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The Distribution and Drug Resistance Characteristics of Methicillin Resistant *Staphylococcus aureous* to be Public and Animal Health Burdon in Ethiopia: Meta-Analysis

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ABSTRACT

Introduction: Antimicrobial resistance to specific antibacterial drugs in bacteria have led many drugs of choice ineffective against pathogens. Methecillin resistant *S.aureus* (MRSA) is one of the pathogens, which looses sensitivity to Methicillin. Methicillin has been considered as the drug of choice of choice to treat infections caused by β-lactams and other antibiotics resistant S. aureus.

Objectives: The objectives of the current study were to analyse the prevalence of MRSA in S. aureus isolates from different sources of samples and to assess the risk factors associated with the prevalence. The multidrug resistance pattern of the pathogen was also one of the outcome of interest of the review.

Methods: The original research articles were collected from PubMed and PMC databases from 12th to 14th December 2021. The English language articles conducting on MRSA prevalence in Ethiopia were included in the analysis. Relevant data were extracted, coded and displayed on Excel spreadsheet. The pooled prevalence of MRSA was determined per S. aureus isolates. The analysis were made by using R statistical software at 95% CI.

Result: 79 research eligible articles were selected for the meta-analysis. 26930 samples were collected from different sampled materials. Of these 4219 (15.65%) were S. aureus positive of which 1695 were found MRSA strains. The overall pooled prevalence of MRASA in S. aureus was found to be 40%. The pooled prevalence of MRSA in human, animal, food and environment was 38%,15%,77%,and 54% respectively. The strain was determined significantly highest in food and environment than in animal and human samples ($p<0.05$). The subgroup analysis based on the health status of the individual in samples of human indicated that MRSA was significantly prevalent in patients than in health individuals ($p<0.05$). The assessment of MDR pattern of MRSA revealed that it was highly resistant to cefuroxime (100%), Tobramycin (100%), Neomycin (99%) and Penicillin (92%), Pipracilin (91%), Erythromycin (88%), Bacitracin(84%) and Amoxacilin-clavulanicacid (80%). In contrast Clindamycin, chloramphenicol, Amikacin, vancomycin, Knamycin and Ceftriaxone with pooled resistance rates of 21%, 22%, 27% , 20%, 25% and 30% respectively were antibiotic of relatively better effective.

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Introduction

Staphylococcus aureus (*S.aureus*) is a Gram positive grouped spherical (cocci) bacteria widely distributed in the world. It resides, as microfilora in the mucosal cavities and on the skin of the hosts without harming them. Researchers have isolated it from hand, nasal, buccal cavity and urogenital organs. However, in some specific conditions, *S.aureus* can be associated with disease conditions as an opportunistic pathogen. As the result it may cause diseases ranging from simple diseases such as pimples and boils to serious infections such as wound infections, pneumonia, and or septicaemia, which result in life-threatening illness particularly in immune compromised patients [1].

The pathogenicity of the *S. aureus* attributes to its antibiotic resistance, enterotoxogenicity, biofilm formation and other virulence factors including adherence factors, nucleases, proteases, lipases, hyaluronidase, and collagenase productions. In addition, S. aureus is becoming important in that it has developed resistance to commonly used antibiotics including methicillin. Methicillin has been used to treat β-lactam resistant *S.aureus* infections. Such characteristics of the microbe made it to be nearing to one of the most non-treatable pathogenic microbe in the globe. Methicillin resistant *Staphylococcus aureus* (MRSA) has emerged and increased its intensity to be one of the global issues of health concerns [2].

Furthermore, studies have found that MRSA strains are resistant to all beta-lactam antibiotics (including penicillin G, ceftiofur sodium, Cloxacillin, cephapirin, and ampicillin) and other antibacterial agents such as tetracycline and sulfonamides [1]. Despite the fact that Vancomycin is the drug of choice for treatment of MRSA infections, studies revealed MRSA has reduced susceptibility to vancomycin, and vancomycin intermediate susceptible *Staphylococcus aureus* (VISA) strains are increasing. Therefore, MRSA strains are approaching to the pathogen with lack of alternative antibiotics [3].

Methicillin resistant *Staphylococcus aureus* (MRSA) has been developed by acquisition of genes of chromosomal cassette "mec" elements. This cassette consists gene (mecA) which encodes the novel penicillin binding protein PBP2a. PBP2a confreres resistance and renders the entire antibiotic class ineffective [4].

The *mec* gene cassette also carries several virulence factors due to the fact that virulence factors and antibiotic resistance are closely linked. A single horizontal gene transfer of the Staphylococcal cassette chromosome (SCC) may contain other several genes coding various virulence factors. This renders methicillin resistant S. aureus strains more virulent than other *S. aureus* [5].

In Ethiopia, many studies have been conducted to isolate MRSA in public health aspects since a decade. However, few systematic reviews made so far in the country have mostly focused on public health issues and the animal health bourdon, environmental and food contaminations by MRSA has not been given emphasis. The aim of this systematic review is, therefore, to assess the distribution of MRSA in food animals, environment and foods to be bourdon on public and animal health in Ethiopia.

Materials and Methods

Inclusion and Exclusion Criterion

Original research articles, which have reported extractable data on the prevalence of MRSA in Ethiopian, and only in English language, were included in the study. On the other hand, studies which did not report MRSA in Ethiopia and were not original research articles were excluded from the study.

Study Selection

The search of the literatures was from PubMed and PMC databases. Accordingly, original research articles accessed online between 12th December to 14th December 2021 and potentially relevant to the study were collected and identified. The search was performed by using "MRSA in Ethiopia" and/or "methicillin resistant *Staphylococcus aureus* in Ethiopia" as keywords. The PDF of the articles accessed in the aforementioned scholars databases during the study period were then retrieved.

