Veterinary Medicine: Research and Reports

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REVIEW

Rate of Beta-Lactam Resistance and Epidemiological Features of *S. Aureus-Associated Bovine Mastitis* in Cross-Bred Ethiopian Cows: Systematic Review

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Background: Dairy cows get mastitis from a common infection called Staphylococcus aureus. Because of its broad distribution across diverse populations and capacity to acquire antibiotic resistance, this particular bacterial strain presents a serious threat to public health. The main goals of this study were to determine the beta-lactam resistance profile of *S. aureus* in Ethiopian dairy cows and to offer thorough epidemiological data.

Methods: We employed manual searches, Web of Science, PubMed Central, and Google Scholar HINARI for electronic bibliographic data.

Results: Twenty-six epidemiological studies were included in this systematic review. Of these studies, 12 articles in Oromia, 4 articles in Addis Ababa, 4 articles in Southern Nations, Nationalities, and People's (SNNPRS), 3 articles in Tigray, and 3 articles in Amhara region. The average prevalence *S. aureus* were 34.3% in Oromia, 40.2% in Amhara, 39.5 in AA, 40% in Tigray and 21% in SNNPRS. The antimicrobial resistance rate of *S. aureus*, specifically in relation to beta-lactam drugs, exhibited an average estimation. Notably, penicillin resistance reached a rate of 75%, while amoxicillin resistance stood at 67%. Furthermore, it was determined that, when treating S. aureus, the resistance rates to ampicillin and cephalosporin were 50% and 57%, respectively.

Conclusion: The results of this analysis have demonstrated a considerable rise in *S. aureus* prevalence and beta-lactam resistance within the Ethiopian geographic environment. This emphasizes the critical need for alternate therapeutic approaches and preventative measures in order to successfully lessen the disease's extensive spread and detrimental effects across the nation.

Keywords: antimicrobial resistance, *beta-lactam*, *bovine mastitis, S. aureus*, systematic review, veterinary epidemiology

Introduction

Bovine mastitis, a grave and substantial ailment, poses a considerable challenge to dairy production.[1,2] Particularly in low-income countries like Ethiopia, it demands special attention from farmers. Numerous factors have been linked to mastitis, including lower milk production, milk that is judged unsafe for human consumption due to antibiotic residues, veterinary expenses, and the eventual culling of long-term sick cows.[3] The categorization of bovine mastitis primarily revolves around the distinction between subclinical and clinical cases, as determined by the severity level.

Over 90% of Ethiopia's total milk production loss is attributed to subclinical mastitis, according to study made by scholars.[4,5] In addition, cross-breed dairy cows are predicted to cost 38 US dollars per lactation. Furthermore, it has an effect on public health since dairy products can shed zoonotic pathogens and their toxin, which poses a major risk to human health.[6] Mastitis, can result from a variety of illnesses caused by bacteria, fungi, and viruses. In domestic animals,

Received: 28 April 2023
Accepted: 8 February 2024
Published: 27 February 2024

mastitis can be caused by at least 137 etiological agents, with bacteria being the most common cause.[7] One of the most infectious bacteria that cause mastitis in cows and spoiling of milk is *S. aureus*.[8]

There is proof of the careless use of antimicrobial agents by medical professionals, unskilled practitioners, and others engaged in drug usage and animal husbandry in Ethiopia. Antibiotic resistance is also greatly influenced by elements related to the delivery of medication itself, such as an unfavorable length of treatment and mode of administration. Both in humans and animals, the incidence of staphylococcal infections has been steadily rising. The reason behind this trend is the increment in multidrug-resistant types of these illnesses, which has made treating them more difficult. There are several different processes underlying the emergence of antimicrobial resistance (AMR) in S. aureus. The most well-known resistance mechanisms include: antibiotics being inactivated by enzymes, changing the targets of antibiotics to reduce their affinity, antibiotics being trapped, efflux, pumps, and limited drug uptake through biofilm formation.[7–11]

It is essential to comprehend the complex interactions among these multifactorial and toxin-specific virulence variables in order to create successful treatment plans to combat *S. aureus* infections. By focusing on these elements, it may be possible to design new intervention strategies and preventative measures to counteract the pathogenicity of these adaptable bacteria. Future studies in this area will probably provide more information about the mechanisms behind *S. aureus* virulence and help develop mitigation methods for its harmful effects on human health.[10,11]

The continuous expression of several virulence factors in response to environmental stimuli during infections suggests the presence of global regulators, in which the expression of numerous unrelated target genes is controlled by a single regulatory determinant.[12] She and Sek genes are detected in isolates and cause subclinical mastitis(SCM), while the *CC479* strains of S. aureus are connected to severe clinical mastitis in cattle.[13] Mean while, sed and sej isolates are mainly associated with continual mastitis.[14] These regulators produce chemicals that aid in the survival of bacteria, allowing them to adapt to harsh settings. Drug resistance is a major public health risk associated with *S. aureus*. The death rate for people with drug-sensitive *S. aureus* infections is 64% lower than that of people with methicillin-resistant infections.

Methicillin resistance[15] is caused by the acquisition of the mecA gene and is typified by the synthesis of *PBP2A*, an alternative penicillin-binding protein. There is a limited affinity of this protein for beta-lactam antibiotics.[16] When it comes to dairy animals, Staphylococcus aureus usually affects the integument, nasal mucosa, and skull. But during milking time, an infected udder quarter serves as the main source of infection for non-infected animals. Depending on the developed standard state of the nation, this can happen through contaminated milkers hands or milking machines[17] separating *S. aureus* from other species by coagulase formation, mannitol fermentation, and trehalose usage is part of the identification and isolation procedures.[18] Staphylococcus aureus is the most common infectious and zoonotic pathogen in Ethiopia that causes mastitis and significantly lowers output. Numerous studies, undertaken in different places and times, have examined the prevalence of S. aureus infection in bovine mastitis, accounting for prevalence at the cow, herd, and quarter levels. Recent studies show that between 66.07% and 10% of both asymptomatic and symptomatic instances of bovine mastitis have S. aureus present.[19–21]

The purpose of this systematic review is aimed to offer useful information about S. aureus, a pathogen spread through milk, to experts in the fields of animal, human, and environmental health. It will function as a thorough information source for putting preventative and control measures, such as infection prevention, resistance reduction, and surveillance design, into practice on dairy farms. In both human and veterinary medicine, systematic reviews are frequently used to compile the results of several research studies. The combined proportion of the epidemiological distribution and the beta-lactam resistance profile of the S. aureus infection among Ethiopian dairy cows was, thus, the purpose of this review.

