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Research Article

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

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Abstract

The current meta-analysis was aimed to analyze the prevalence rate of MRSA in S. aureus isolates from different sources of samples in Ethiopia. The multidrug resistance pattern of the pathogen was also one of the outcome of interest of the analysis. The data for the current study were extracted from original research articles published in journals indexed in PubMed databases, accessed online from 12th to 14th December 2021, whose pdf were freely downloadable, English language articles, and conducted on MRSA prevalence in Ethiopia. The data were displayed on Excel spreadsheet, coded, exported to R statistical software and the pooled prevalence of MRSA was calculated per S. aureus isolates and analyzed at 95% CI. Accordingly, 79 eligible articles were selected for the meta-analysis. The result of the study revealed that 26930 samples have been collected from different specimens of which 4219 (15.65%) were S. aureus positive. Of the total S. aureus, 1695 were found MRSA strains and the overall pooled prevalence of MRASA per S. aureus isolates was 40%. In terms of the sources of the specimen, the pooled prevalence of MRSA in human, animal, food and environment were 38%, 15%, 77%, and 54% respectively and it was significantly higher in food and environment than in animal and human samples ($p<0.05$). The analysis also showed that that MRSA was highly prevalent in patients than in health people ($p<0.05$). Furthermore, the study revealed that MRSA was highly resistant to cefuroxime (100%), Tobramycin (100%), Neomycin (99%) and Penicillin (92%), Pipracilin (91%), Erythromycin (88%), Bacitracin(84%) and Amoxacilin-clavulanicacid (80%).-However, clindamycin (21%), chloramphenicol (22%), Amikacin (27%), vancomycin (20%), Knamycin (25%) and Ceftriaxone (30%) were antibiotic of relatively better effective against MRSA.

Keywords: MRSA, Meta-Analysis, Prevalence, Ethiopia

Introduction

Staphylococcus aureus (S.aureus), is a Gram positive grouped spherical (cocci) bacteria widely distributed in the world [1]. *S. aureus* is living in and on the bodies of animals and human as microfilora. It resides-in-the mucosal cavities and on the skin without harming the host. Researchers have isolated it from hand, nasal, buccal cavity and urogenital organs. The residence of the bacteria as microfilora in and on animals and human body, however, make it associate with some disease conditions as an opportunistic pathogen. It can therefore be associated with simple diseases such as pimples and boils to serious infections such as wound infections, pneumonia, and/or septicaemia, and result in life-threatening illness particularly in immune compromised patients (Torrence and Isaacson, 2003).

The pathogenicity of the *S. aureus* is associated with its antibiotic resistance, enterotoxogenicity, biofilm formation and other virulence factors imcluding adherence factors, nucleases, proteases, lipases, hyaluronidase, and collagenase productions. Furthermore, *S. aureus* is becoming important in that it has developed resistance to-commonly used antibiotics drugs-including methicillin, and vancomycin. Such characteristics of the microbe made it to be nearing to one of the most non-treatable microbials in the globe [7]. As the fact that methcillin is-the most effective antibiotic against *S. aureus*,-the emergence ofmethcillin resistant *Staphylococcus aureus* (MRSA) has been emerged and increases its intensity to be one of the global issues of health concerns [7].

Furthermore, studies MRSA strains have been found resistant to all beta-lactam antibiotics (including penicillin G, ceftiofur sodium, Cloxacillin, cephapirin, and ampicillin) and other anticaterial agents such as tetracycline and sulfonamides (Torrence & Isaacson, 2003). Vancomycin is the drug of choice for MRSA infections now days. However, studies revealed that MRSA, has reduced susceptibility to vancomycin, and vancomycin intermediate susceptible *Staphylococcus aureus* (VISA) strains, are increasing. There-

fore, MRSA strains are approaching to the pathogen with lack of alternative antibiotics.- [1].

