362-028X.JFP-13-253>
- [75] Karageorgou E, Armeni M, Moschou I, Samanidou V. Ultrasound-assisted dispersive extraction for the high pressure liquid chromatographic determination of tetracyclines residues in milk with diode array detection. *Food Chem* 2014; 150:328–34; <https://doi.org/10.1016/j.foodchem.2013.11.008>
- [76] Liu X, Yu Y, Zhao M, Zhang H, Li Y, Duan G. Solid phase extraction using magnetic core mesoporous shell microspheres with C18-modified interior pore-walls for residue analysis of cephalosporins in milk by LC-MS/MS. *Food Chem* 2014; 150:206–12; <https://doi.org/10.1016/j.foodchem.2013.10.145>
- [77] De Albuquerque Fernandes SA, Magnavita AP, Ferrao SP, Gualberto SA, Faleiro AS, Figueiredo AJ, et al. Daily ingestion of tetracycline residue present in pasteurized milk: a public health problem. *Environ Sci Pollut Res Int* 2014; 21(5):3427–34; <https://doi.org/10.1007/s11356-013-2286-5>
- [78] Mi T, Wang Z, Eremin SA, Shen J, Zhang S. Simultaneous determination of multiple (Fluoro)quinolone antibiotics in food samples by a one-step fluorescence polarization immunoassay. *J Agric Food Chem* 2013; 61(39):9347–55; <https://doi.org/10.1021/jf403972r>
- [79] Kaufmann A, Widmer M. Quantitative analysis of polypeptide antibiotic residues in a variety of food matrices by liquid chromatography coupled to tandem mass spectrometry. *Anal Chim Acta* 2013; 797:81–8; <https://doi.org/10.1016/j.aca.2013.08.032>
- [80] Peng J, Cheng G, Huang L, Wang Y, Hao H, Peng D, et al. Development of a direct ELISA based on carboxy-terminal of penicillin-binding protein BlaR for the detection of  $\beta$ -lactam antibiotics in foods. *Anal Bioanal Chem* 2013; 405(27):8925–33; <https://doi.org/10.1007/s00216-013-7311-5>
- [81] Xia X, Xu Y, Ke R, Zhang H, Zou M, Yang W, et al. A highly sensitive europium nanoparticle-based lateral flow immunoassay for detection of chloramphenicol residue. *Anal Bioanal Chem* 2013; 405(23):7541–4; <https://doi.org/10.1007/s00216-013-7210-9>
- [82] Cámara M, Gallego-Picó A, Garcinuño RM, Fernández-Hernando P, Durand-Alegría JS, Sánchez P. An HPLC-DAD method for the simultaneous determination of nine  $\beta$ -lactam antibiotics in ewe milk. *J Food Chem* 2013; 141(2):829–34; <https://doi.org/10.1016/j.foodchem.2013.02.131>
- [83] Hou XL, Wu YL, Lv Y, Xu XQ, Zhao J, Yang T. Development and validation of an ultra high performance liquid chromatography tandem mass spectrometry method for determination of 10 cephalosporins and desacetylcefapirin in milk. *J Chromatogr B Analyt Technol Biomed Life Sci* 2013; 931:6–11; <https://doi.org/10.1016/j.jchromb.2013.05.006>
- [84] Gorden PJ, van der List M, Lehman FD, Lantz RK, Constable PD. Elimination kinetics of cephalosporin sodium in milk after an 8-day extended therapy program of daily intramammary infusion in healthy lactating Holstein-Friesian cows. *J Dairy Sci* 2013; 96(7):4455–64; <https://doi.org/10.3168/jds.2012-6487>
- [85] Nebot C, Regal P, Miranda JM, Fente C, Cepeda. Rapid method for quantification of nine sulfonamides in bovine milk using HPLC/MS/MS and without using SPE. *Food Chem* 2013; 141(3):2294–9; <https://doi.org/10.1016/j.foodchem.2013.04.099>
- [86] Mokhtari A, Hosseini B, Panahi P.  $\beta$ -lactams and tetracyclines antibiotic residue detection in bulk tank milk in Iran. *J Public Health* 2013; 42(4):447–8.
- [87] Karageorgou E, Myridakis A, Stephanou EG, Samanidou V. Multiresidue LC-MS/MS analysis of cephalosporins and quinolones in milk following ultrasound-assisted matrix solid-phase dispersive extraction combined with the quick, easy, cheap, effective, rugged, and safe methodology. *J Sep Sci* 2013; 36(12):2020–7; <https://doi.org/10.1002/jssc.201300194>
- [88] Beltrán MC, Romero T, Althaus RL, Molina MP. Evaluation of the Charm maximum residue limit  $\beta$ -lactam and tetracycline test for the detection of antibiotics in ewe and goat milk. *J Dairy Sci* 2013; 96(5):2737–45; <https://doi.org/10.3168/jds.2012-6044>
- [89] Zeng K, Zhang J, Wang Y, Wang ZH, Zhang SX, Wu CM, et al. Development of a rapid multi-residue assay for detecting  $\beta$ -lactams using penicillin binding protein 2x. *Biomed Environ Sci* 2013; 26(2):100–9; <https://doi.org/10.3967/0895-3988.2013.02.004>
- [90] Parab SR, Amritkar PN. Development and validation of a procedure for determination of sulfonamide residues in pasteurized milk using modified QuEChERS method and liquid chromatography/tandem mass spectrometry. *J AOAC Int* 2012; 95(5):1528–33. [91] Chiesa OA, Idowu OR, Heller D, Smith M, Nochetto C, Chamberlain PL, et al. A holstein cow-calf model for the transfer of ciprofloxacin through milk after a long-term intravenous infusion. *J Vet Pharmacol Ther* 2013; 36(5):425–33; <https://doi.org/10.1111/jvp.12014>
- [92] Piñero MY, Garrido-Delgado R, Bauza R, Arce L, Valcárcel M. Easy sample treatment for the determination of enrofloxacin and ciprofloxacin residues in raw bovine milk by capillary electrophoresis. *Electrophoresis* 2012; 33(19–20):2978–86; <https://doi.org/10.1002/elps.201200316>
- [93] Maia Toaldo I, Zandonadi Gamba G, Almeida Picinin L, Rubensam G, Hoff R, Bordignon-Luiz M. Multiclass analysis of antibacterial residues in milk using RP-liquid chromatography with photodiode array and fluorescence detection and tandem mass spectrometer confirmation. *Talanta* 2012; 99:616–24; <https://doi.org/10.1016/j.talanta.2012.06.047>
- [94] Springer VH, Lista AG. Micellar nanotubes dispersed electrokinetic chromatography for the simultaneous determination of antibiotics in bovine milk. *Electrophoresis* 2012; 33(13):2049–55; <https://doi.org/10.1002/elps.201100713>
- [95] Kaur K, Saini S, Singh B, Malik AK. Highly sensitive synchronous fluorescence measurement of danofloxacin in pharmaceutical and milk samples using aluminium (III) enhanced fluorescence. *J Fluoresc* 2012; 22(5):1407–13; <https://doi.org/10.1007/s10895-012-1079-4>