Methodology

The STROBIE (Preferred Reporting Items for Systematic Reviews and Meta-analysis) checklist (Supplementary file-1 STROBIE checklist for included cross-sectional studies) served as the basis for the systematic review. Based on the highlighted protocols, the checklists were utilized to verify that pertinent data from the chosen publications had been included.

Search Engine/Strategy

The systematic review was based on the STROBIE (Preferred Reporting Items for Systematic Reviews and Meta-analysis) criteria (Supplementary file-1 STROBIE checklist for included cross-sectional studies). The checklists used to confirm that the relevant data from the selected publications was incorporated in compliance with the protocols that were indicated. The literature search was conducted between November 20, 2021, and December 30, 2022. A comprehensive search strategy was independently devised by two authors (M.B. and B.M.) to locate included studies. Both manual methods and databases, such as PubMed, Web of Science, Google Scholar, and HINARI, were used for the literature searches. What is the prevalence or percentage of *S. aureus* infection among the bacteria that cause mastitis in Ethiopian dairy cows that are milked? How does this affect both clinical and subclinical mastitis? The CoCoPop (Condition, Context, and Population) paradigm was applied in order to locate relevant articles. The context was Ethiopia (Co), the condition was staphylococcus infection (Co), and the population was cows (Pop).

The search approach used a range of crucial keywords and Medical Subject Heading (MeSH) terms. At this point, epidemiology, mastitis/infection of the mammary gland, bovine/lactating cows, cross-sectional study, staphylococcus aureus, and staphylococcus infection are the MeSH terms used. Subsequently, pertinent terms and expressions were integrated, and the Boolean operator "AND /OR" was employed to do an online search. The search procedures that were used included Staphylococcus OR Staphylococcus infection OR Staphylococcus aureus AND (occurrence OR prevalence OR infection rate) AND (cows OR dairy cows OR) AND mastitis OR AND Ethiopia. The only language that could be published in was English. All identified studies were imported into End-Note 20 to remove duplicates.

Criteria for Selection of Articles

The following points were important considerations when selecting relevant studies such as all studies should have observational study designs, there should be precise estimations at the quarter- and cow-levels of the percentage of *S. aureus* infection in mastitis among bacterial pathogens; and studies was selected based on the occurrence of *S. aureus* in bovine species. All positive cases are chosen for SCM based on the primary clinical indicators and CMT. In the subsequent selection of all positive cases, the specimens that were cultivated, papers dictating *S. aureus* isolation and identification using conventional bacteriology techniques, the research was published in English, and the study was carried out in Ethiopia, were considered in their review work. Indexed and published papers that met the aforementioned inclusion requirements were chosen. Exclusion criteria included cohort and case control studies, case series, conventional reviews, experimental (clinical) research, and outbreak reports. Lastly, the data extraction process employed these inclusion and exclusion criteria (study screening strategy and reasons for exclusion). (Figure 1).

Data Extraction Tools

The form contained studies from which M.D. and B.M. separately extracted the following data: the first author's name, the year the study was conducted, the study design, the study regions, the geographic allocation, the number of animals, the number of CMT positive and culture positive quarters, and the actual prevalence of Staphylococcus aureus infection in cattle mastitis.

Quality Assessment and Evaluation of Study

The AMSTAR-2 (Supplementary file-2) quality evaluation was used in this review to evaluate the research protocols methodological quality and evidence strength in relation to the review question. The quality evaluation of the included studies in this systematic review and meta-analysis is what determines the outcomes (https://drive.google.com/file/d/186it7bH)

Data Synthesis and Statistical Analysis

Based on the papers that were examined, an estimate of the average prevalence of *S. aureus* in both clinical and subclinical instances of bovine mastitis was made using the SPSS software version 25. To ascertain the average prevalence of S. aureus, a subgroup calculation was carried out, taking into account the degree of mastitis, the "study year" and the study location. Three groups (earlier, middle, and latest) were created for the research year in order to track