Methicillin resistant *Staphylococcus aureus* (MRSA) has been developed by acquisition of genes of chromosomal cassette *"mec"* elements. The cassette consists gene (*mecA*) which encodes the novel penicillin binding protein PBP2a. PBP2a confreres resistance and renders the entire antibiotic class ineffective (Wielders ,*et al*.,2002; Enright *et al*.,2002).

β-lactam antibiotics inhibit transpeptidase, and activate autolysis by degrading peptidoglycan. Therefore-the method by which S. aureus resist to β-lactam antibiotics is,-by producing PBP2a (the substitution of PBPs) which has low affinity for all β-lactams . PBPs are naturally existing enzymes responsible for the transpeptidation (transpeptidase) and transglycosylation (transglycosylase) of peptidoglycan units of the cell wall of the bacteria .-As the result, PBP2a enable the bacterium to synthesise cell wall in the presence of β-lactams antibiotics [1, 3- 5] .

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*. [2].

In Ethiopia, many studies have been conducted to isolate MRSA in public health aspects since a decade. The systematic reviews made so far in the country have mostly focused on public health issues. However, the animal health bourdon and environmental contaminations byMRSA has not been given emphasis. The aim of this systematic review is, therefore, to assess the distribution, and bourdon of MRSA on public, and-animal haelath 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 conducted in the 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 terms "MRSA in Ethiopia" and "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 the articles were obtained, first the titles of the articles were checked for whether they full fill the set criterion. 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.

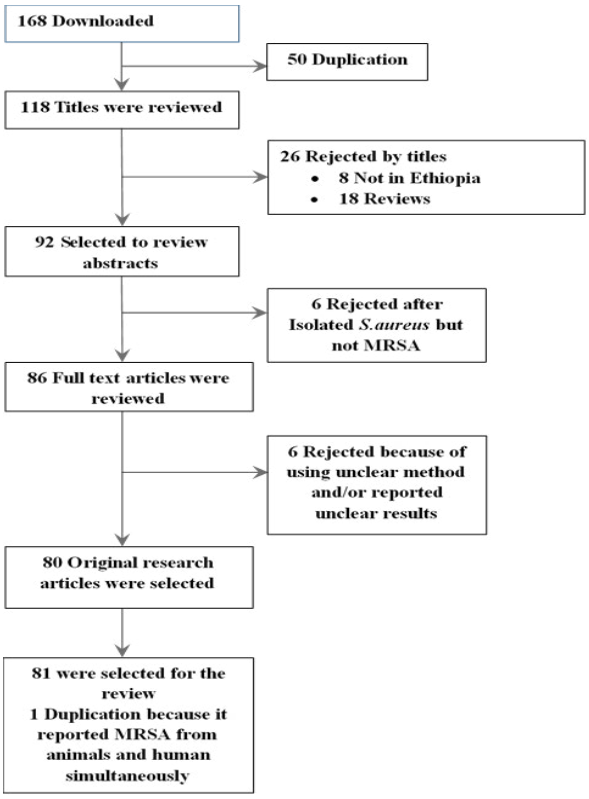

Figure 1: Flow chart shows selected articles for meta-analysis

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) (Der Simonian and Laird, 1986) approach- [6]. 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 et al., 2013). The heterogeneity of study results was assessed by the use of-$\tau 2$, I2 and Q-statistics tests. Significant heterogeneity was considered when p-value < 0.05 and $I2 > 75\%$ were observed (DerSimonian and Laird, 1986, Rücker et al., 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) (R Core Team, 2021) [10].

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 6(3.5%) used unclear methods and/or report unclear results. Therefore, 80 (47.6%) of the articles were eligible for the meta-analysis. One research article was replicated in the analysis because it conducted the research on both human and animals (Figure.1).

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%) andfood issues 4(5%). The regions in which the studies were conducted were summarized in Table 1 and Figure 2. One research was conducted by collecting samples from Amhara,Oromia and Addis Ababa and 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 category.