- [96] Bremus A, Dietrich R, Dettmar L, Usleber E, Märtilbauer E. A broadly applicable approach to prepare monoclonal anti-cephalosporin antibodies for immunochemical residue determination in milk. *Anal Bioanal Chem* 2012; 403(2):503–15; <https://doi.org/10.1007/s00216-012-5750-z>
- [97] Wang L, Wu J, Wang Q, He C, Zhou L, Wang J, et al. Rapid and sensitive determination of sulfonamide residues in milk and chicken muscle by microfluidic chip electrophoresis. *J Agric Food Chem* 2012; 60(7):1613–8; <https://doi.org/10.1021/jf2036577>
- [98] Kukulamude C, Burakham R, Chailapakul O, Srijaranai S. High performance liquid chromatography for the simultaneous analysis of penicillin residues in beef and milk using ion-paired extraction and binary water-acetonitrile mixture. *Talanta* 2012; 92:38–44; <https://doi.org/10.1016/j.talanta.2012.01.020>

- [99] KM1, Jeong E, Jeon W, Cho M, Ban C. Aptasensor for ampicillin using gold nanoparticle based dual fluorescence–colorimetric methods Song. *Anal Bioanal Chem* 2012; 402(6):2153–61; <https://doi.org/10.1007/s00216-011-5662-3>
- [100] Kantiani L, Farré M, Barceló D. Rapid residue analysis of fluoroquinolones in raw bovine milk by online solid phase extraction followed by liquid chromatography coupled to tandem mass spectrometry. *J Chromatogr A* 2011; 1218(50):9019–27; <https://doi.org/10.1016/j.chroma.2011.09.079>
- [101] Nagel OG, Molina MP, Althaus RL. Use chemometric techniques in the optimization of a specific bioassay for betalactams in milk. *Lett Appl Microbiol* 2012; 54(1):32–8; <https://doi.org/10.1111/j.1472-765X.2011.03169.x>
- [102] Burkin MA, Gal'vidis IA. Development and application of indirect competitive enzyme immunoassay for detection of neomycin in milk. *Prikl Biokhim Mikrobiol* 2011; 47(3):355–61.
- [103] Tolika EP, Samanidou VF, Papadoyannis IN. Development and validation of an HPLC method for the determination of ten sulfonamide residues in milk according to 2002/657/EC. *J Sep Sci* 2011; 34(14):1627–35; <https://doi.org/10.1002/jssc.201100171>
- [104] Chen GL, Fang YY. The LC-MS/MS methods for the determination of specific antibiotics residues in food matrices. *Methods Mol Biol* 2011; 747:309–55; [https://doi.org/10.1007/978-1-61779-136-9\\_13](https://doi.org/10.1007/978-1-61779-136-9_13)
- [105] Junza A, Amatya R, Barrón D, Barbosa J. Comparative study of the LC-MS/MS and UPLC-MS/MS for the multi-residue analysis of quinolones, penicillins and cephalosporins in cow milk, and validation according to the regulation 2002/657/EC. *J Chromatogr B Analyt Technol Biomed Life Sci* 2011; 879(25):2601–10; <https://doi.org/10.1016/j.jchromb.2011.07.018>
- [106] Wu Y, Yu S, Yu F, Yan N, Qu L, Zhang H. Chemiluminescence enzyme immunoassay for the determination of sulfamethoxydiazine. *Spectrochim Acta A Mol Biomol Spectrosc* 2011; 81(1):544–7; <https://doi.org/10.1016/j.saa.2011.06.047>
- [107] Karageorgou EG, Samanidou VF. Development and validation European Union Decision 2002/657/EC of an HPLC-DAD method for milk multi-residue analysis of penicillins and amphenicols based on dispersive extraction. *J Sep Sci* 2011; 34(15):1893–901; <https://doi.org/10.1002/jssc.201100194>
- [108] Su P, Liu N, Zhu M, Ning B, Liu M, Yang Z, et al. Simultaneous detection of five antibiotics in milk by high-throughput suspension array technology. *Talanta* 2011; 85(2):1160–5; <https://doi.org/10.1016/j.talanta.2011.05.040>
- [109] Wei Z, Wang J. Detection of antibiotic residues in bovine milk by a voltammetric electronic tongue system. *Anal Chim Acta* 2011; 694(1–2):46–56; <https://doi.org/10.1016/j.aca.2011.02.053>
- [110] Comunian R, Paba A, Dupré I, Daga ES, Scintu MF. Evaluation of a microbiological indicator test for antibiotic detection in ewe and goat milk. *J Dairy Sci* 2010; 93(12):5644–50; <https://doi.org/10.3168/jds.2010-3474>
- [111] Liu C, Wang H, Jiang Y, Du Z. Rapid and simultaneous determination of amoxicillin, penicillin G, and their major metabolites in bovine milk by ultra-high-performance liquid chromatography–tandem mass spectrometry. *J Chromatogr B Analyt Technol Biomed Life Sci* 2011; 879(7–8):533–40; <https://doi.org/10.1016/j.jchromb.2011.01.016>
- [112] Liu C, Wang H, Jiang Y, Du Z. Optimization of bioassay for tetracycline detection in milk by means of chemometric techniques. *J Chromatogr B Analyt Technol Biomed Life Sci* 2011; 879(7–8):533–40; <https://doi.org/10.1016/j.jchromb.2011.01.016>
- [113] Thal J, Steffen M, Meier B, Schneider E, Adriany A, Usleber E. Development of an enzyme immunoassay for the antibiotic cefquinome and its application for residue determination in cow's milk after therapeutical mastitis treatment. *Anal Bioanal Chem* 2011; 399(3):1051–9; <https://doi.org/10.1007/s00216-010-4421-1>
- [114] Solomun B, Bilandzic N, Varenina I, Scortichini G. Validation of an enzyme-linked immunosorbent assay for qualitative screening of neomycin in muscle, liver, kidney, eggs and milk. *Food Addit Contam Part A Chem Anal Control Expo Risk Assess* 2011; 28(1):11–8; <https://doi.org/10.1080/19440049.2010.527376>
- [115] Mohamadi Sani A, Nikpooyan H, Moshiri R. Aflatoxin M. contamination and antibiotic residue in milk in Khorasan province, Iran. *Food Chem Toxicol* 2010; 48(8–9):2130–2; <https://doi.org/10.1016/j.fct.2010.05.015>
- [116] Lu Y, Shen Q, Dai Z, Zhang H. Multi-walled carbon nanotubes as solid-phase extraction adsorbent for the ultra-fast determination of chloramphenicol in egg, honey, and milk by fused-core C18-based high-performance liquid chromatography–tandem mass spectrometry. *Anal Bioanal Chem* 2010; 398(4):1819–26; <https://doi.org/10.1007/s00216-010-4095-8>