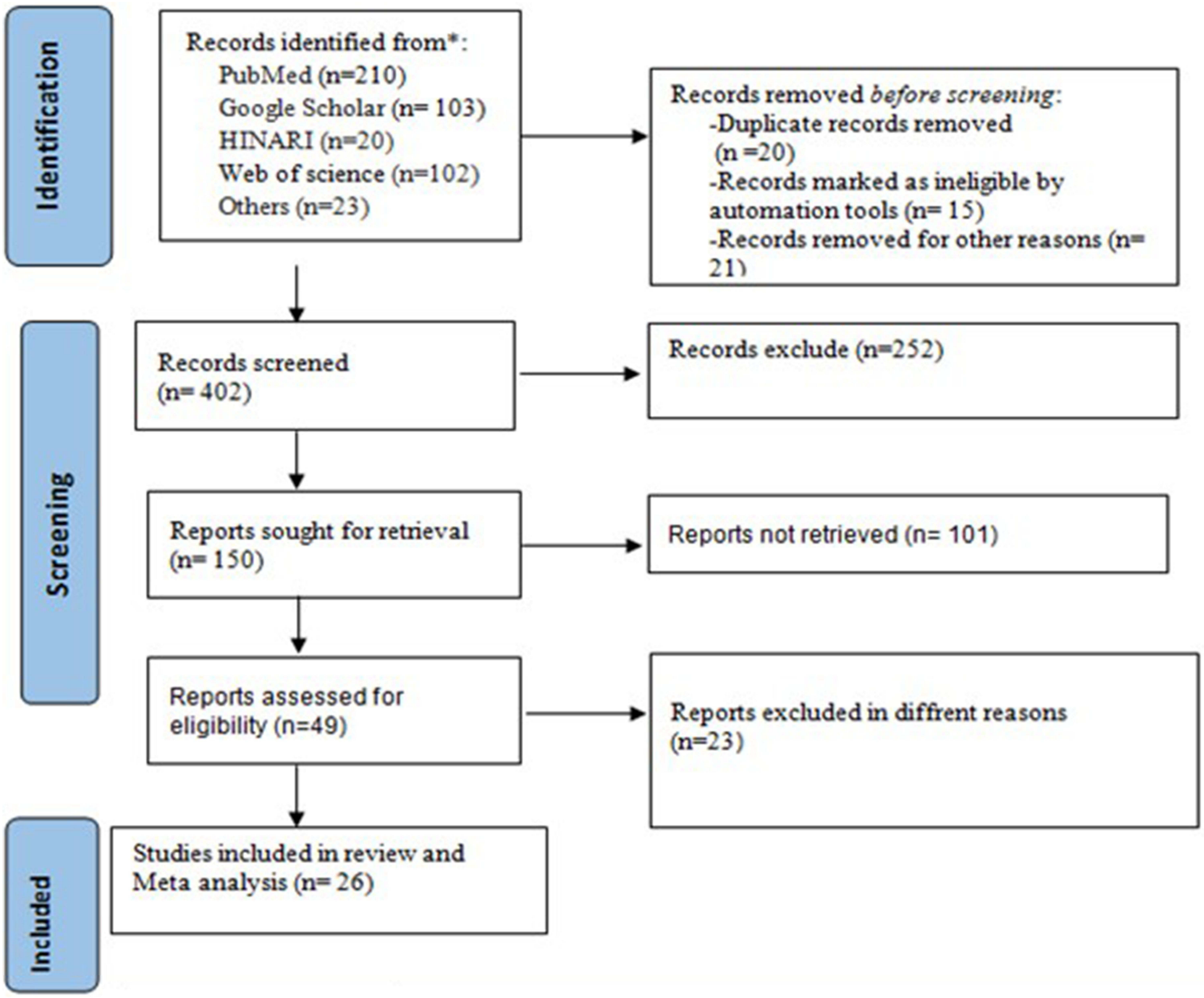

Figure 1 PRISMA flow chart for selection of included and excluded of studies.
Notes: PRISMA figure adapted from Page MJ, McKenzie JE, Bossuyt PM et al The PRISMA 2020 statement: an updated guideline for reporting systematic reviews. *BMJ*. 2021;372:n71. doi: 10.1136/bmj.n71. Creative Commons.[22]

the evolution of *S. aureus* prevalence in cows during the course of the study. Furthermore, depending on the pooled papers, research year categories were created, including groups like (≤2012), (2013–2017), and (≥2018).

Results

Search results for Quarter Wise Prevalence Studies

Figure 1 illustrates how 458 articles were read using a variety of extra techniques and electronic resources. Using duplicate removal and eligibility tagging, a total of fifty-six articles were eliminated. After the titles and abstracts were screened, a total of 252 papers were disqualified. 49 of the 150 objects that were reported were retrieved once eligibility was established. In the end, only 26 full-text publications for the synthesis of *S. aureus* could be found.

Characteristics of Included Studies

Publicly available reports of staphylococcal infection in bovine mastitis in cross-breed, nursing cows from Ethiopia are included in this review. The complete study consists of twenty-six (26) relevant studies that address *S. aureus* infection in both clinical and subclinical bovine mastitis. All the studies included in this review, with one exception, used a cross-sectional methodology. This review includes studies conducted in different regions of Ethiopia between 2008 and 2022. For every study included in this evaluation, the minimum sample size was 4119, and the largest was 1502.[23]

All of the included investigations used standard microbiological techniques to isolate S. aureus. These techniques are detailed by NMC.[1] Furthermore, the usual procedures for bacterial isolation and identification, bacteriological culture, and CMT for subclinical mastitis were used. In order to assess the pooled proportion of *S. aureus* infection in Ethiopia, 8441 cows total and 10,346 milk samples at the quarter level were used. The apparent prevalence of *S. aureus* in bovine mastitis ranged from 10 to 66 point six percent. The detailed elements of the investigation are presented in Table 1 and Figure 2. According to Hailemelekot et al (2018), 66% of *S. aureus* cases were detected in the Amhara area.[24] However, according to Balemi et al,[19] the Oromia regional state had the lowest frequency (10%) in 2018.

The extracted data pertaining to the primary components of the Materials and Methods sections of the reviewed papers is compiled in Table 2. The aspects that were most thoroughly explained were sample size calculations, study designs, ethical issues, and suitable explanations of sampling, environments, and correct laboratory practices (isolation techniques). On the other hand, the farm's management system, housing arrangement, hygienic methods, and statistical management of the results were all either incompletely explained. In relation to the study animals descriptions (eg g. Risk factors), it was determined that this element lacked clarity.

Geographical Distribution of Bovine Mastitis Associated *S. Aureus* in Ethiopia

According to Figure 3 and Table 3, the Amhara and Tigray regions had the highest average prevalence of *S. aureus* (40%), followed by AA (39 point 5%), Oromia (34 point 3%), and SNNPRS (21%). Twelve of the 26 investigations were conducted in the region of Tigray, three in Amhara, four in AA, four in SNNPRS, and three in Oromia.