Table 1: Summary of 81 Studies reporting the prevalence of MRSA in Human, Food Animals Food and Environment in Ethiopia, 2010-2021

Studies	Study design	Regions	Sample collected from	Cultured specimens	Sample size	S. aureus	MRSA	MRSA Prevalence (%)	
								Per S. aureus	Per Sample Size
			Human Samples						

Eshetu *et al*., 2020	Cohort	Oro,Am, Ad	Preterm babies	blood	690	41	35	86	5
Kejela-and Bacha 2013	Cro-Sect	Oro	primary school children and prisoners	Nasal swab	354	169	39	23	11
Godebo *et al*., 2013	Cro-Sect	Oro	Surgical incisions, burns, abscess and traumatic wounds	Wound swab	322	73	56	77	17
Dagnew *et al*., 2012	Cro-Sect	Am	Food Han-dlers	Nasal swab	200	41	4	10	2
Shibabaw *et al.*, 2013	Cro-Sect	Am	Health Care Workers	Nasal swab	118	34	15	44	13
Kahsay *et al*., 2014	Cro-Sect	Am	surgical site infection	Wound swab	184	73	36	49	20
Ayehubizu *et al*., 2021	Cro-Sect	Am	Patients suspected of-ocular infection	Ocular swab	360	77	8	10	2
Dilnessa and Bitew 2016	Cro-Sect	A .A	Inpatients and Outpa-tients	Nasal swab, pus, ear discharge, blood, throat swab, eye swab, vaginal discharge, urethral discharge, urine, stool, spu-tum, CSF and body fluids	1360	194	34	18	3
Tewelde-medhin *et al*., 2017	Cro-Sect	Tig	Patients suspected of-ocular infection	ophthalmic surgeon collected specimens	270	40	7	18	3
Getahun *et al*., 2017	Cro-Sect	Am	patients with ocular infec-tions	Ocular swab	312	69	23	33	7
Tadesse *et al*., 2019	Cro-Sect	Sid	patients having ear discharge	Ear swab	152	41	7	17	5

Kasew *et al*., 2021	Cro-Sect	Am	patients with ultrasound confirmed urinary stone	urine sample	300	7	2	29	1
Gorems *et al*., 2018	Cro-Sect	Oro	patients with draining otitis	Ear swab	173	55	19	35	11
Kalayu *et al*., 2020	Cro-Sect	Tig	Farm workers	Nasal Swabs	71	22	0	00	00
Ramos *et al*., 2014	Cro-Sect	Oro	leprosy patients with chronic ulcers	Pus swab	68	15	3	20	4
Biset *et al*., 2020	Cro-Sect	Am	Pregnant women	Urine sample	384	11	4	36	1
Abie *et al*., 2020	Cro-Sect	Am	hospital janitors	Nasal swabs	436	101	21	21	5
Reta *et al*., 2017	Cro-Sect	Am	pre-school children (1–6 years) attending their kindergarten education	Nasal swabs	400	52	0	00	00
Legese *et al*., 2018	Cro-Sect	Tig	healthcare workers	Nasal swab	242	29	14	48	6
Kahsay et al., 2018	Cro-Sect	Tig y	University Janitors	Nasal swabs	184	69	45	65	24
Belyhun *et al*., 2018	Cro-Sect	Am	Patients with ocular infections	Ocular swab	210	35	32	91	15
Feleke *et al*., 2018	Cro-Sect	Am	Patient with Nosocomial infection	Nasal swab	260	77	52	68	20
Temesgen *et al.*, 2019	Cro-Sect	Am	Pneumonic Patients	sputum	414	24	18	75	4
Wasihun *et al*., 2015	Cro-Sect	Tig	Febrile patients	blood	514	54	38	70	7
Hailu *et al*., 2016	Cro-Sect	Am	Patients with ear problem	Pus swabs from discharging ears	368	78	27	35	7
Gebremedhn *et al*., 2016	Cro-Sect	Tig	HIV positive individuals attending HIV care service	Nasal and throat swabs	249	81	6	7	2
Deyno *et al*., 2017	Cro-Sect	Sid	Patients with Ear infection	Ear swab	117	33	30	91	26