- [117] Kneebone J, Tsang PC, Townson DH. Rapid antibiotic screening tests detect antibiotic residues in powdered milk products. *J Dairy Sci* 2010; 93(9):3961–4; <https://doi.org/10.3168/jds.2010-3057>
- [118] Burkin MA, Galvidis IA. Development of a Competitive Indirect ELISA for the determination of lincomycin in milk, eggs, and honey. *J Agric Food Chem* 2010; 58(18):9893–8; <https://doi.org/10.1021/jf101731h>
- [119] Karageorgou EG, Samanidou VF. Application of ultrasound-assisted matrix solid-phase dispersion extraction to the HPLC confirmatory determination of cephalosporin residues in milk. *J Sep Sci* 2010; 33(17–18):2862–71; <https://doi.org/10.1002/jssc.201000385>
- [120] Vera-Candiotti L, Olivieri AC, Goicoechea HC. Development of a novel strategy for preconcentration of antibiotic residues in milk and their quantitation by capillary electrophoresis. *Talanta* 2010; 82(1):213–21; <https://doi.org/10.1016/j.talanta.2010.04.023>
- [121] Fernández F, Hegnerová K, Piliarik M, Sanchez-Baeza F, Homola J, Marco MP. A label-free and portable multichannel surface plasmon resonance immunosensor for on site analysis of antibiotics in milk samples. *Biosens Bioelectron* 2010; 26(4):1231–8; <https://doi.org/10.1016/j.bios.2010.06.012>
- [122] Cronly M, Behan P, Foley B, Malone E, Martin S, Doyle M, et al. Rapid multi-class multi-residue method for the confirmation of chloramphenicol and eleven nitroimidazoles in milk and honey by liquid chromatography–tandem mass spectrometry (LC-MS). *Food Addit Contam Part A Chem Anal Control Expo Risk Assess* 2010; 27(9):1233–46; <https://doi.org/10.1080/19440049.2010.489579>
- [123] Reybroeck W, Ooghe S, De Brabander HF, Daeseleire E. Validation of the beta-s.t.a.r. 1 + 1 for rapid screening of residues of  $\beta$ -lactam antibiotics in milk. *Food Addit Contam Part A Chem Anal Control Expo Risk Assess* 2010; 27(8):1084–95; <https://doi.org/10.1080/19440041003724871>
- [124] Kukusamude C, Santalad A, Boonchiangma S, Burakham R, Srijaranai S, Chailapakul O. Mixed micelle-cloud point extraction for the analysis of penicillin residues in bovine milk by high performance liquid chromatography. *Talanta* 2010; 81(1–2):486–92; <https://doi.org/10.1016/j.talanta.2009.12.029>
- [125] Van Holthoon F, Mulder PP, van Bennekom EO, Heskamp H, Zuidema T, van Rhijn H. Quantitative analysis of penicillins in porcine tissues, milk and animal feed using derivatisation with piperidine and stable isotope dilution liquid chromatography tandem mass spectrometry. *J Anal Bioanal Chem* 2010; 396(8):3027–40; <https://doi.org/10.1007/s00216-010-3523-0>
- [126] Segura PA, Tremblay P, Picard P, Gagnon C, Sauvé S. High-throughput quantitation of seven sulfonamide residues in dairy milk using laser diode thermal desorption-negative mode atmospheric pressure chemical ionization tandem mass spectrometry. *J Agric Food Chem* 2010; 58(3):1442–6; <https://doi.org/10.1021/jf903362v>
- [127] Wu JX, Zhang SE, Zhou XP. Indirect competitive enzyme-linked immunosorbent assay (ELISA) and a colloidal gold-based

- immunochromatographic assay (CGIA). *J Zhejiang Univ Sci B* 2010; 11(1):52–60; <https://doi.org/10.1631/jzus.B0900215>
- [128] Sierra D, Contreras A, Sánchez A, Luengo C, Corrales JC, Morales CT, et al. Detection limits of non- $\beta$ -lactam antibiotics in goat's milk by microbiological residues screening tests. *J Dairy Sci* 2009; 92(9):4200–6; <https://doi.org/10.3168/jds.2009-2101>
- [129] Gaugain-Juhel M, Delepine B, Gautier S, Fourmond MP, Gaudin V, Hurtaud-Pessel D, et al. Validation of a liquid chromatography-tandem mass spectrometry screening method to monitor 58 antibiotics in milk: a qualitative approach. *Food Addit Contam Part A Chem Anal Control Expo Risk Assess* 2009; 26(11):1459–71; <https://doi.org/10.1080/02652030903150575>
- [130] Rebe Raz S, Bremer MG, Haasnoot W, Norde W. Label-free and multiplex detection of antibiotic residues in milk using imaging surface Plasmon resonance-based immunosensor. *Anal Chem* 2009; 81(18):7743–9; <https://doi.org/10.1021/ac901230v>
- [131] Sierra D, Sánchez A, Contreras A, Luengo C, Corrales JC, Morales CT, et al. Detection limits of four antimicrobial residue screening tests for  $\beta$ -lactams in goat's milk. *J Dairy Sci* 2009; 92(8):3585–91; <https://doi.org/10.3168/jds.2008-1981>
- [132] Bohm DA, Stachel CS, Gowik P. Multi-method for the determination of antibiotics of different substance groups in milk and validation in accordance with Commission Decision 2002/657/EC. *J Chromatogr A* 2009; 1216(46):8217–23; <https://doi.org/10.1016/j.chroma.2009.06.058>
- [133] Stockler RM, Morin DE, Lantz RK, Hurley WL, Constable PD. Effect of milk fraction on concentrations of cephapirin and desacetylcephapirin in bovine milk after intramammary infusion of cephapirin sodium. *J Vet Pharmacol Ther* 2009; 32(4):345–52; <https://doi.org/10.1111/j.1365-2885.2008.01048.x>
- [134] Bogialli S, Di Corcia A. Recent applications of liquid chromatography-mass spectrometry to residue analysis of antimicrobials in food of animal origin. *Anal Bioanal Chem* 2009; 395(4):947–66; <https://doi.org/10.1007/s00216-009-2930-6>
- [135] Kloth K, Rye-Johnsen M, Didier A, Dietrich R, Märtlbauer E, Niessner R, et al. A regenerable immunochip for the rapid determination of 13 different antibiotics in raw milk. *Analyst* 2009; 134(7):1433–9; <https://doi.org/10.1039/b817836d>
- [136] Adrian J, Pasche S, Diserens JM, Sánchez-Baeza F, Gao H, Marco MP, et al. Waveguide interrogated optical immunosensor (WIOS) for detection of sulfonamide antibiotics in milk. *Biosens Bioelectron* 2009; 24(11):3340–6; <https://doi.org/10.1016/j.bios.2009.04.036>
- [137] De Oliveira RC, Paschoal JA, Sismotto M, Airoidi FP, Reyes FG. Development and validation of an LC-APCI-MS-MS analytical method for the determination of streptomycin and dihydrostreptomycin residues in milk. *J Chromatogr Sci* 2009; 47(9):756–61.