After obtaining the articles, first the titles of the articles were checked for whether they full fill the set criterion. Accordingly, only the original research articles were passed to the next step of screening. Next, the abstracts of the selected articles were then reviewed to determine if they have studied the drug resistance pattern of *Staphylococcus aureus* and/or identified MRSA. Finally, the relevant articles were accessed in full text to obtain detail information included in the meta-analysis.

Outcome of Interest

The major outcome of interest was to determine the prevalence of MRSA among total sample size and among total *S. aureus* isolates in the samples. The prevalence was calculated by dividing the numbers of MRSA isolates by the total number of sample size, or *S. aureus* isolates. The study has also determined the pooled resistance pattern of MRSA isolates to specific antibiotics.

Data Extraction

Data from eligible studies were extracted and summarized into an excel spreadsheet. For each of the included studies, the following prominent information was extracted.

- Name of the authors
- Years of publication
- Study design
- Period of the study
- Region in which the study was conducted
- Sudy population
- Sample type
- Sample sizes
- Total numbers of *S. aureus* isolates
- Total number of *S.aureus isolates* tested for MRSA
- Types of drug used to test MRSA
- Total number of MRSA isolates
- Drug resistance pattern of MRSA (if any)

The current review has collected data of total sample size, number of *S. aureus* isolates and total MRSA isolates. However, in studies aimed to identify multiple bacteria and MRSA in due the process, the prevalence of MRSA get smaller. However, in the studies aimed to isolate and identify MRSA, the proportion of MRSA got increasing as the number of the *S.aureus* isolates were considered as sample size. As the result, in order to report consisten results re, we prefer to conduct the meta-analysis based on the proportion of MRSA per *S.aureus* isolates. Therefore, it should be noted that the pooled proportions of MRSA in the review were per number of *S.aureus* isolates.

Quality Control

The quality of eligible studies was checked using a set of predetermined criteria such as research design, quality of paper, and methods employed to isolate and identify MRSA. As the result, only original research articles performed the research by isolating and identifying MRSA, and of which full article could be downloaded from PubMed and PMC were included in the analysis.

Data Analysis

The random effects size model was accepted to determine pooled prevalence at 95% confidence interval (CI) using momentum estimate Der Simonian and Laird method approach Harrer. In addition, the analysis needed transformation; because there were reports with zero percent prevalence. As the result, the double arcsine transformation method was preferred to logit transformation or analyzing without transformation Barendregt. The heterogeneity of study results was assessed by the use of τ^2 , I^2 and Q-statistics tests. Significant heterogeneity was considered when p-value < 0.05 and I^2 > 75% were observed Der Simonian and Laird, 1986, Rücker, 2008. The pooled resistance pattern of MRSA to specific antibiotics was calculated, and presented using table. All the statistical analyses were performed by the use of the R-software (Ri386 4.2.1.lnk) [6].

Results and Discussions

The Selected Publications

Total of 168 articles were downloaded through search of the electronic PubMed and PMC databases, of which 50(30%) of them were duplicated. Eight (4.8%) were conducted not in Ethiopia, and 18 (10.7%) were not original research articles, 6(3.5%) isolated *S.aureus* but did not identify MRSA, and 7(4.2%) used unclear methods and/or report unclear results. Therefore, 79(47%) of the articles were eligible for the meta-analysis. Two research articles were replicated in the analysis because they conducted the research on both human and animals (Figure 1).

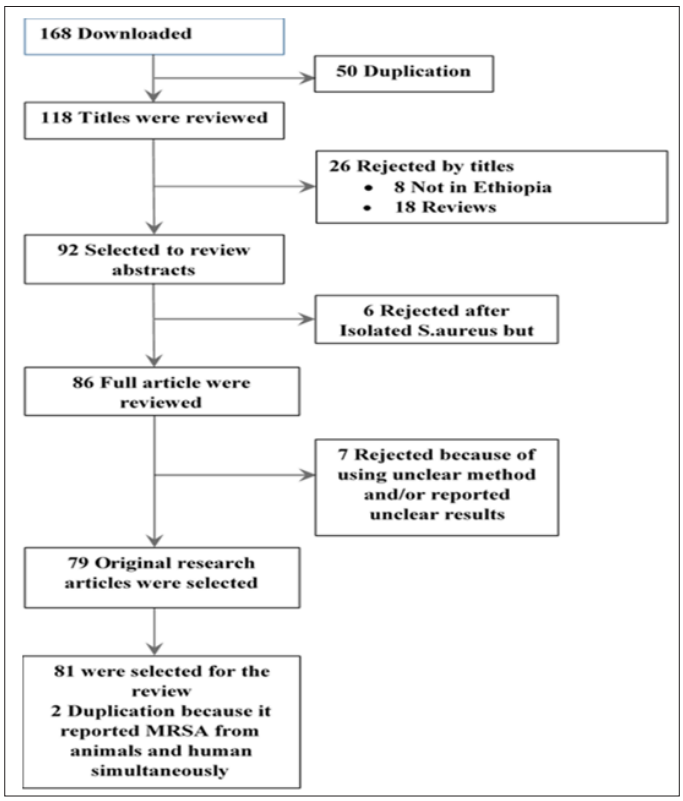

Figure 1: Flow Chart Shows Selected Articles for Meta-Analysis

The year of the publications were between 2010 and 2021. The highest number of publications was recorded in 2021 (27%) followed by 2020 (16%). This indicates that researches on MRSA have been becoming increasing in the country since recent. Most of the publications we found were related with public health 60(74%) and only few were with environments 10(12.4%), food animal 7(8.6%) and food issues 4(5%). The regions in which the studies conducted and the types of sampled materials were summarized in Tables 1-3 and Figure 2. One research was conducted by collecting samples from Amhara, Oromia and Addis Ababa, and it was assigned as AmOrAd on the figure. It was determined that highest number of the studies were conducted in Amhara (37%) followed by Oromia (18%) regional state. Seventy four percent of the articles collected samples from human followed by environment (12.3%). Figure 2 summarize the percentage of articles in respect to the regions and sampled categories.