Tadesse *et al*., 2018	Cro-Sect	A .A	Patients suspected-infections	Wound and corre-sponding nasal swabs	188	79	77	97	41
Birru *et al*., 2021	Cro-Sect	SNNP	Septicemia suspected patients	blood	225	7	4	57	2
Tolera *et al*., 2018	Cro-Sect	Oro	Patients admitted in Medical, Surgical, Obstetrics, Gynecology, Malnutrition, and Pediatric wards	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	patients with Visceral leishmania-sis (VL)	Blood samples	83	11	2	18	2
Alebachew *et al*., 2016	Cro-Sect	Am	HIV positive patients with sepsis	Blood	100	13	5	38	5
Semret *et al*., 2020	Cohort	A .A	Patients with suspected Hospital-as-sociated infection (HAI)	Blood	777	82	62	76	8
Tigist *et al*., 2012	Cro-Sect	A .A	Burn wound Infection	pus	114	66	51	77	45
Sewunet *et al*., 2013	Cro-Sect	A .A	Burned Patients	Blood and burn wound swab	100	24	5	21	5
Beyene *et al*., 2019	Cro-Sect	Oro	Food han-dlers	Nasal and hand swabs	300	86	6	7	2
Abosse *et al*., 2021	Cro-Sect	Am	Patients with surgical wound infec-tions	wound secretion/ pus swab	165	24	10	42	6
Fentie *et al*., 2018	Cro-Sect	Am	Cancer patients	Blood, urine and wound swabs	216	12	3	25	1
Ameya *et al*., 2020	Cro-Sect	SNNP	Pediatric patients	Blood	238	9	2	22	1

Mitiku *et al*., 2021	Cro-Sect	SNNP	Patients with urinary infection	Urine	422	53	23	43	5
Yitayeh *et al*., 2021	Cro-Sect	Am	Patients suspected of-infection	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	patients with urinary catheter	Urine	231	3	1	33	0.40
Tefera *et al*., 2021	Cro-Sect	Am	Surgical ward inpa-tients	Wound swab	242	71	32	45	13
Alelign *et al*., 2021	Cro-Sect	SNNP	Patients with Peritonitis	ascitic fluid	147	4	1	25	1
Dessie *et al*., 2016	Cro-Sect	A .A	Patients was made surgery	Wound Swab	107	19	2	10	2
Moham-med *et al*., 2017	Cro-Sect	Am	Patients with Wound infection	Wound swab	137	39	30	77	22
Mama *et al*., 2019	Cro-Sect	SNNP	Patient with wound infec-tion	Wound Swab	161	79	65	82	40
Diriba *et al*., 2020	Cro-Sect	Oro	Patients suspected of ocular infection	Eye swab	319	29	4	14	1
Jemal *et al*., 2020	Cro-Sect	Am	Bacteremia suspected HIV/AIDS Patients	Blood	384	38	28	74	7
Dessie *et al*., 2021	Cro-Sect	Am	Pneumonic Patients	Swab of washed sputum	406	29	10	34	2
Tamire *et al*., 2021	Cro-Sect	A .A	Patients developing infection	Pus and blood	413	160	57	36	14
Jemal *et al*., 2021	Retro	Am	Neonates with sepsis	Blood	1854	118	13	11	1