- [138] Berruga MI, Rodriguez A, Rubio R, Gallego R, Molina A. Short communication: antibiotic residues in milk following the use of intravaginal sponges for estrus synchronization in dairy ewes. *J Dairy Sci* 2008; 91(10):3917–21; <https://doi.org/10.3168/jds.2008-1085>
- [139] Suárez G, Jin YH, Auerswald J, Berchtold S, Knapp HF, Diserens JM, et al. Lab-on-a-chip for multiplexed biosensing of residual antibiotics in milk. *Lab Chip* 2009; 9(11):1625–30; <https://doi.org/10.1039/b819688e>
- [140] Chen L, Wang Z, Ferreri M, Su J, Han B. Cephalixin residue detection in milk and beef by ELISA and colloidal gold based one-step strip assay. *J Agric Food Chem* 2009; 57(11):4674–9; <https://doi.org/10.1021/jf900433d>
- [141] Tang Q, Yang T, Tan X, Luo J. Simultaneous determination of fluoroquinolone antibiotic residues in milk sample by solid-phase extraction-liquid chromatography-tandem mass spectrometry. *J Agric Food Chem* 2009; 57(11):4535–9; <https://doi.org/10.1021/jf900513b>
- [142] Nagel OG, Molina MP, Basílico JC, Zapata ML, Althaus RL. Robust experimental design for optimizing the microbial inhibitor test for penicillin detection in milk. *Lett Appl Microbiol* 2009; 48(6):744–9; <https://doi.org/10.1111/j.1472-765X.2009.02602.x>
- [143] Kantiani L, Farré M, Sibum M, Postigo C, López de Alda M, Barceló D. Fully automated analysis of  $\beta$ -lactams in bovine milk by online solid phase extraction-liquid chromatography-electrospray-tandem mass spectrometry. *Anal Chem* 2009; 81(11):4285–95; <https://doi.org/10.1021/ac9001386>
- [144] Unusan N. Occurrence of chloramphenicol, streptomycin and tetracycline residues in ultra-heat-treatment milk marketed in Turkey. *Int J Food Sci Nutr* 2009; 60(5):359–64; <https://doi.org/10.1080/09637480701664555>
- [145] Gamba V, Terzano C, Fioroni L, Moretti S, Dusi G, Galarini R. Development and validation of a confirmatory method for the determination of sulphonamides in milk by liquid chromatography with diode array detection. *Anal Chim Acta* 2009; 637(1–2):18–23; <https://doi.org/10.1016/j.aca.2008.09.022>
- [146] Herrera-Herrera AV, Hernández-Borges J, Rodríguez-Delgado MA. Fluoroquinolone antibiotic determination in bovine, ovine and caprine milk using solid-phase extraction and high-performance liquid chromatography-fluorescence detection with ionic liquids as mobile phase additives. *J Chromatogr A* 2009; 1216(43):7281–7; <https://doi.org/10.1016/j.chroma.2009.02.025>
- [147] Zhang H, Ren Y, Bao X. Simultaneous determination of (fluoro) quinolones antibacterials residues in bovine milk using ultra performance liquid chromatography-tandem mass spectrometry. *J Pharm Biomed Anal* 2009; 49(2):367–74; <https://doi.org/10.1016/j.jpba.2008.10.043>
- [148] Xie H, Ma W, Liu L, Chen W, Peng C, Xu C, et al. Development and validation of an immunochromatographic assay for rapid multi-residues detection of cephem in milk. *Anal Chim Acta* 2009; 634(1):129–33; <https://doi.org/10.1016/j.aca.2008.12.004>
- [149] Inoue K, Nitta S, Hino T, Oka H. LC-MS/MS and centrifugal ultrafiltration method for the determination of novobiocin in chicken, fish tissues, milk and human serum. *J Chromatogr B Analyt Technol Biomed Life Sci* 2009; 877(4):461–4; <https://doi.org/10.1016/j.jchromb.2008.12.039>
- [150] Althaus R, Berruga MI, Montero A, Roca M, Molina MP. Evaluation of a microbiological multi residue system on the detection of antibacterial substances in ewe milk. *Anal Chim Acta* 2009; 632(1):156–62; <https://doi.org/10.1016/j.aca.2008.10.058>
- [151] Fletouris DJ, Papapanagiotou EP, Nakos DS. Liquid chromatographic determination and depletion profile of oxytetracycline in milk after repeated intramuscular administration in sheep. *J Chromatogr B Analyt Technol Biomed Life Sci* 2008; 876(1):148–52; <https://doi.org/10.1016/j.jchromb.2008.10.026>
- [152] Bando E1, Oliveira RC, Ferreira GM, Machinski M Jr. Occurrence of antimicrobial residues in pasteurized milk commercialized in the state of Paraná, Brazil. *J Food Prot* 2009; 72(4):911–4.