Table 1 Characteristics of Included Studies (n=26)

Study Name	Year	Region	Location	No. cows	TQE	NQP+	TCP+	Staph+	OBP+	PS*
Abebe et al[21]	2016	Oromia	Southern	529	2026	729	172	88	84	51
Beyne et al[25]	2020	SNNPRS	Southern	686	1662	132	64	26	38	40
Mekibib et al[26]	2008	AA	Central	107	428	192	153	72	81	47
Tesfaye et al[27]	2015	Oromia	Central	384	1536	484	121	37	84	30
Wubshet et al[28]	2013	Oromia	Southern	28	112	112	66	20	46	30
Yohanes and Alemu[29]	2018	SNNPRS	Sothern	245	980	173	51	11	40	23
Zeryehun and Abera[30]	2015	Oromia	Eastern	384	1536	877	187	45	142	24
Tekle and Berihe[31]	2011	SNNPRS	Southern	384	384	70	52	11	41	21
Birhanu et al[5]	2016	AA	Central	262	1048	170	153	69	84	45
Bitew et al[32]	2010	Amhara	Northern	302	1208	134	79	16	63	20
Demissie et al[31]	2015	Tigray	Northern	360	1440	229	179	55	124	30
Fesseha et al[33]	2019	Oromia	Southern	384	1536	536	144	58	86	40
Hailemelekot et al[24]	2018	Amhara	Northern	302	1208	126	112	74	38	66
Balemi et al[19]	2018	Oromia	Southern	60	240	41	10	1	9	10
Duguma et al[34]	2009	AA	Central	90	340	275	180	78	102	43
Abera et al[20]	2008	Oromia	Southern	245	960	288	217	61	156	28
Seid et al[35]	2014	Oromia	Southern	358	1422	490	83	37	46	44
Mekonen and Tesfaye[36]	2008	Oromia	Sothern	206	824	790	95	14	81	14
Abunna et al[37]	2008	AA	Central	331	1324	146	71	15	56	21
Belayneh et al[38]	2008	SNNPRS	Northern	303	1172	244	183	59	124	32
Girma et al[23]	2010	Oromia	Eastern	384	1536	1502	121	43	78	35
Adane et al[39]	2010	Oromia	southern	460	1840	712	641	208	433	32
Bihon et al[40]	2017	Amhara	Northern	334	1054	238	50	17	33	34
Abebe et al[41]	2018	Oromia	Southern	686	2633	773	307	176	131	57
Zenebe et al[42]	2011	Tigray	Northern	322	1288	696	698	361	337	52
Haftu et al[43]	2009	Tigray	Northern	305	1220	187	128	46	82	35

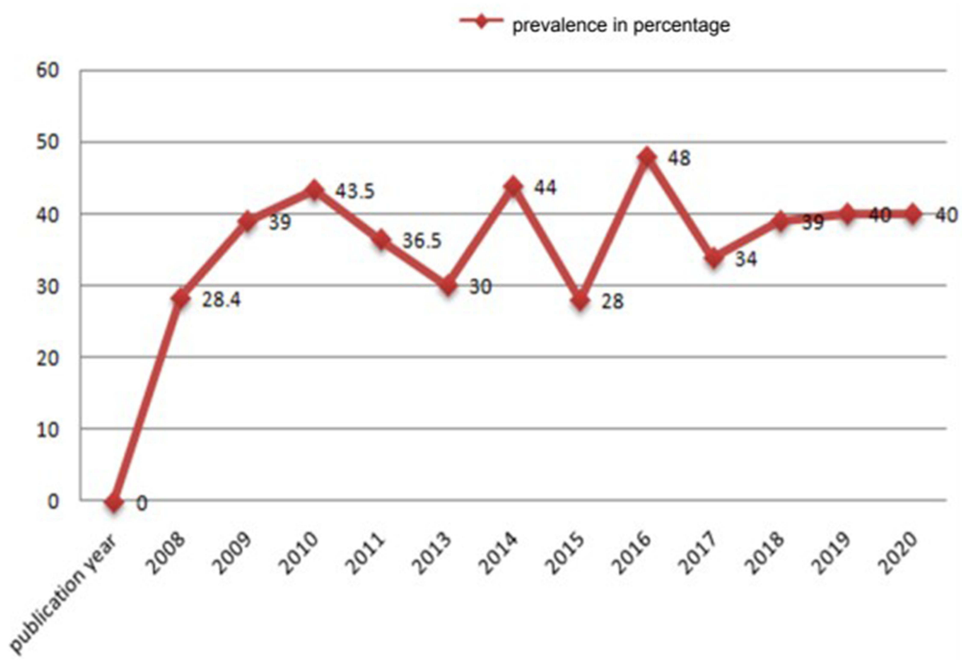

Figure 2 Prevalence of S. aureus in the respect of the study year.
Notes: The horizontal -axis represents the publication year listed while the y-axis is average prevalence of S. aureus.

Prevalence of *S. aureus* in Different Study Year Categories

>2018 (43%) was the study year category with the greatest average proportion of *S. aureus* in mastitis, followed by <2012 (32%), and 2013–2017 (34%). Figure 4 illustrates how *S. aureus* infections in mastitis became more common over time.

The Average Prevalence of *S. Aureus* in Clinical and Subclinical Mastitis

As depicted in Figure 5, the staphylococcal infection rate in subclinical mastitis was 84%, but it was only 16% in clinical mastitis. Table 4 demonstrates that most research employed the California Mastitis Test to identify subclinical mastitis

Table 2 Studies Distributed According to Clarity Scores of the Elements of the Materials and Methods Sections

Materials and Methods	Clarity Score		
	0	1	2
Ethical approval	7.7%	15.4%	80.8%
Sample size determination			100%
Proper clarification of sampling and setting(eg map)	7.6%	15.4%	77%
Proper Laboratory methods(eg biochemical test used)	0	7.7%	92.3%
Proper description of study design	0	0	100%
Description of study animals(eg Risk factors)	30.7%	11.8%	57.5%
Description of management, housing system and hygienic practice of the farm	15.4%	11.5%	73.1%
Proper Statistical methods and measurements(eg odds ratio, Relative Risk)	0	23.1%	76.9%

Notes: 0, information not provided; 1, information incomplete; 2, information clear.