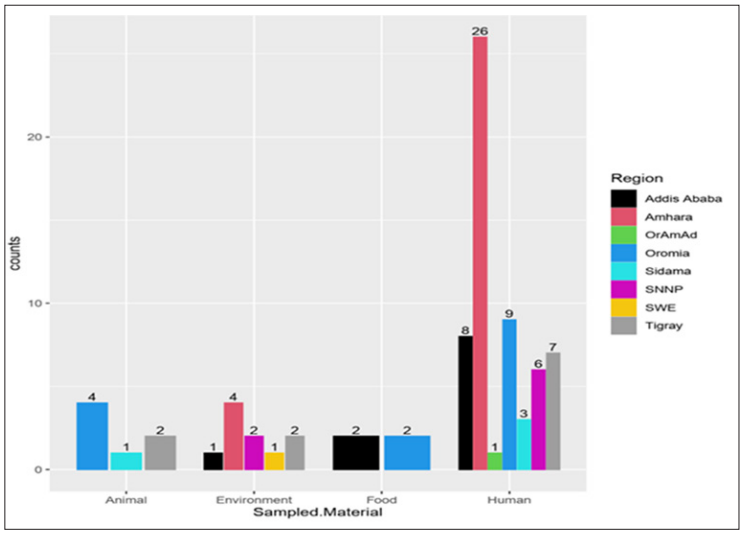

Figure 2: The Number of the Articles according to Study Area and Sampled Materials

OrAmAd=Oromia, Amhara, and Addis Ababa

Table 1: Summary of 81 Studies reporting the prevalence of MRSA in Human, 2010-2021

Studies	Study design	Regions	Cultured specimens	Sample size	S. aureus	MRSA	MRSA Prevalence (%)	
							Per S. aureus	Per Sample Size
(Eshetu et al., 2020)	Cohort	Oro,Am, Ad	blood	690	41	35	86	5
(Kejela & Bacha, 2013)	Cro-Sect	Oro	Nasal swab	354	169	39	23	11
(Godebo et al., 2013)	Cro-Sect	Oro	Wound swab	322	73	56	77	17
(Dagnew et al., 2012)	Cro-Sect	Am	Nasal swab	200	41	4	10	2
(Shibabaw et al., 2013)	Cro-Sect	Am	Nasal swab	118	34	15	44	13
(A. Kahsay et al., 2014)	Cro-Sect	Am	Wound swab	184	73	36	49	20
(Ayehubizu et al., 2021)	Cro-Sect	Am	Ocular swab	360	77	8	10	2
(Dilnessa & Bitew, 2016)	Cro-Sect	A .A	Nasal swab, pus, ear discharge, blood, throat swab, eye swab, vaginal discharge, urethral discharge, urine, stool, sputum, CSF and body fluids	1360	194	34	18	3
(Teweldemedhin et al., 2017)	Cro-Sect	Tig	ophthalmic surgeon collected specimens	270	40	7	18	3
(Getahun et al., 2017)	Cro-Sect	Am	Ocular swab	312	69	23	33	7
(B. Tadesse et al., 2019)	Cro-Sect	Sid	Ear swab	152	41	7	17	5
(Kasew et al., 2021)	Cro-Sect	Am	urine sample	300	7	2	29	1
(Gorems et al., 2018)	Cro-Sect	Oro	Ear swab	173	55	19	35	11

(Kalayu et al., 2020)	Cro-Sect	Tig	Nasal Swabs	71	22	0	00	00
(Ramos et al., 2014)	Cro-Sect	Oro	Pus swab	68	15	3	20	4
(Biset et al., 2020)	Cro-Sect	Am	Urine sample	384	11	4	36	1
(Abie et al., 2020)	Cro-Sect	Am	Nasal swabs	436	101	21	21	5
(Reta et al., 2017)	Cro-Sect	Am	Nasal swabs	400	52	0	00	00
(Legese et al., 2018)	Cro-Sect	Tig	Nasal swab	242	29	14	48	6
(A. G. Kahsay et al., 2018)	Cro-Sect	Tig y	Nasal swabs	184	69	45	65	24
(Belyhun et al., 2018)	Cro-Sect	Am	Ocular swab	210	35	32	91	15
(Feleke et al., 2018)	Cro-Sect	Am	Nasal swab	260	77	52	68	20
(Temesgen et al., 2019)	Cro-Sect	Am	sputum	414	24	18	75	4
(Wasihun et al., 2015)	Cro-Sect	Tig	blood	514	54	38	70	7
(Hailu et al., 2016)	Cro-Sect	Am	Pus swabs from discharging ears	368	78	27	35	7
(Gebremedhn et al., 2016)	Cro-Sect	Tig	Nasal and throat swabs	249	81	6	7	2
(Deyno, Toma, et al., 2017)	Cro-Sect	Sid	Ear swab	117	33	30	91	26
(S. Tadesse et al., 2018)	Cro-Sect	A .A	Wound and corresponding nasal swabs	188	79	77	97	41
(Birru, Woldemariam, et al., 2021)	Cro-Sect	SNNP	blood	225	7	4	57	2
(Tolera et al., 2018)	Cro-Sect	Oro	urine, blood, wound swab, throat swab, nasal swab, and other body fluids w	394	10	9	90	2
(Endris et al., 2014)	Cro-Sect	Am	Blood samples	83	11	2	18	2
(G. Alebachew et al., 2016)	Cro-Sect	Am	Blood	100	13	5	38	5
(Semret et al., 2020)	Cohort	A .A	Blood	777	82	62	76	8
(T. Alebachew et al., 2012)	Cro-Sect	A .A	pus	114	66	51	77	45
(Sewunet et al., 2013)	Cro-Sect	A .A	Blood and burn wound swab	100	24	5	21	5
(Beyene et al., 2019)	Cro-Sect	Oro	Nasal and hand swabs	300	86	6	7	2
(Abosse et al., 2021)	Cro-Sect	Am	wound secretion/pus swab	165	24	10	42	6
(Fentie et al., 2018)	Cro-Sect	Am	Blood, urine and wound swabs	216	12	3	25	1
(Ameya et al., 2020)	Cro-Sect	SNNP	Blood	238	9	2	22	1
(Mitiku et al., 2021)	Cro-Sect	SNNP	Urine	422	53	23	43	5