- [153] Aguilera-Luiz MM, Vidal JL, Romero-González R, Frenich AG. Multi-residue determination of veterinary drugs in milk by ultra-high-pressure liquid chromatography-tandem mass spectrometry. *J Chromatogr A* 2008; 1205(1–2):10–6; <https://doi.org/10.1016/j.chroma.2008.07.066>
- [154] Zafra-Gómez A, Garballo A, Ballesteros O, Navalón A, García-Ayuso LE. Simultaneous determination of quinolone antibacterials in bovine milk by liquid chromatography-mass spectrometry. *Biomed Chromatogr* 2008; 22(11):1186–93; <https://doi.org/10.1002/bmc.1041>
- [155] Samanidou V, Nisyriou S. Multi-residue methods for confirmatory determination of antibiotics in milk. *J Sep Sci* 2008; 31(11):2068–90; <https://doi.org/10.1002/jssc.200700647>
- [156] Adrian J, Pinacho DG, Granier B, Diserens JM, Sánchez-Baeza F, Marco MP. A multianalyte ELISA for immunochemical screening of sulfonamide, fluoroquinolone and  $\beta$ -lactam antibiotics in

- milk samples using class-selective bioreceptors. *Anal Bioanal Chem* 2008; 391(5):1703–12; <https://doi.org/10.1007/s00216-008-2106-9>
- [157] Hermo MP, Nemutlu E, Kir S, Barrón D, Barbosa J. Improved determination of quinolones in milk at their MRL levels using LC–UV, LC–FD, LC–MS and LC–MS/MS and validation in line with regulation 2002/657/EC. *Anal Chim Acta* 2008; 613(1):98–107; <https://doi.org/10.1016/j.aca.2008.02.045>
- [158] Reguera C, Ortiz MC, Herrero A, Sarabia LA. Optimization of a FIA system with amperometric detection by means of a desirability function determination of sulfadiazine, sulfamethazine and sulfamerazine in milk. *Talanta* 2008; 75(1):274–83; <https://doi.org/10.1016/j.talanta.2007.11.030>
- [159] Font H, Adrian J, Galve R, Estévez MC, Castellari M, Gratacós-Cubarsí M, et al. Immunochemical assays for direct sulfonamide antibiotic detection in milk and hair samples using antibody derivatized magnetic nanoparticles. *J Agric Food Chem* 2008; 56(3):736–43; <https://doi.org/10.1021/jf072550n>
- [160] Khosrokhavar R, Hosseini MJ, Amini M, Pirali-Hamedani M, Ghazi-Khansari M, Bakhtiarian A. Validation of an analytical methodology for determination of oxytetracycline residue in milk by HPLC with UV detection. *Toxicol Mech Methods* 2008; 18(4):351–4; <https://doi.org/10.1080/15376510701610984>
- [161] Linage B, Gonzalo C, Carriedo JA, Asensio JA, Blanco MA, De La Fuente LF, et al. Performance of blue-yellow screening test for antimicrobial detection in ovine milk. *J Dairy Sci* 2007; 90(12):5374–9; <https://doi.org/10.3168/jds.2007-0245>
- [162] Zhao C, Liu W, Ling H, Lu S, Zhang Y, Liu J, et al. Preparation of anti-gatifloxacin antibody and development of an indirect competitive enzyme-linked immunosorbent assay for the detection of gatifloxacin residue in milk. *J Agric Food Chem* 2007; 55(17):6879–84; <https://doi.org/10.1021/jf070978g>
- [163] Gaudin V, Hédou C, Sanders P. Validation of a Biacore method for screening eight sulfonamides in milk and porcine muscle tissues according to European decision 2002/657/EC. *J AOAC Int* 2007; 90(6):1706–15.
- [164] Wu Y, Zhao L, Liu Y, Jiang Y, Liu X, Shen J. Simultaneous determination of nine sulfonamide residues in milk using solid phase extraction and high performance liquid chromatography. *Se Pu* 2007; 25(5):728–31.
- [165] Cherlet M, De Baere S, De Backer P. Quantitative determination of dihydrostreptomycin in bovine tissues and milk by liquid chromatography electrospray ionization-tandem mass spectrometry. *J Mass Spectrom* 2007; 42(5):647–56; <https://doi.org/10.1002/jms.1194>
- [166] De Ruyck H, De Ridder H. Determination of tetracycline antibiotics in cow's milk by liquid chromatography/tandem mass spectrometry. *Rapid Commun Mass Spectrom* 2007; 21(9):1511–20; <https://doi.org/10.1002/rcm.2991>
- [167] Lamar J, Petz M. Development of a receptor-based microplate assay for the detection of beta-lactam antibiotics in different food matrices. *Anal Chim Acta* 2007; 586(1–2):296–303; <https://doi.org/10.1016/j.aca.2006.09.032>
- [168] Le Breton MH, Savoy-Perroud MC, Diserens JM. Validation and comparison of the Copan Milk Test and Delvotest SP-NT for the detection of antimicrobials in milk. *Anal Chim Acta* 2007; 586(1–2):280–3; <https://doi.org/10.1016/j.aca.2006.11.060>
- [169] Díez R, Sarabia L, Ortiz MC. Rapid determination of sulfonamides in milk samples using fluorescence spectroscopy and class modeling with n-way partial least squares. *Anal Chim Acta* 2007; 585(2):350–60; <https://doi.org/10.1016/j.aca.2006.12.038>
- [170] Litterio NJ, Calvino LF, Flores MM, Tarabla HD, Boggio JC. Microbiological screening test validation for detection of tylosin excretion in milk of cows with low and high somatic cell counts. *J Vet Med A Physiol Pathol Clin Med* 2007; 54(1):30–5; <https://doi.org/10.1111/j.1439-0442.2007.00901>
- [171] Oliveira RV, De Pietro AC, Cass QB. Quantification of cephalixin as residue levels in bovine milk by high-performance liquid chromatography with on-line sample cleanup. *Talanta* 2007; 71(3):1233–8; <https://doi.org/10.1016/j.talanta.2006.06.024>
- [172] Huang JF, Zhang HJ, Feng YQ. Chloramphenicol extraction from honey, milk, and eggs using polymer monolith microextraction followed by liquid chromatography-mass spectrometry determination. *J Agric Food Chem* 2006; 54(25):9279–86; <https://doi.org/10.1021/jf062246e>
- [173] Serrano JM, Silva M. Trace analysis of aminoglycoside antibiotics in bovine milk by MEKC with LIF detection. *Electrophoresis* 2006; 27(23):4703–10; <https://doi.org/10.1002/elps.200600184>
- [174] Goudah A, Shin HC, Shim JH, Abd El-Aty AM. Characterization of the relationship between serum and milk residue disposition of ceftriaxone in lactating ewes. *J Vet Pharmacol Ther* 2006; 29(4):307–12; <https://doi.org/10.1111/j.1365-2885.2006.00749.x>
- [175] García-Mayor MA, Garcinuño RM, Fernández-Hernando P, Durand-Alegría JS. Liquid chromatography–UV diode-array detection method for multi-residue determination of macrolide antibiotics in sheep's milk. *J Chromatogr A* 2006; 1122(1–2):76–83; <https://doi.org/10.1016/j.chroma.2006.04.019>
- [176] Wan EC, Ho C, Sin DW, Wong YC. Detection of residual bacitracin A, colistin A, and colistin B in milk and animal tissues by liquid chromatography tandem mass spectrometry. *Anal Bioanal Chem* 2006; 385(1):181–8; <https://doi.org/10.1007/s00216-006-0325-5>
- [177] Jin Y, Jang JW, Lee MH, Han CH. Development of ELISA and immunochromatographic assay for the detection of neomycin. *Clin Chim Acta* 2006; 364(1–2):260–6.