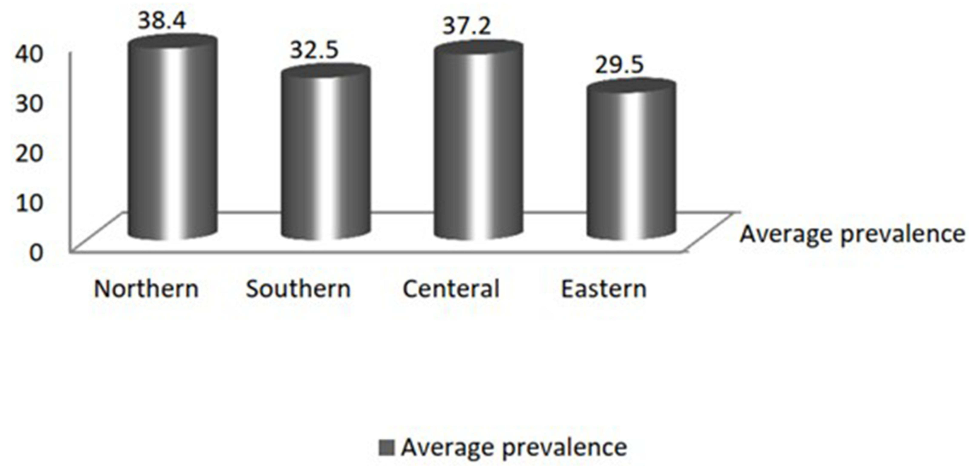

Figure 3 Geographical distribution of *S. aureus* in Ethiopia.

and clinical observation to identify clinical mastitis. Abebe et al,[21] discovered that the highest percentage / prevalence (48%) of *S. aureus* in subclinical mastitis, and Zeryehun and Abera,[30] discovered that the prevalence of clinical mastitis was the lowest at 1%.

Beta Lactam Antimicrobial Resistance Rate of *S. aureus*

Antibiotics are the sole known treatment for bovine mastitis in Ethiopia. The most often used class of antibiotics is specifically beta-lactams, which include ceftriaxone, cefotaxime, ampicillin, penicillin, and amoxicillin. The percentage of glands that experience bacteriological cure following antimicrobial therapy for clinical mastitis has been observed to vary widely.[44]

The pace of recovery is affected by bacterial factors, such as antibiotic resistance and strain, management variables, and cow-specific factors. These variables also affect the proportion of treatments that are successful.[25,45–47] The existence of plasmids of various sizes has been connected to a number of antimicrobial resistances. It has been discovered that *S. aureus* possesses two main plasmid types, which may be involved in the pathogenicity and/or antibiotic resistance of the bacteria. Agar disc-diffusion studies, resistance-encoding gene identification, and broth dilution testing are just a few of the methods that can be used to assess antimicrobial resistance.

The beta-lactam antibiotic resistance rate of *S. aureus* linked to bovine mastitis is the subject of 14 investigations (Table 5) in total (containing ampicillin, cephalosporin resistance, penicillin, and amoxicillin). Most of the included papers offer a comprehensive account of the whole pathogen isolation procedure in cases of both clinical and subclinical bovine mastitis, together with the results of many antibiotic susceptibility testing. A minimum of one *S. aureus* isolate

Table 3 Mean Prevalence of the *S. aureus* with Number of Studies in Regions of Ethiopia

Regions	No of Studies	Average prevalence (%)	References
Oromia	12(46.2%)	34	Abebe et al,[21] Tesfaye et al,[27] Wubshet et al,[28] Zeryehun and Abebe,[30] Abera et al,[20] Girma et al,[23] Adane et al,[39] Seid et al,[35] Mekonen and Tesfaye,[36] Fesseha et al,[33] Abebe et al,[41] Balemi et al[19]
Amhara	3(11.5%)	40	Bihon et al,[40] Hailemelekot et al,[24] Bitew et al[32]
SNNPRS	4(15.4%)	29	Yohanes and Alemu,[29] Tekle and Berihe,[31] Beyne et al,[25] Belayneh et al[38]
AA	4(15.4%)	39.5	Mekibib et al,[26] Duguma et al,[34] Birhanu et al,[5] Abunna et al[37]
Tigray	3(11.5%)	40	Haftu et al,[43] Zenebe et al,[42] Demisse et al[31]

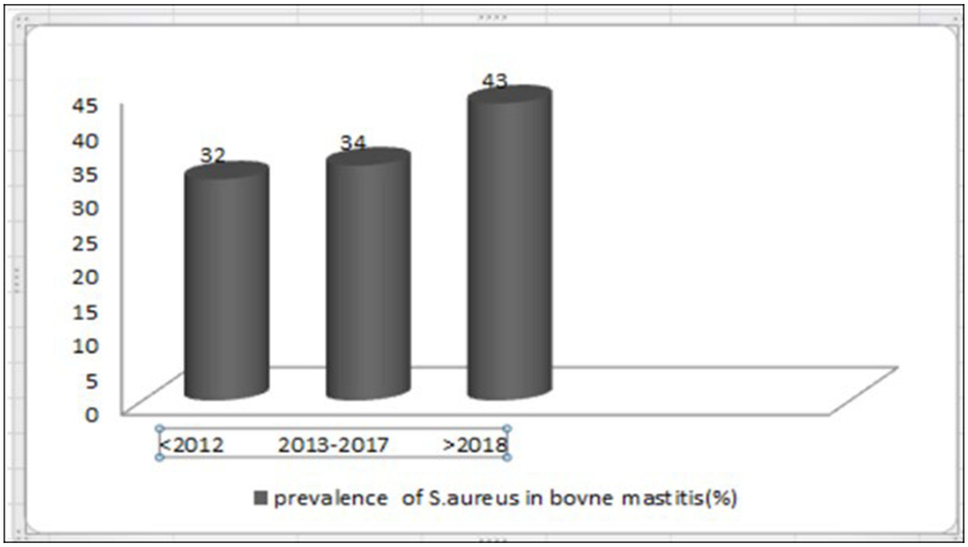

Figure 4 Prevalence of *S. aureus* in different study year categories in Ethiopia.

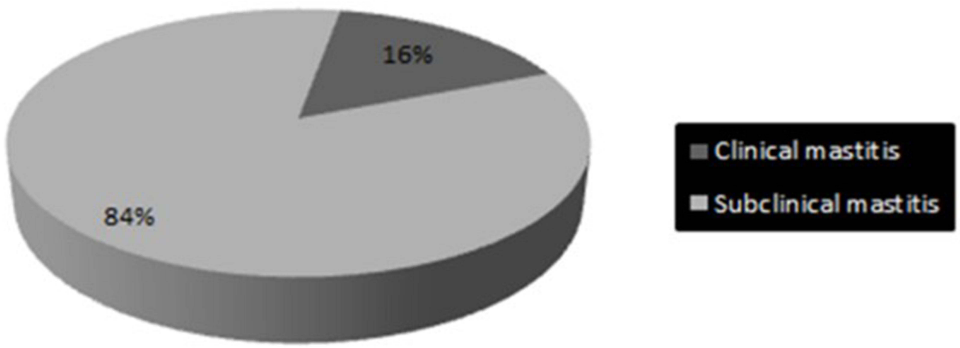

Figure 5 Average prevalence of *S. aureus* in clinical and subclinical mastitis in Ethiopia.

has been reported from the selected publications, and they ought to have included one beta-lactam antibiotic. There is only one paper that appears more than once in this systematic review.