(Yitayeh et al., 2021)	Cro-Sect	Am	wound, urine, ear discharge, blood, stool, urethral or cervical discharge, nasal or throat swab, semen and CSF	716	9	5	56	1
(Oumer et al., 2021)	Cro-Sect	SNNP	Urine	231	3	1	33	0.40
(Tefera et al., 2021)	Cro-Sect	Am	Wound swab	242	71	32	45	13
(Alelign et al., 2021)	Cro-Sect	SNNP	ascitic fluid	147	4	1	25	1
(W. Dessie et al., 2016)	Cro-Sect	A .A	Wound Swab	107	19	2	10	2
(Mohammed et al., 2017)	Cro-Sect	Am	Wound swab	137	39	30	77	22
(Mama et al., 2019)	Cro-Sect	SNNP	Wound Swab	161	79	65	82	40
(Diriba et al., 2020)	Cro-Sect	Oro	Eye swab	319	29	4	14	1
(Jemal et al., 2020)	Cro-Sect	Am	Blood	384	38	28	74	7
(T. Dessie et al., 2021)	Cro-Sect	Am	Swab of washed sputum	406	29	10	34	2
(Tamire et al., 2021)	Cro-Sect	A .A	Pus and blood	413	160	57	36	14
(Jemal et al., 2021)	Retro	Am	Blood	1854	118	13	11	1
(Tsige et al., 2020)	Cro-Sect	Am	Wound swab	266	92	26	28	1
(Efa et al., 2019)	Cro-Sect	Oro	Nasal Swab	371	82	31	38	8
(Negussie et al., 2015)	Cro-Sect	A .A	Blood	201	13	5	38	2
(M. T. Lemma et al., 2015)	Cro-Sect	Am	swabs from the anterior nares, the skin and the perineum	1200	281	73	26	6
(Mulu et al., 2018)	Cro-Sect	Am	pharyngeal swab	300	88	29	33	10
(Weldu et al., 2020)	Cro-Sect	Tig	Blood	317	9	6	67	2
(Tibebu et al., 2021)	Cro-Sect	Oro	Hand swab	52	10	0	00	00
(Hailemariam et al., 2021)	Cro-Sect	Sid	clinical sample including Urine, CSF, Blood, pus, discharge, stool and sputums	1085	56	3	5	0.30

A.A=Addis Ababa, Am=Amhara, Tig=Tigray, SNPP=South Nations Nationalities and People, Sid=Sidama, SW=South West, OroAmAd=Oromia, Amhara and Addis Ababa, Oro= Oromia, Cro-Sect=cross Sectional,

Table 2: Summary of 81 Studies Reporting the Prevalence of MRSA in Food Animals, 2010-2021

Studies	Study design	Regions	Cultured specimens	Sample size	S. aureus	MRSA	MRSA Prevalence (%)	
							Per S. aureus	Per Sample Size
(Tesfaye et al., 2021)	Cro-Sect	Oro	milk	121	37	12	0.32	0.099
(Daka et al., 2012)	Cro-Sect	Sid	milk	160	78	47	0.60	0.29
(Kalayu et al., 2020)	Cro-Sect	Tig	Milk	385	48	1	0.02	0.003
(Girmay et al., 2020)	Cro-Sect	Tig	Milk	64	21	7	0.33	0.109
(Dabele et al., 2021)	Cro-Sect	Oro	Milk samples	1528	7	0	0	0
(Tibebu et al., 2021)	Cro-Sect	Oro	Milk and Udder swab	181	40	2	0.05	0.01
(Grima et al., 2021)	Cro-Sect	Oro	Milk	116	18	1	0.06	0.01

Oro=Oromia, Tig=Tigray, Sid=Sidama, Cro-Sect=cross Sectional,

Table 3: Summary of 81 Studies Reporting the Prevalence of MRSA in Environment and Foods, 2010-2021