Tsige *et al*., 2020	Cro-Sect	Am	Patients with Wound Infection	Wound swab	266	92	26	28	1
Efa *et al*., 2019	Cro-Sect	Oro	Medical students	Nasal Swab	371	82	31	38	8
Negussiea *et al*., 2015	Cro-Sect	A .A	Septicemia Suspected Children	Blood	201	13	5	38	2
Lemma *et al*., 2015	Cro-Sect	Am	HIV-infect-ed, under 15 years of age, receiving medical care	swabs from-the anterior nares, the skin and the perine-um	1200	281	73	26	6
Mulu *et al*., 2018	Cro-Sect	Am	HIV infected children	pharyngeal swab	300	88	29	33	10
Weldu *et al*. 2020	Cro-Sect	Tig	Septicemia Suspected Children at neonatal in-tensive care unit,	Blood	317	9	6	67	2
Tibebu *et al*., 2021	Cro-Sect	Oro	Cow Milers' hand	Hand swab	52	10	0	00	00
Hailemari-am *et al*., 2021	Cro-Sect	Sid	Patients complaining bacterial infections	clinical sample including Urine, CSF, Blood, pus, discharge, stool and sputums	1085	56	3	5	0.30
			Food Ani-mals						
Tesfaye *et al*., 2021	Cro-Sect	Oro	Mastitic cow	milk	121	37	12	0.32	0.099
Daka *et al*., 2012	Cro-Sect	Sid	Lactated cow	milk	160	78	47	0.60	0.29
Kalayu *et al*., 2020	Cro-Sect	Tig	Dairy cow	Milk	385	48	1	0.02	0.003
Girmay *et al*., 2020	Cro-Sect	Tig	Mastitic-cow	Milk	64	21	7	0.33	0.109
Dabele *et al*., 2021	Cro-Sect	Oro	lactating Zebu cows	1528	7	0	0	0	
Tibebu *et al*., 2021	Cro-Sect	Oro	Cow	Milk and Udder swab	181	40	2	0.05	0.01
Letebrhan *et al*., 2021	Cro-Sect	Oro	Mastitic cow	Milk	116	18	1	0.06	0.01

			Environment Related Samples						
Moges *et al*., 2014	Cro-Sect	Am	Waste Water	Water	60	10	1	0.10	0.02
Firesbhat *et al*., 2021	Cro-Sect	Am	urfaces, and leftover drugs and antiseptics	Swabs	384	15	13	0.87	0.03
Solomon *et al*., 2017	Cro-Sect	SNNP	Wolaita Sodo University teaching and referral Hospital (WSUTRH) wards (Delivery room, operation theater, and intensive care unit)	Air sample with Agar plate	216	64	28	0.44	0.13
Kahsay *et al*., 2019	Cro-Sect	Tig	buses surfaces	Surface swab	300	54	17	0.31	0.06
Darge *et al*., 2019	Cro-Sect	Tig	intensive care units medical equipment and inanimate surfaces	Surface swab	130	40	34	0.85	0.26
Tsegaw *et al*., 2017	Cro-Sect	Am	eye medications in-use	drop of eye medications in-use	100	5	4	0.8	0.04
Sebre *et al*., 2020	Cro-Sect	A .A	surfaces and medical devices in hospital	Surface swab	164	63	54	0.86	0.33
Getachew *et al*., 2018	Cro-Sect	Am	Air and surface	Air sample and surface swab	356	71	18	0.25	0.05
			Food Samples						
Solomon *et al*., 2018	Cro-Sect	Oro	cockroaches	cockroaches	114	15	8	0.53	0.13
Adugna *et al*., 2018	Cro-Sect	A .A	beef meat at the butchers and Addis Ababa abattoir	Meat	888	133	133	1	0.15

Haimanot *et al*., 2010	Cro-Sect	Oro	food establishments, butcher shops and a slaughter houses	Meat	165	20	18	0.9	0.11
Lemma *et al*., 2021	Cro-Sect	A .A	from farms and retail markets.	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, Sid=Sidama, SW=South West, Oro-AmAd=Oromia, Amhara and Addis Ababa, Cro-Sect=cross Sectional,