Among the 14 included trials, the resistance rate of *S. aureus* to various beta lactam antibiotics ranged from 0% to 100%.

Of the total studies (14), two of those[48,57] found that 100% of the patients had penicillin resistance when treating *S. aureus* mastitis in cattle. Nonetheless, a study of 52 found that penicillin was 100% successful in getting rid of S. aureus. This study includes cefoxitin, ceftriaxone, and cefotaxime among other cephalosporins. Cefotaxime and cefoxitin showed the highest resistance rates (80%) among the three cephalosporins. When treated with penicillin, *S. aureus* had the highest average resistance rate (75%) to that of amoxicillin (67%), cephalosporin (57%), and ampicillin (50%), in that order (Figure 6).

Discussion

These 26 studies provide an average prevalence of 35.4% (95% confidence interval: 0.31–0.41) among bacterial pathogens, with an emphasis on *S. aureus* in Ethiopia. Girma et al[28] in Ethiopia's Tigray regional state reported similar results. The overall percentage of *S. aureus* linked to bovine mastitis was lower than the results of several separate investigations carried out in Ethiopia, including 51% by Abebe et al,[21] 47% by Fessha.[33] 66% by Hailemelekot,[24] and 45% by Birhanu et al.[5] The total percentage of the pathogen in mastitis in domestic cows, however, was higher than in several of the included studies, among which Tesfaye et al (24%),[27,28] Zerihun et al (21%), and Abebe et al[30] reported 21%.[20]

Table 4 Average Prevalence of Bovine Mastitis Associated *S. Aureus* in the Level of Mastitis

Authors	LM	ID_X	FD	P	ST	PE	N	TP
Abebe et al[21]	Clinical mastitis	CS	Culture Isolation	4	88	0.04	172	0.023
	Subclinical mastitis	CMT	Culture Isolation	84	88	0.95	172	0.48
Mekibib et al[26]	Clinical mastitis	CS	Culture Isolation	6	72	0.08	153	0.04
	Subclinical mastitis	CMT	Culture Isolation	66	72	0.92	153	0.43
Wubshet et al[28]	Clinical mastitis	CS	Culture Isolation	2	20	0.10	66	0.03
	Subclinical mastitis	CMT	Culture Isolation	18	20	0.95	66	0.27
Yohannes and Alemu[29]	Clinical mastitis	CS	Culture Isolation	5	11	0.45	51	0.10
	Subclinical mastitis	CMT	Culture Isolation	6	11	0.55	51	0.12
Zeryehun and Abera[30]	Clinical mastitis	CS	Culture Isolation	2	66	0.03	187	0.01
	Subclinical mastitis	CMT	Culture Isolation	64	66	0.97	187	0.34
Bitew et al[32]	Clinical mastitis	CS	Culture Isolation	4	16	0.25	79	0.05
	Subclinical mastitis	CMT	Culture Isolation	12	16	0.75	79	0.15
Demissie et al[31]	Clinical mastitis	CS	Culture Isolation	7	55	0.13	179	0.04
	Subclinical mastitis	CMT	Culture Isolation	48	55	0.87	179	0.27
Fesseha et al[33]	Clinical mastitis	CS	Culture Isolation	11	20	0.55	144	0.08
	Subclinical mastitis	CMT	Culture Isolation	9	20	0.45	144	0.06
Hailemelekot et al[24]	Clinical mastitis	CS	Culture Isolation	13	45	0.28	187	0.07
	Subclinical mastitis	CMT	Culture Isolation	32	45	0.71	187	0.17
Girma et al[23]	Clinical mastitis	CS	Culture Isolation	25	43	0.58	128	0.19
	Subclinical mastitis	CMT	Culture Isolation	18	43	0.42	128	0.14

(*Continued*)

Table 4 (Continued).

Authors	LM	IDx	FD	P	ST	PE	N	TP
Haftu et al[43]	Clinical mastitis	CS	Culture Isolation	3	46	0.07	169	0.02
	Subclinical mastitis	CMT	Culture Isolation	43	46	0.93	169	0.25
Duguma et al[34]	Clinical mastitis	CS	Culture Isolation	5	78	0.06	183	0.03
	Subclinical mastitis	CMT	Culture Isolation	73	78	0.94	183	0.39
Belayneh et al[38]	Clinical mastitis	CS	Culture Isolation	5	59	0.08	121	0.04
	Subclinical mastitis	CMT	Culture Isolation	54	59	0.92	121	0.44

Notes: ST is sum of positive samples in both clinical and sub clinical mastitis; N is total sample of animals examined; PE is percentage of positive cases respected to positive cases; TP is prevalence of clinical and subclinical mastitis with respect to total sample examined; IDx & FD is initial and final diagnosis.
Abbreviations: LM, level of mastitis; P, Positive; ST, sub-total; CS, clinical sign, MT, California mastitis Test.

Table 5 Summary of Various Beta-Lactam Resistance for *S. aureus* in the Treatment of Bovine Mastitis (n=14)

Author	Antimicrobials	SA+ Isolated	Resistance	Susceptible	percentage
Ayana et al[48]	Penicillin	110	110	0	1.000
	Amoxicillin	110	65	45	0.590
	Ampicillin	110	57	53	0.520
Tassew et al[49]	Penicillin	53	0	53	0.000
	Cefoxitin	53	28	25	0.470
	Amoxicillin	53	53	0	1.000
Gebremedhin et al[50]	Ampicillin	40	38	2	0.950
	Amoxicillin	40	38	2	0.950
	Cefotaxime	40	32	8	0.800
Reta et al[51]	Penicillin	29	28	1	0.034
	Amoxicillin	29	10	19	0.345
Tesfaye et al[27]	Amoxicillin	12	9	3	0.750
	Ceftriaxone	12	7	5	0.583
Mekonen et al[36]	Penicillin	17	14	3	0.824
	Ampicillin	17	3	14	0.176
Getahun et al[52]	Penicillin	85	45	40	0.530
	Ampicillin	85	38	47	0.450

(*Continued*)

Table 5 (Continued).