Studies	Study design	Regions	Cultured specimens	Sample size	S. aureus	MRSA	MRSA Prevalence (%)	
							Per S. aureus	Per Sample Size
(Moges et al., 2014)	Cro-Sect	Am	Water	60	10	1	0.10	0.02
(Firesbhat et al., 2021)	Cro-Sect	Am	Swabs	384	15	13	0.87	0.03
(F. B. Solomon et al., 2017)	Cro-Sect	SNNP	Air sample with Agar plate	216	64	28	0.44	0.13
(A. G. Kahsay et al., 2019)	Cro-Sect	Tig	Surface swab	300	54	17	0.31	0.06
(Darge et al., 2019)	Cro-Sect	Tig	Surface swab	130	40	34	0.85	0.26
(Tefera Abula2, 2017)	Cro-Sect	Am	drop of eye medications in-use	100	5	4	0.8	0.04
(Sebre et al., 2020)	Cro-Sect	A .A	Surface swab	164	63	54	0.86	0.33
(Getachew et al., 2018)	Cro-Sect	Am	Air sample and surface swab	356	71	18	0.25	0.05
(Worku et al., 2018)	Cro-Sect	SW	Surface Swabs	201	19	14	0.74	0.07
(Birru, Mengistu, et al., 2021)	Cro-Sect	SNNP	Surface Swab	99	42	8	0.19	0.08
(F. Lemma et al., 2021)	Cro-Sect	A .A	milk and traditionally processed dairy products	255	52	20	0.38	0.08

A.A=Addis Ababa, Am=Amhara, Tig=Tigray, SNPP=South Nations Nationalities and People, Oro=Oromia, SW=South West, Cro-Sect=cross Sectional,

Prevalence of MRSA in *S.aureus* Isolates

The total of 26930 samples were collected by the researches of which, 20943 (77.78%) were from human, 2555 (9.5%) from food animals, 2010 (7.5%) from environment and1422 (5.3%) from foods and related materials. All the articles included in this review have identified MRSA based on the resistibility of the *S. aureus* to methicillin or other alternative antibiotic discs by using disc diffusion method. Accordingly, 59.76%, 25.61%, 13.41% and 1.22% of the articles have used Cefoxitin, Oxacillin, Methicilin and Cloxacillin respectively. Of 4219 (15.65%) *S. areus* positive samples, 1695(40.2%) were found MRSA strains. Of the total MRSA isolates, 1254 (74%) were from human samples, 68 (4%) were from food animals, 192(11.3%) were from environmental and 180 (10.6 %)were from food samples.

The overall pooled proportion of MRSA in *S. aureus* was found to be 40% (95% CI: 32-48%) (Figure 3). However, its proportion was highly diversified. The between-study heterogeneity was $\tau^2 = 0.1085$ (95% CI: 0.07 -0.15), $H^2 = 23.60$ (95% CI:16.54-31.34), $I^2 = 95.76\%$ (95%CI:93.95 -96.81%), and Q=1887.8927, $p<0.0001$) all of which suggests significant heterogeneity in the effect sizes of the study. As it is observed visually from the forest plot, the proportion of MRSA in the articles were highly diversified that they are deviated from the center, which is the estimate of the pooled proportion.

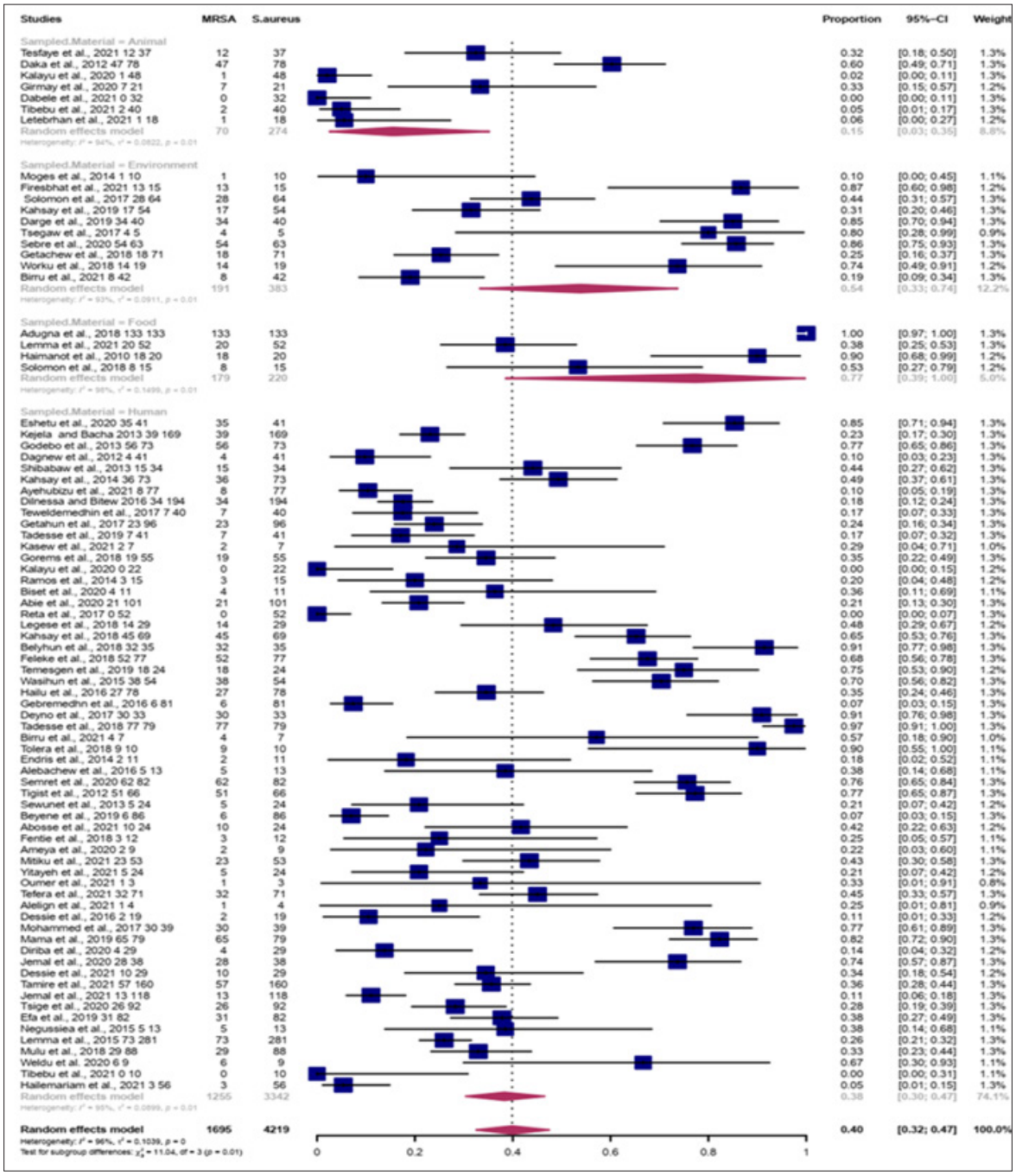

Figure 3: Forest Plot of the Total Pooled Prevalence and Subgroup Analysis Based on Sampled Materials