- [178] Wan GH, Cui H, Zheng HS, Pang YQ, Liu LJ, Yu XF. Flow-injection determination of streptomycin residues in milk using the luminol-periodate–Mn<sup>2+</sup> chemiluminescence system. *Luminescence* 2006; 21(1):36–42; <https://doi.org/10.1002/bio.880>
- [179] Heller DN, Peggins JO, Nochetto CB, Smith ML, Chiesa OA, Moulton K. LC/MS/MS measurement of gentamicin in bovine plasma, urine, milk, and biopsy samples taken from kidneys of standing animals. *J Chromatogr B Analyt Technol Biomed Life Sci* 2005; 821(1):22–30; <https://doi.org/10.1016/j.jchromb.2005.04.015>
- [180] Fitzgerald SP, O'Loan N, Mcconnell RI, Benchikh el O, Kane NE. Stable competitive enzyme-linked immunosorbent assay kit for rapid measurement of 11 active beta-lactams in milk, tissue, urine, and serum. *J AOAC Int* 2007; 90(1):334–42.
- [181] Penney L, Smith A, Coates B, Wijewickreme A. Determination of chloramphenicol residues in milk, eggs, and tissues by liquid chromatography/mass spectrometry. *J AOAC Int* 2005; 88(2):645–53.
- [182] Ho C, Sin DW, Tang HP, Chung LP, Siu SM. Determination and on-line clean-up of (fluoro)quinolones in bovine milk using column-switching liquid chromatography fluorescence detection. *J Chromatogr A* 2004; 1061(2):123–31.
- [183] Van Bruijnsvoort M1, Ottink SJ, Jonker KM, de Boer E. Determination of streptomycin and dihydrostreptomycin in milk and honey by liquid chromatography with tandem mass spectrometry. *J Chromatogr A* 2004; 1058(1–2):137–42.
- [184] Gustavsson E, Sternesjö A. Biosensor analysis of beta-lactams in milk: comparison with microbiological, immunological, and receptor-based screening methods. *J AOAC Int* 2004; 87(3):614–20.
- [185] Smith GW, Gehring R, Riviere JE, Yeatts JL, Baynes RE. Elimination kinetics of ceftiofur hydrochloride after intramammary administration in lactating dairy cows. *J Am Vet Med Assoc* 2004; 224(11):1827–30; <https://doi.org/10.2460/javma.2004.224.1827>
- [186] Marazuela MD, Moreno-Bondi MC. Multiresidue determination of fluoroquinolones in milk by column liquid chromatography with fluorescence and ultraviolet absorbance detection. *J Chromatogr A* 2004; 1034(1–2):25–32.
- [187] Berruga MI, Yamaki M, Althaus RL, Molina MP, Molina A. Performances of antibiotic screening tests in determining the



- persistence of penicillin residues in ewe's milk. *J Food Prot* 2003; 66(11):2097–102.
- [188] Molina A, Molina MP, Althaus RL, Gallego L. Residue persistence in sheep milk following antibiotic therapy. *Vet J* 2003; 165(1):84–9; [https://doi.org/10.1016/S1090-0233\(02\)00173-9](https://doi.org/10.1016/S1090-0233(02)00173-9)
- [189] Cinquina AL, Roberti P, Giannetti L, Longo F, Draisci R, Fagiolo A, et al. Determination of enrofloxacin and its metabolite ciprofloxacin in goat milk by high-performance liquid chromatography with diode-array detection. Optimization and validation. *J Chromatogr A* 2003; 987(1–2):221–6.
- [190] Hornish RE, Hamlow PJ, Brown SA. Multilaboratory trial for determination of ceftiofur residues in bovine and swine kidney and muscle, and bovine milk. *J AOAC Int* 2003; 86(1):30–8.
- [191] Ramirez A, Gutiérrez R, Diaz G, González C, Pérez N, Vega S, et al. High-performance thin-layer chromatography-bioautography for multiple antibiotic residues in cow's milk. *J Chromatogr B Analyt Technol Biomed Life Sci* 2003; 784(2):315–22.
- [192] Ferguson JP, Baxter GA, McEvoy JD, Stead S, Rawlings E, Sharman M. Detection of streptomycin and dihydrostreptomycin residues in milk, honey and meat samples using an optical biosensor. *Analyst* 2002; 127(7):951–6.
- [193] Althaus RL, Molina MP, Rodriguez M, Fernandez N. Detection limits of beta-lactam antibiotics in ewe milk by penzym enzymatic test. *J Food Prot* 2001; 64(11):1844–7; <https://doi.org/10.4315/0362-028X-64.11.1844>
- [194] Gibbons-Burgener SN, Kaneene JB, Lloyd JW, Leykam JF, Erskine RJ. Reliability of three bulk-tank antimicrobial residue detection assays used to test individual milk samples from cows with mild clinical mastitis. *Am J Vet Res* 2001; 62(11):1716–20; <https://doi.org/10.2460/ajvr.2001.62.1716>
- [195] Riediker S, Diserens JM, Stadler RH. Analysis of beta-lactam antibiotics in incurred raw milk by rapid test methods and liquid chromatography coupled with electrospray ionization tandem mass spectrometry. *J Agric Food Chem* 2001; 49(9):4171–6; <https://doi.org/10.1021/jf010057k>
- [196] Bruno F, Curini R, di Corcia A, Nazzari M, Samperi R. Solid-phase extraction followed by liquid chromatography-mass spectrometry for trace determination of beta-lactam antibiotics in bovine milk. *J Agric Food Chem* 2001; 49(7):3463–70; <https://doi.org/10.1021/jf010046r>
- [197] Baxter GA, Ferguson JP, O'Connor MC, Elliott CT. Detection of streptomycin residues in whole milk using an optical immunobiosensor. *J Agric Food Chem* 2001; 49(7):3204–7; <https://doi.org/10.1021/jf001484l>
- [198] Dubois M, Fluchard D, Sior E, Delahaut P. Identification and quantification of five macrolide antibiotics in several tissues, eggs and milk by liquid chromatography-electrospray tandem mass spectrometry. *J Chromatogr B Biomed Sci Appl* 2001; 753(2):189–202; <https://doi.org/10.1007/s002160000543>
- [199] Furusawa N. Rapid liquid chromatographic determination of residual penicillin G in milk. *Fresenius J Anal Chem* 2000; 368(6):624–6.