Author	Antimicrobials	SA+ Isolated	Resistance	Susceptible	percentage
Sori et al[53]	Penicillin	86	75	11	0.872
	Amoxicillin	86	40	46	0.460
Moges et al[54]	Penicillin	27	22	5	0.815
	Amoxicillin	27	22	5	0.810
Haftu et al[55]	Penicillin	46	38	8	0.830
	Ampicillin	46	14	3	0.304
Belayneh et al[38]	Penicillin	59	38	21	0.650
	amoxicillin	59	37	22	0.620
Belayneh et al[38]	Penicillin	32	24	8	0.750
	amoxicillin	32	24	8	0.750
Elemo et al[56]	Ampicillin	112	62	50	0.550
	Amoxicillin	112	59	53	0.530
	Cefoxitin	112	65	47	0.580
	Penicillin	112	97	15	0.870
Overvliet et al[57]	Penicillin	32	32	0	1.000
	Cefoxitin	32	10	22	0.300

In cases of both clinical and subclinical mastitis, the sub-total occurrence of *S. aureus* infection varied depending on the study year: 32% (>2012), 34% (2013–2017), and 43% (> 2018) for each study year group. This systematic review found that the rate of S. aureus infection in bovine mastitis increased when the included publications were categorized

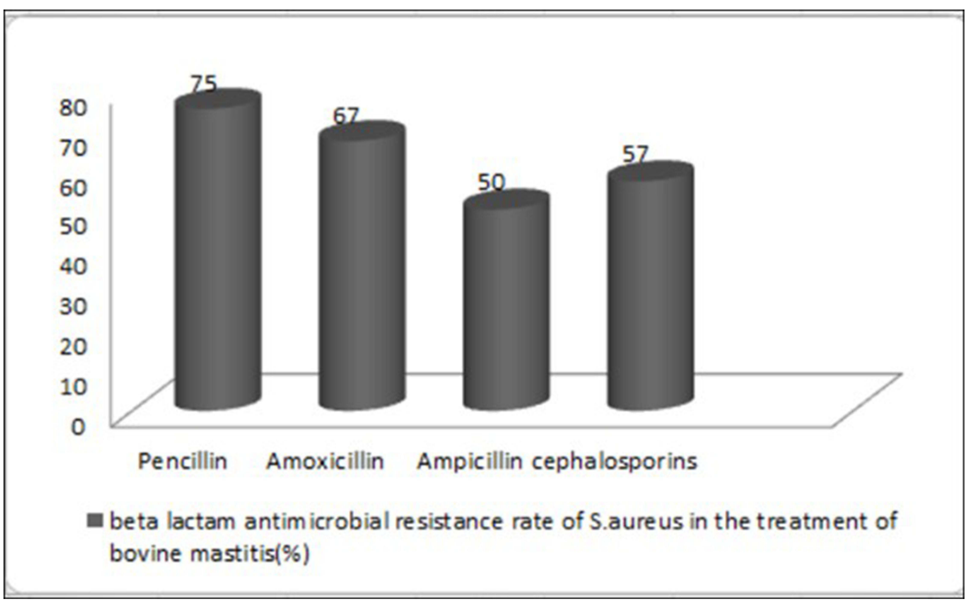

Figure 6 Beta lactam antimicrobial resistance rate of *S. aureus* in the treatment of bovine mastitis.

based on the study year. It is estimated that approximately 50% of *S. aureus*-induced mastitis generate β-lactamase, which may be due to increased antibiotic resistance via a variety of mechanisms.[47] The proliferation of resistant strains in people, animals, and the environment may be related to this. Contributing causes could also include Ethiopia's restricted access to therapeutic treatment and the underuse of antibiotics in veterinary medicine. The development of *S. aureus* biofilms in cow mastitis is likewise associated with a reduction in antibiotic sensitivity. This is explained by a decrease in the metabolic activity of the bacteria within biofilms and a reduction in the amount of antibiotics that pass through the biofilm matrix.[58] There are other circumstances as well, like sub-inhibitory antibiotic concentrations. Moreover, lactose and proteases found in milk promote the growth of *S. aureus* biofilms inside the mammary gland of cows.[59,60]

The Amhara Region had the highest percentage of *S. aureus* infections (40.2%) among the study areas, while the SNNPRS region had the lowest (21%). This may have to do with the average annual relative humidity, the cleanliness of the farming system, and the prudent use of antibiotics.

Moreover, the production and consumption of raw milk and other dairy products often take place in unhygienic conditions in Ethiopia.[61] Consequently, there is an extremely high chance of coming into contact with *S. aureus* as a result of consuming dairy products.[62] Research conducted in Ethiopia has demonstrated that *S. aureus* is present in milk at several points throughout the milk value chain. This phenomenon may be explained by contamination from mastitis-affected cows, cross-infection of milk at collection sites from contaminated milk from infected farms, improper handling practices, and use of unclean equipment.[63]

Within the global context, this particular study found that the mean incidence of S. aureus-associated bovine mastitis (35.4%) was almost identical to the percentage found in a study conducted in China (36.23%) by Wang et al[64] The estimated percentages for the US, Kenya, and Canada are as follows: 20.8–23.3% in the US, 20–22% in Canada, and 15.7% in Kenya.[65] However, the result was lower than Elhaig and Selim's claimed 56.7%, with[66] in Nigeria.