The sources of the heterogeneity were determined by assessment of outliers and/or moderators (factors) .The outliers were tested to estimate the potential impact of the outliers on the overall pooled proportion ., The first screening test for outliers was made by using student function to assess the presence of studentized residual. Accordingly, two articles were found having the z values above 2. However, since the number of studies in the current review was large enough, our cutting point was expected to be at 3. Hence there was no outlier, which potentially affects the summary effect size, and the heterogeneity observed in the above assessment might be due to moderators.

Subgroup Analysis

Sampled Materials

The subgroup analysis was conducted to determine the factors associated with the prevalence of MRSA in the isolates of *S. areus*. The comparison was made based on the types of sampled materials as human, food animal, environmental and food related. The human samples were collected from either patients or apparently normal individuals. The articles studied food animals have collected samples from food animals and their products for the purpose of animal health assessments. The samples collected from the environment include, inanimate surfaces swabs, water and air in health settings and other public services to investigate the distribution of MRSA in the environment.

The subgroup analysis based on the sampled materials was displayed on forest plot (Figure 3). In the subgroup analysis based on sampled materials, the pooled prevalence of MRSA was 0.38 (95% CI: 0.31-0.46) in human isolates, 0.15(95%CI:0.01-0.38) in food animals isolates, 0.54 (95%CI: 0.34-0.73) in environmental isolates and 0.77 (95% CI: 0.29 1.00) in food isolates Figure 3. Moreover, the result of the τ^2 and Q tests were τ^2= 0.0847& Q= 1167.065 in human, τ^2 = 0.1095& Q= 106.3283 in animals, τ^2 = 0.0890 & Q= 128.3886 in environmental and τ2 = 0.2379 & Q= 123.1971 in food isolates. The heterogeneity level of the proportion in human, animals, environmental and food isolates were 95%,94%,93% and 98% respectively. In all of the categories of the types of sampled materials at 95% confidence the p-values were less than 0.05. Therefore, the types of the sampled materials were found associated with the prevalence of MRSA in *S.aureus* isolates. The result of the subgroup analysis revealed that significantly high rate of the strain was identified in *Staphylococcus areus* isolates from food followed by environmental samples than from human and food animals ($p<0.05$).

Human Health Status

The human related articles were in turn further sub-grouped according to the health status of the individual from which the samples were collected and the subgroup analysis was conducted. As the result the pooled prevalence of MRSA strain in the *S.aureus* identified from samples of apparently health individuals was 0.15 (0.01-0.38) whereas it was 0.38 (0.31-0.46) in *S. aureus* isolated from patient samples. In the overall subgroup analysis result, there was significant difference in the prevalence of MRSA between the two groups that *S. aureus* in isolated from the patients were more resistant to methicillin than those isolated from the health individuals. ($p>0.05$). However, the proportion of the strain was highly heterogeneous between the articles that the τ^2 was 0.0859 with I2=95% in patients and 0.0597 with I2 =93%.

Publication Bias

As determined from funnel plot (Figure 4) most of the publications were placed at the top of the plot. Only one study was found at the right bottom of the funnel and two were at the middle. As the result there was no evidence to decide the presence of publication bias in the current review and the variation in effect sizes might be due to sampling error.

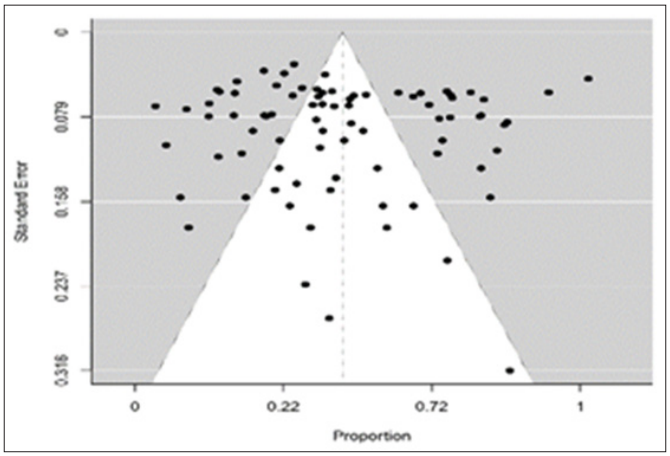

Figure 4: Funnel Plot of the Publication Bias of the of the Meta Analysis

Antibiotic Resistance Patterns of MRSA

Furthermore, of the selected articles, twenty two studies had extractable data on the antibiotic resistance profile of MRSA isolates. In this review, the pooled proportion of MRSA to 32 antibiotics has been determined. Accordingly, the pooled resistance rates of MRSA for each tested antibiotics was presented in Table 4.The result indicated that more than 90% pooled resistance rates were observed to penicillin, Neomycin, , cefuroxime, Pipracilin and Tobramycin. In addition, MRSA was found highly resistant to amoxacilin-clavulanicacid (80%), Bacitracin(84%) and Erythromycin (88%). In contrast, relatively less pooled resistance rate was observed to clindamycin (21%), chloramphenicol (22%), Amikacin (27%), vancomycin (20%), Knamycin (25%) and Ceftriaxone (30).