- [200] Van Coillie E, De Block J, Reybroeck W. Development of an indirect competitive ELISA for flumequine residues in raw milk using chicken egg yolk antibodies. *J Agric Food Chem* 2004; 52(16):4975–8; <https://doi.org/10.1021/jf049593d>
- [201] Gaudin V, Maris P, Fuselier R, Ribouchon JL, Cadieu N, Rault A. Validation of a microbiological method: the STAR protocol, a five-plate test, for the screening of antibiotic residues in milk. *Food Addit Contam* 2004; 21(5):422–33; <https://doi.org/10.1080/02652030410001667575>
- [202] Gustavsson E, Degelaen J, Bjurling P, Sternesjö A. Determination of  $\beta$ -lactams in milk using a surface plasmon resonance-based biosensor. *J Agric Food Chem* 2004; 52(10):2791–6; <https://doi.org/10.1021/jf0344284>
- [203] Knecht BG, Strasser A, Dietrich R, Märtilbauer E, Niessner R, Weller MG. Automated microarray system for the simultaneous detection of antibiotics in milk. *Anal Chem* 2004; 76(3):646–54; <https://doi.org/10.1021/ac035028i>
- [204] Loomans EE, Van Wiltenburg J, Koets M, Van Amerongen A. Neamin as an immunogen for the development of a generic ELISA detecting gentamicin, kanamycin, and neomycin in milk. *J Agric Food Chem* 2003; 51(3):587–93; <https://doi.org/10.1021/jf020829s>
- [205] Dreassi E, Corti P, Bezzini F, Furlanetto S. High-performance liquid chromatographic assay of erythromycin from biological matrix using electrochemical or ultraviolet detection. *Analyst* 2000; 125(6):1077–81; <https://doi.org/10.1039/a909876c>
- [206] Kurittu J, Lönnberg S, Virta M, Karp M. Qualitative detection of tetracycline residues in milk with a luminescence-based microbial method: the effect of milk composition and assay performance in relation to an immunoassay and a microbial inhibition assay. *J Food Prot* 2000; 63(7):953–7; <https://doi.org/10.4315/0362-028X-63.7.953>
- [207] Meyer UJ, Zhi ZL, Loomans E, Spener F, Meusel M. Automated stand-alone flow injection immunoanalysis system for the determination of cephalixin in milk. *Analyst* 1999; 124(11):1605–10; <https://doi.org/10.1039/a907121k>
- [208] McEvoy JD, Mayne CS, Higgins HC, Kennedy DG. Transfer of chlortetracycline from contaminated feeding stuff to cows' milk. *Vet Rec* 2000; 146(4):102–6; <https://doi.org/10.1136/vr.146.4.102>
- [209] Haasnoot W, Stouten P, Cazemier G, Lommen A, Nouws JF, Keukens HJ. Immunochemical detection of aminoglycosides in milk and kidney. *Analyst* 1999; 124(3):301–5; <https://doi.org/10.1039/a807846g>
- [210] Gaudin V, Pavy ML. Determination of sulfamethazine in milk by biosensor immunoassay. *J AOAC Int* 1999; 82(6):1316–20.
- [211] Dudriková E, Jozef S, Jozef N. Liquid chromatographic determination of tylosin in mastitic cow's milk following therapy. *J AOAC Int* 1999; 82(6):1303–7.
- [212] Gips M, Soback S. Norfloxacin pharmacokinetics in lactating cows with sub-clinical and clinical mastitis. *J Vet Pharmacol Ther* 1999; 22(3):202–8; <https://doi.org/10.1046/j.1365-2885.1999.00210.x>
- [213] Suhren G1, Knapstein K. Detection of incurred dihydrostreptomycin residues in milk by liquid chromatography and preliminary confirmation methods. *Analyst* 1998; 123(12):2797–801; <https://doi.org/10.1039/a805050c>
- [214] Ibach A, Petz M, Heer A, Mencke N, Krebber R. Oxacillin residues in milk after drying off with Stapenor Retard TS. *Analyst* 1998; 123(12):2763–5; <https://doi.org/10.1039/a805044i>
- [215] Pena AL, Lino CM, Silveira IN. Determination of oxytetracycline, tetracycline, and chlortetracycline in milk by liquid chromatography with postcolumn derivatization and fluorescence detection. *J AOAC Int* 1999; 82(1):55–60.
- [216] D'Haese E1, Nelis HJ, Reybroeck W. Chemiluminometric beta-galactosidase detection as a basis for a tetracycline screening test in milk. *J Biolumin Chemilumin* 1998; 13(5):279–83; [https://doi.org/10.1002/\(SICI\)1099-1271\(199809\)13:5<279::AID-BIO499>3.0.CO;2-4](https://doi.org/10.1002/(SICI)1099-1271(199809)13:5<279::AID-BIO499>3.0.CO;2-4)
- [217] Nouws JF, Loeffen G, Schouten J, Van Egmond H, Keukens H, Stegeman H. Testing of raw milk for tetracycline residues. *J Dairy Sci* 1998; 81(9):2341–5; [https://doi.org/10.3168/jds.S0022-0302\(98\)70124-9](https://doi.org/10.3168/jds.S0022-0302(98)70124-9)
- [218] Zeng SS, Hart S, Escobar EN, Tesfai K. Validation of antibiotic residue tests for dairy goats. *J Food Prot* 1998; 61(3):344–9; <https://doi.org/10.4315/0362-028X-61.3.344>
- [219] Mellgren C, Sternesjö A. Optical immunobiosensor assay for determining enrofloxacin and ciprofloxacin in bovine milk. *J AOAC Int* 1998; 81(2):394–7.
- [220] Abjean JP, Lahogue V. Planar chromatography for quantitative determination of ampicillin residues in milk and muscle. *J AOAC Int* 1997; 80(6):1171–6.
- [221] Pérez B, Prats C, Castells E, Arboix M. Determination of cloxacillin in milk and blood of dairy cows by high-performance liquid

- chromatography. *J Chromatogr B Biomed Sci Appl* 1997; 698(1-2):155-60; [https://doi.org/10.1016/S0378-4347\(97\)00289-2](https://doi.org/10.1016/S0378-4347(97)00289-2)
- [222] Dudriková E, Sokol J, Burdová O, Turek P, Cabada R. Oxytetracycline in the milk of dairy cows with clinical signs of mastitis during the lactation period. *Vet Med (Praha)* 1996; 41(11):329-33.