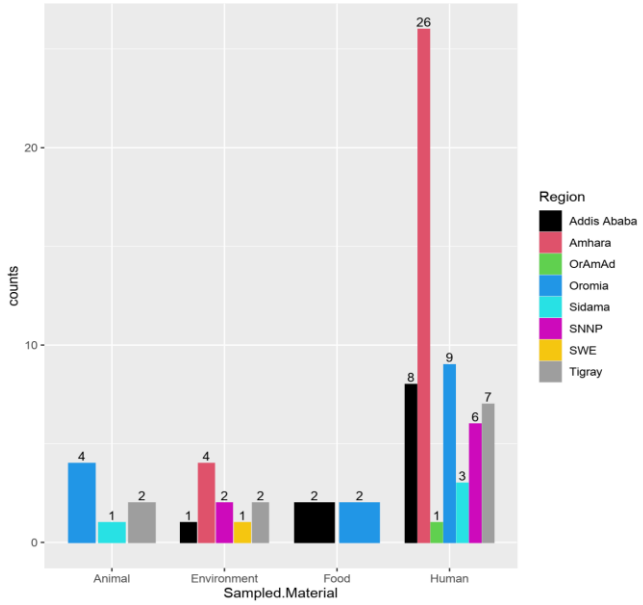

Figure 2: The Number of the Articles according to Study Area and Sampled Materials

OrAmAd=Oromia, Amhara, and Addis ababa

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%) (Fig.3). However, its proportion was highly diversified. The between-study heterogeneity was τ^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.

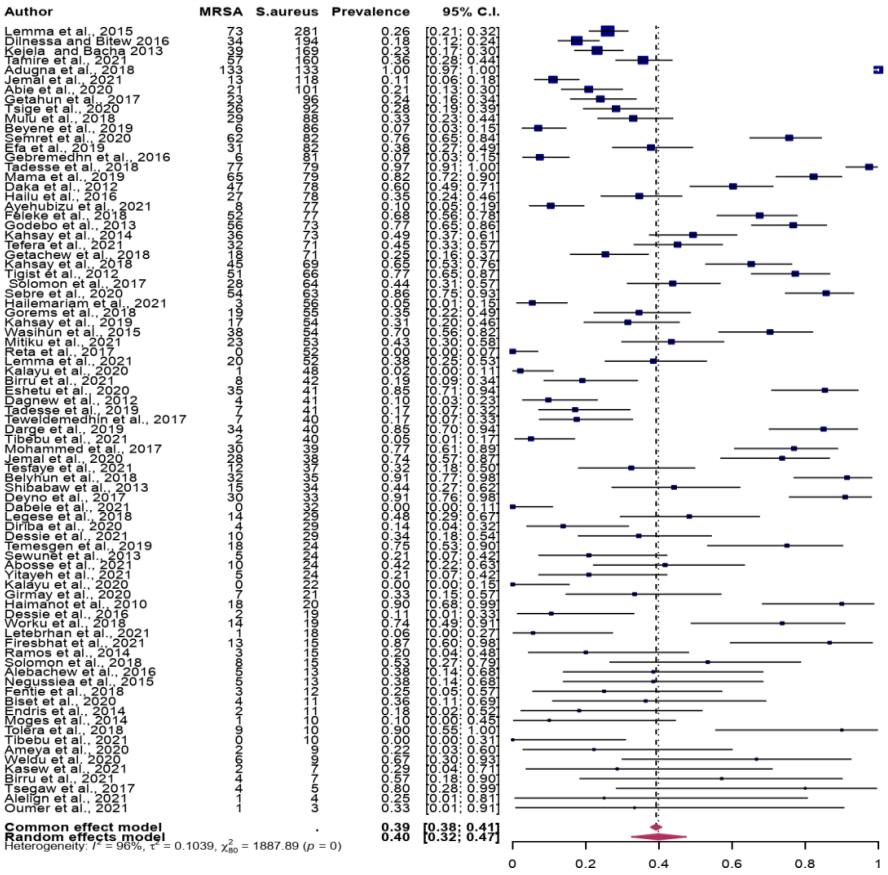

Figure 3: Forest Plot of Summary pooled proportion of MRSA in *S. aureus* isolates

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 rstudent-function to assess the presence of studentized residual. Accordingly, two articles were found having the z values above 2 (Fig.4). 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.