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Table 4: Pooled Multidrug Resistance Rates of MRSA Strains

Isolates and Antibiotics	Studies																								
	(Tesfaye et al., 2021)	(Daka et al., 2012)	(Kejela & Bacha, 2013)	(A. Kahsay et al., 2014)	(Dilnessa & Bitew, 2016)	(B. Tadesse et al., 2019)	(F. B. Solomon et al., 2017)	(Abie et al., 2020)	(Legese et al., 2018)	(A. G. Kahsay et al., 2018)	(A. G. Kahsay et al., 2019)	(Deyno, Toma, et al., 2017)	(S. Tadesse et al., 2018)	(G. Alebachew et al., 2016)	(Adugna et al., 2018)	(F. Lemma et al., 2021)	(Tassew et al., 2011)	(Mitiku et al., 2021)	(Mama et al., 2019)	(Tsige et al., 2020)	(Efa et al., 2019)	(M. T. Lemma et al., 2015)	Pooled proportion	95% CI	
																								L	U
S. aureus	12	47	39	36	34	7	28	21	14	45	17	9	77	5	133	20	18	23	65	26	31	73			
Am.	9	24		36	34							6	31		0	17	9						0.65	0.26	0.95
Cef.	4												51			1						15	0.30	0.05	0.62
Kan.	0		25									2											0.25	0.00	0.76
Nal.	5																						0.42	0.15	0.71
Tet.			13	15			4	15	9		1		58	2	127	7			47		20	53	0.54	0.37	0.72
OxyTTC.	8																						0.67	0.37	0.91
Sulp.	6																						0.50	0.22	0.78
Stre.	4																6						0.33	0.17	0.52
Pen.		47	39	36	34			21	14	17				2	66					26			0.92	0.72	1.00
Amp.		47	39	36					14				75	3	0		14	23					0.88	0.43	1.00
Ery.		23	24	35	34			5	9	10	2		48	1	0	6	6		19	16	9	17	0.42	0.23	0.63
Van.		13	5	2	10							6			61		2		0				0.20	0.06	0.39
Amik.			11						6				47						0				0.27	0.01	0.70
Baci.			24										56		133								0.84	0.46	1.00
CAF.			23				4		3	13	4		48		0	1			18	7		4	0.22	0.07	0.40
Genta.			6	34			4	6	8			2	42			3			4	14			0.35	0.16	0.58
Kana.			25																				0.64	0.48	0.79
Clind.				22		2	11	5	2				56		0				2	2	5	6	0.21	0.05	0.42
Cotri.				36					9		2							15	28	14		4	0.50	0.18	0.82
Cefu.					34																		1.00	0.95	1.00
Ceph.					34							3	55			3							0.61	0.19	0.96
Cipro.							4	8	6	1			46					16	6	16	16	17	0.34	0.18	0.52
Doxycy.							4			9			45							8			0.31	0.11	0.54
Trimatho.		5	7		34		11	12					62	1		8					26		0.53	0.26	0.79
Agu.												6				17							0.80	0.60	0.95
Neo.															133								1.00	0.99	1.00
Clox.															60								0.45	0.37	0.54
Norf.															18			18					0.43	0.00	0.98
Nitro.																		12					0.52	0.32	0.72
Pipra.																		21					0.91	0.76	1.00
Tobra.																		23					1.00	0.93	1.00

Am.=Amoxicillin, Cef.=Ceftriaxone, Kan.= Kanamycin, Nal.=Nalidixic acid, Tet.=Tetracycline, OxyTTC.=Oxytetracycline, Sulp.=Sulphonamide, Stre.=Streptomycin, Pen.=Penicillin, Amp.=Ampicillin, Ery.=Erythromycin, Van.= Vancomycin, Amik.=Amikacin, Baci=Bacitracin, CAF= Chloramphenicol, Genta.= Gentamicin, Kana.=Kanamycin, Clind.=Clindamycin, Cotri.=Cotrimoxazole, Cefu.=cefuroxime, Ceph.= Cephalothin, Cipro.=Ciproflxacin, Doxycy.=doxycycline, Trimatho.=trimethoprimsulphamethoxazole, Agu.=amoxacilin-clavulanicacid, Neo.=Neomycin, Clox.=Cloxacillin, Norf.=Norfoxacin, Nitro.=Nitrofurantoin, Pipra.=Pipracilin, Tobra. =Tobramycin

Discussion

MRSA, which was previously considered as health care associated pathogen is seen highly distributed in the surroundings. Of the total 26,930 samples collected 4219 (15.7%) were *S. aureus* positive. According to the publications when these *S.aureus* isolates were tested for Methicillin resistance, 1695(40%) were found to be MRSA. The pooled prevalence of MRSA was 6.45% in the total samples and 41% among the *S.aureus* isolates. The review also determined that the prevalence of the strain in samples collected from human was 6.5% per total sample size and 38% in *S.aureus* isolates. The result was less than the report of and who reported the pooled prevalence of MRSA in total sample size collected from human to be 32.5% in Ethiopia and 42% in Iran respectively [2,7]. Our result is also less than the analysis of which reported the pooled prevalence of MRSA among S.auresu in Ethiopia as 47% [8]. However, it is coincided with the report of who reported the pooled prevalence of MRSA among *S.aureus* as (38.2%) [9]. According to the assessment of WHO, the resistance rate of S.auresus to methicillin exceeds 50% in the community and hospitals in WHO regions and ranged between [10]. The document of WHO also indicated that the prevalence of MARSA in Ethiopia was reported as 31.6%. A meta-analysis with aim of determining the prevalence of MRSA among the S. areus in Africa reported that the overall pooled prevalence of the strain in Ethiopia was estimated to be 55% [11].