During milking, *S. aureus* spreads among cows; thus, it is necessary to work together to minimize the spread of the infection to healthy animals. *S. aureus* isolates from cows are also a major source of foodborne illnesses, and raw milk and bulk tank products are crucial conduits for the spread of infection to people. Researchers in Ethiopia have shown that adult milkers between the ages of 30 and 40 had higher prevalence of *S. aureus* on their hands. These factors included inadequate udder cleaning, not washing hands before milking, using a shared towel, not dipping the teat after milking, routinely disinfecting the milking area, and lacking knowledge about the contagious nature of *S. aureus* and MRSA. Additionally, farms with semi-intensive management systems, inadequate barn drainage systems, and cows who had previously been exposed to mastitis showed greater prevalence of the organism.[67]

This systematic study revealed that, in relation to the degree of mastitis, the average occurrence of *S. aureus* infection was higher in subclinical mastitis (26%) than in clinical mastitis in cows (5%). As a result, our finding demonstrated that *S. aureus* infection has a significant economic impact on Ethiopia's dairy industry, as subclinical mastitis is the main obstacle facing the industry in poor nations.[68] Due to decreased milk quality and production, *S. aureus* is a very opportunistic infection that usually co-occurs with subclinical mastitis and results in large economic losses.[69] It has been demonstrated that intramuscular infection by CC97 strains in nursing cows can lead to asymptomatic, subclinical, or chronic infections, making pathogen control in dairy herds more challenging.[70]

Despite significant variance in the overall rate of resistance among different types of antimicrobial drugs, *S. aureus* resistance to these agents poses a significant concern. According to the epidemiological estimate, 68% of Ethiopians were resistant to beta-lactam antibiotics overall. This rate is quite high, and may be caused by the production of beta-lactamase by S. aureus, which degrades the beta-lactam ring in the drug. Another possible reason could be a changed PBP with reduced affinity for most beta-lactam antibiotics.

S. aureus had a 75% beta-lactam resistance rate to penicillin, a 67% rate to amoxicillin, a 57% rate to cephalosporin, and a 50% rate to ampicillin. The penicillin resistance to *S. aureus* was the highest. This might be because penicillin is widely available and utilized. Even non-professionals (farmers, drug dealers, and animal owners) possess penicillin, which they self-administer without understanding the proper dosage or timing.[71] Compared to other beta lactam medicines, *S. aureus* had the highest resistance to penicillin in the current investigation. As reported by Gianneechini et al,[72] André et al,[73] Turutoglu et al,[74] Kalmus et al,[75] Sakwinska et al,[76] Peles et al,[77] Jørgensen et al,[78] Anderson et al,[78] and Tenhagen et al,[79] respectively, this percentage was higher than the values reported in Argentina (47.6%), Brazil (69.9%), Turkey (62%), Estonia (61%), France (30%), Hungary (30%), Germany (17%), the United States (10%), and Norway (6%), respectively. However, the percentage of resistance exhibited a lesser magnitude in comparison to the values that have been previously documented in, Tigray (90%),[80] Addis Ababa (95.3%),[81] Hawassa (100%),[82] Iran (100%),[83] India (74.7%)[84] and 80% in Sweden.[85]

The results of the systematic review show that *S. aureus* had a 50% mean rate of ampicillin resistance. Our results, which are somewhat inferior to those of prior Ethiopian research on ampicillin resistance in Tigray (100%) and Hawassa (70.9%),[86] it was shown that *S. aureus* had the lowest level of ampicillin resistance (50%), in this particular investigation. However, it has been noted that ampicillin resistance may increase to 76.1–89.7% in Japan.[87] The majority of S. aureus isolates from bovine mastitis in Nepal showed total resistance (100%) to ampicillin (73.2%), whereas in Uganda (73.2%), India (74.42%), and Nepal (20.5%) showed resistance to ampicillin.[88]

In order to prevent antibiotic resistance and minimize the use of antibiotics, society must be empowered through education. The aforementioned therapies are required under the current standard guidelines for the use of antibiotics. The objective areas also include continuing professional development and pre- and in-service education for health professionals. The public and society have been empowered through the dissemination of mass media information regarding the usage of antibiotics and resistance. The system's ability to manage the threats that AMR has introduced is still lacking.

Thus, continuous intervention for scaling up is necessary for both AMR containment and prevention. Empowerment and education remain crucial strategies for stopping and containing MRSA. MRSA containment and prevention require a coordinated and integrated approach at the global, institutional, national, and individual levels. A comprehensive, evidence-based response approach is necessary due to the multidimensional character of MRSA, which encompasses biological, behavioral, technical, economic, regulatory, and educational components. Preventive and control measures must be put into place in healthcare facilities as well as the general public in order to lessen the danger of infection and the need for antibiotics. This will help to stop the emergence of resistant strains, which need to be quickly found and contained to stop them from spreading to other areas. In order to effectively address the challenges posed by MRSA, foster stewardship practices, and drive innovation, collaboration among all sectors is important.

Conclusion

The thorough investigation's findings demonstrate the widespread distribution of S. aureus, with particularly high sub-group average prevalence in the Amhara and Tigray regions. Furthermore, a rise in S. aureus prevalence in recent years has been shown by sub-group calculation depending on study year. The incidence of S. aureus in subclinical mastitis in dairy cows is five times higher than in clinical mastitis. In general, S. aureus exhibits a high rate of beta lactamase resistance; however, in cases of mastitis in local breed cattle, the rate of resistance to Penicillin is highest. The relevance for the economy and public health is shown by the prevalence of S. aureus in subclinical mastitis. Veterinarians, medical professionals, veterinary pharmacists, farm laborers, milkers, and consumers of raw milk must thus make it a top priority to control and prevent S. aureus in bovine mastitis while also lowering the incidence of beta-lactam resistance.

Data Sharing Statement

The datasets generated during and/or analyzed during the current study are available from the corresponding author on reasonable request.

Acknowledgments

We would like to acknowledge these authors in the included studies in this systematic review.

Author Contributions

Whether it was through ideation, study design, execution, data acquisition, analysis, and interpretation, or all of these areas combined, all authors made a significant contribution to the work reported. They also agreed on the journal to which the article was submitted, helped draft, revise, or critically review the article, and approved the final version that was published.

Disclosure

The authors report no conflicts of interest in this work.

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