- [223] Krcmár P, Růzicková V. High-voltage electrophoretic identification of residual antibiotics in milk. *Vet Med (Praha)* 1996; 41(3):93-5.
- [224] Anderson KL, Moats WA, Rushing JE, Wesen DP, Papich MG. Ampicillin and amoxicillin residue detection in milk, using microbial receptor assay (Charm II) and liquid chromatography methods, after extra-label administration of the drugs to lactating cows. *Am J Vet Res* 1996; 57(1):73-8.
- [225] Carson MC, Breslyn W. Simultaneous determination of multiple tetracycline residues in milk by metal chelate affinity chromatography: collaborative study. *J AOAC Int* 1996; 79(1):29-42.
- [226] Harik-Khan R, Moats WA. Identification and measurement of beta-lactam antibiotic residues in milk: integration of screening kits with liquid chromatography. *J AOAC Int* 1995; 78(4):978-86.
- [227] Blanchflower WJ, Hewitt AS, Kennedy DG. Confirmatory assay for the simultaneous detection of five penicillins in muscle, kidney and milk using liquid chromatography-electrospray mass spectrometry. *Analyst* 1994; 119(12):2595-601; <https://doi.org/10.1039/AN9941902595>
- [228] Parker RM, Patel RK. Determination of tilmicosin in ovine milk using high-performance liquid chromatography. *Analyst* 1994; 119(12):2577-9; <https://doi.org/10.1039/an9941902577>
- [229] Straub R, Linder M, Voyksner RD. Determination of beta-lactam residues in milk using perfusive-particle liquid chromatography combined with ultrasonic nebulization electrospray mass spectrometry. *Anal Chem* 1994; 66(21):3651-8; <https://doi.org/10.1021/ac00093a019>
- [230] Van Eenennaam AL, Cullor JS, Perani L, Gardner IA, Smith WL, Dellinger J, et al. Evaluation of milk antibiotic residue screening tests in cattle with naturally occurring clinical mastitis. *J Dairy Sci* 1993; 76(10):3041-53.
- [231] Moretain JP, Boisseau J. Elimination of aminoglycoside antibiotics in milk following intramammary administration. *Vet Q* 1993; 15(3):112-7; <https://doi.org/10.1080/01652176.1993.9694386>
- [232] Roudaut B, Garnier M. Sulphonamide and dapsone residues in bovine milk following intramammary infusion. *Food Addit Contam* 1993; 10(4):461-8; <https://doi.org/10.1080/02652039309374169>
- [233] Krainock RJ. Prolonged milk residue in two cows after subcutaneous injections of penicillin at an extra-label dose. *J Am Vet Med Assoc* 1991; 198(5):862-3.
- [234] Seymour EH, Jones GM, McGilliard ML. Persistence of residues in milk following antibiotic treatment of dairy cattle. *J Dairy Sci* 1988; 71(8):2292-6; [https://doi.org/10.3168/jds.S0022-0302\(88\)79806-9](https://doi.org/10.3168/jds.S0022-0302(88)79806-9)
- [235] Zhou SN. Antibiotic residue in milk, milk products and its lasting time in milk secreted by sick cows in Jiangsu Province. *Chi J Prev Med* 1988; 22(3):167-9.
- [236] Arnold D, Somogyi A. Trace analysis of chloramphenicol residues in eggs, milk, and meat: comparison of gas chromatography and radioimmunoassay. *J Assoc Off Anal Chem* 1985; 68(5):984-90.
- [237] Hill BM, Small JM. Antibiotic residue release at the beginning of lactation following dry cow therapy. *Vet J* 1985; 33(7):105-7; <https://doi.org/10.1080/00480169.1985.35185>
- [238] Van der Lee JJ, Nouws JF, Bloemendal FW. Physicochemical methods for pharmacokinetic and residue analysis of chloramphenicol and degradation products in dairy cows. *J Vet Pharmacol Ther* 1982; 5(3):161-75.
- [239] Miura T, Kouno H, Kitagawa T. Detection of Residual penicillin in milk by sensitive enzyme immunoassay. *J Pharmacobiodyn* 1981; 4(9):706-10.
- [240] Wal JM, Peleraan JC, Bortes GF. High performance liquid chromatographic determination of chloramphenicol in milk. *J Assoc Off Anal Chem* 1980; 63(5):1044-8.
- [241] Inglis JM, Katz SE. Improved microbiological assay procedures for dihydrostreptomycin residues in milk and dairy products. *Appl Environ Microbiol* 1978; 35(3):517-20.
- [242] Johnson ME, Martin JH, Baker RJ, Parsons JG. Persistence of antibiotics in milk from cows treated late in the dry period. *J Dairy Sci* 1977; 60(10):1655-61; [https://doi.org/10.3168/jds.S0022-0302\(77\)84085-X](https://doi.org/10.3168/jds.S0022-0302(77)84085-X)
- [243] Gonzalo C, Carriedo JA, García-Jimeno MC, Pérez-Bilbao M, de la Fuente LF. Factors influencing variation of bulk milk antibiotic residue occurrence, somatic cell count, and total bacterial count in dairy sheep flocks. *J Dairy Sci* 2010; 93:1587-95; <https://doi.org/10.3168/jds.2009-2838>
- [244] Weaver L. Antibiotic residues in milk and meat: perceptions and realities. *Vet Med* 1992; 12:1222-8.
- [245] Singh S, Shukla S, Tandia N, Kumar N, Paliwal R. Antibiotic residues: a global challenge. *Pharma Sci Monitor* 2014; 5(3):184-97.
- [246] Hamann J, Tolle A, Hesscheu W. Antibiotic and sulfonamides. *Int Dairy Fed Bull* 1979; 113:43.
- [247] Mensah SE, Koudandé OD, Sanders P, Laurentie M, Mensah GA. Antimicrobial residues in foods of animal origin in Africa: public health risks. *Rev Sci Tech* 2014; 33:987-96, 975-86; <https://doi.org/10.20506/rst.33.3.2335>
- [248] European Union. Council Regulation (EEC) No. 2377/90 of 26 June 1990 laying down a Community procedure for the establishment of maximum residue limits of veterinary medical products in foodstuffs of animal origin. *Off J L* 1990; 224:1-8; <https://doi.org/10.1111/j.1467-9280.1990.tb00204.x>