The review found that the health status of the individual was found as factor associate with the prevalence of MRSA that the strain is significantly prevalent in the patients than in apparently health individuals. The pooled prevalence of MRSA in the apparently normal person was estimated to be 15% whereas; it was 38% in isolates from patients. With similar pace, Hassoun et al (Hassoun et al., 2017) determined that the pooled prevalence of MRSA in *S.aureus* isolated from patients (1.8%),was higher than that of apparently health individuals(0.76%).

In the current review 15% (95%CI:1-38%) of S. aureus isolates from food animals were MRSA. MRSA in food animals isolates was less prevalent than in environmental samples and human. In agreement with the findings of which reported MRSA pooled prevalence among the *S.aureus* isolates from African pigs as ranged from 10 to 100%, the current finding lied in the range [12]. However, it is higher than the previous report by who reported the prevalence of animal associated MRSA among S. aureus in different African countries including Ethiopia as ranged between 0 and 3% [13]. It is expected that the Livestock Associated Methicillin-resistant S. aureus (LA-MRSA) is highly associated with usage of antibiotics in animal feed as growth promoter and as prophylaxis. The clonal complex 398 (LA-MRSA CC 398) has been considered to be zoonotically important because of its capacity to colonize a wide range of hosts and can jump between hosts. These species may act as carriers of MRSA originating from humans (so called "humanosis"). Moreover, bovine and human MRSA strains are indistinguishable by phenotyping and genotyping methods providing evidence for MRSA transmission between human and cattle [14]. However, in most of the cases the LA-MRSA remained non pathogenic in human and even when occur they cause less sever infections than HA- and CA-MRSA [15].

Apart from its ability to resist antibiotics, the concern of *S.aureus* to be burden in public, and animal health arise from its adaptation to diversity of environmental conditions [16]. The environmental isolates of *S.aureus* were found highly resistant to Methicillin than human and food animals isolates that about 54% (95%CI: 34-73%) of the isolates were MRSA. The isolates were recovered from samples collected from different materials in and around health settings including floor, stethoscope, surface of drug ruminants, air and west waters from hospitals, and other public services such as buses. This might be from the reason that majority of the samples were collected from health care settings which might have exposed to the drug.

Staphylococcus aureus has long been mentioned as food-born pathogen as enterotoxin producer and is one of the public health problematics worldwide. The extraordinarily use of antibiotics in food animals might result in the spread of the resistant microorganisms in foods [17]. The spread of MRSA strains in food, therefore, adds other difficulty in control of the diseases in food industry particularly from the view point of enterotoxogenicity nature of the bacterium. In the current review, the researches collected samples from raw milk and processed milk, meat and cockroach contacting with the food materials. MRSA isolates from food samples (77% (95% CI: 29-100%)) were the most prevalent of all other sample categories. The presence of S. aureus in food materials for human consumption is indicative for the spoilage of the food and the suspicious of food intoxication.

More over 22 of the studies have determined the multidrug resistance ability of MRSA to different antimicrobial agents. Accordingly, the isolates were found highly resistant (more than 80% pooled resistance proportion) to cefuroxime (100%), Tobramycin (100%), Neomycin (99%) and Penicillin (92%), Pipracilin (91%), Erythromycin (88%), Bacitracin (84%) and Amoxacilin-clavulanicacid (80%). According to the review, the drug of relatively better effective against MRSA were Clindamycin, chloramphenicol, Amikacin, vancomycin, Knamycin and Ceftriaxone with resistance rates of 21%, 22%, 27% , 20%, 25% and 30% respectively.

Similarly, the previous systematic reviews conducted by and have also documented that MRSA strains were found to be too highly resistant to most of the above mentioned antibiotics [2,18]. It is obvious that MRSA strains are able to express beta-lactam hydrolyzing enzymes so called betalactamases or capable of modifying penicillin binding proteins so that MRSA strains are capable of inactivating the beta-lactam agents such as penicillin, ampicillin, cephalosporins, and carbapenems [19]. Even more, MRSA has a tendency to resist non-beta- lectam antibiotics due largely to co-existence of other resistance gene along with mecA or mecC gen. Most importantly, vancomycin is considerably the most effective and considered as the last resort treatment for resistant infections of MRSA. The emergence of vancomycin resistant MRSA has, therefore, disadvantaged the usefulness of this drug [20]. In this meta-analysis 14.31% (95% CI:4.87-35.29) of MRSA was found vancomycin resistant indicating huge blow, especially for the future.

Conclusion

The studies concerning MRSA has been increasing in Ethiopia specially since a decade. However, majority of the studies are giving more attention to public pathogens. The distribution of the pathogen in the environments apart from health settings have remain mysterious yet. In addition, MRSA in the livestock and pets have not been dug well in the country. The studies so far conducted covered few part of the country. The status of the pathogen in the remote areas far from the capital Addid Ababa seemed to remain unstudied. Despite that all the MRSA studying

articles in the country might not be obtained, the current review showed us that MRSA is spreading in the country. The prevalence rate of MRSA was highest in *S.aureus* isolates from food than other ones. Moreover, the pathogen was prevalent in patients than in health individuals [21-100].

The reviewer, therefore, provide advise that care should be given to food preparation and handling in the country. Awareness on the antibiotic utilization should be given to all level of the community. Furthermore, the environments in the health settings need to be clean and disinfected regularly. Lastly, conventional and molecular based identification of MRSA is very important to identify the types of MRSA spreading in the area.

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