	resid	se	z
1	-0.07792	0.342999	-0.22718
2	0.202335	0.338348	0.59801
3	0.485221	0.338728	1.432481
4	-0.18719	0.338584	-0.55288
5	0.380255	0.335719	1.13266
6	-0.35926	0.340457	-1.05524
7	-0.3178	0.365873	-0.8686
8	0.040937	0.343765	0.119085
9	0.092159	0.33945	0.271494
10	-0.35605	0.336162	-1.05915
11	0.484173	0.3545	1.365794
12	-0.25697	0.336704	-0.76319
13	-0.24911	0.341621	-0.72921
14	-0.17538	0.338419	-0.51824
15	-0.25485	0.34138	-0.74652
16	-0.09736	0.378858	-0.25698
17	-0.05727	0.340563	-0.16817
18	-0.52099	0.336698	-1.54736
19	-0.58985	0.346261	-1.7035
20	0	0.355551	-0.57478
21	0.036486	0.340006	0.107311
22	-0.02944	0.363403	-0.08101
23	-0.21352	0.33784	-0.63201
24	-0.62688	0.333595	-1.87917
25	0.082057	0.345298	0.237641
26	0.253373	0.338144	0.749304
27	0.574012	0.339314	1.691682
28	0.278093	0.337332	0.82439
29	-0.08956	0.340562	-0.26298
30	0.479956	0.33907	1.415508
31	0.352656	0.346588	1.01751
32	0.307478	0.338776	0.907615
33	-0.05738	0.339513	-0.16902
34	-0.40782	0.334738	-1.21832
35	0.564353	0.340228	1.65875
36	0.715638	0.324215	2.207297
37	0.162553	0.37881	0.429116
38	-0.06518	0.349579	-0.18645
39	0.515394	0.365272	1.410986
40	0.368594	0.394246	0.934935
41	-0.21806	0.363236	-0.60033
42	-0.01069	0.359022	-0.02976
43	0.851189	0.301207	2.825931
44	-0.01672	0.340871	-0.04905
45	0.367834	0.335303	1.097018
46	0.538956	0.348286	1.547453
47	0.386405	0.336248	1.149165
48	-0.20236	0.347354	-0.58258
49	-0.41648	0.334142	-1.24642
50	0.017516	0.347674	0.05038
51	-0.14478	0.360963	-0.4011
52	-0.16786	0.369495	-0.4543
53	0.494131	0.334342	1.477921
54	-0.60784	0.340228	-1.78657
55	0.033132	0.340753	0.097233
56	-0.20236	0.347354	-0.58258
57	-0.03346	0.426066	-0.07853
58	0.04967	0.339687	0.146221
59	-0.11452	0.407032	-0.28136
60	-0.33195	0.350523	-0.94702
61	0.379015	0.34058	1.112853
62	-0.1582	0.339173	-0.46642
63	0.335524	0.350451	0.957405
64	0.449259	0.333539	1.346946
65	-0.29419	0.344527	-0.8539
66	0.342022	0.341205	1.002395
67	-0.05542	0.345354	-0.16047
68	-0.04779	0.340341	-0.14041
69	-0.34881	0.334428	-1.043
70	-0.12626	0.338949	-0.37251
71	-0.02429	0.339509	-0.07154
72	0.130572	0.355658	0.367129
73	-0.01069	0.359022	-0.02976
74	-0.15392	0.341768	-0.45037
75	-0.07519	0.339302	-0.22159
76	0.253675	0.369367	0.686782
77	-0.54051	0.365227	-1.47992
78	-0.44505	0.339704	-1.3101
79	-0.23005	0.341366	-0.6739
80	-0.41166	0.351141	-1.17235
81	-0.44363	0.336656	-1.31776

Figure 4: Residual test of the outliers in MRSA Prevalence

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 (Fig.5). 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 Fig (3).-Moreover, the result of the τ2 and Q tests were τ2= 0.0847& Q= 1167.065 in human, τ2 = 0.1095& Q= 106.3283 in animals, τ2 = 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 ($p<0.05$).

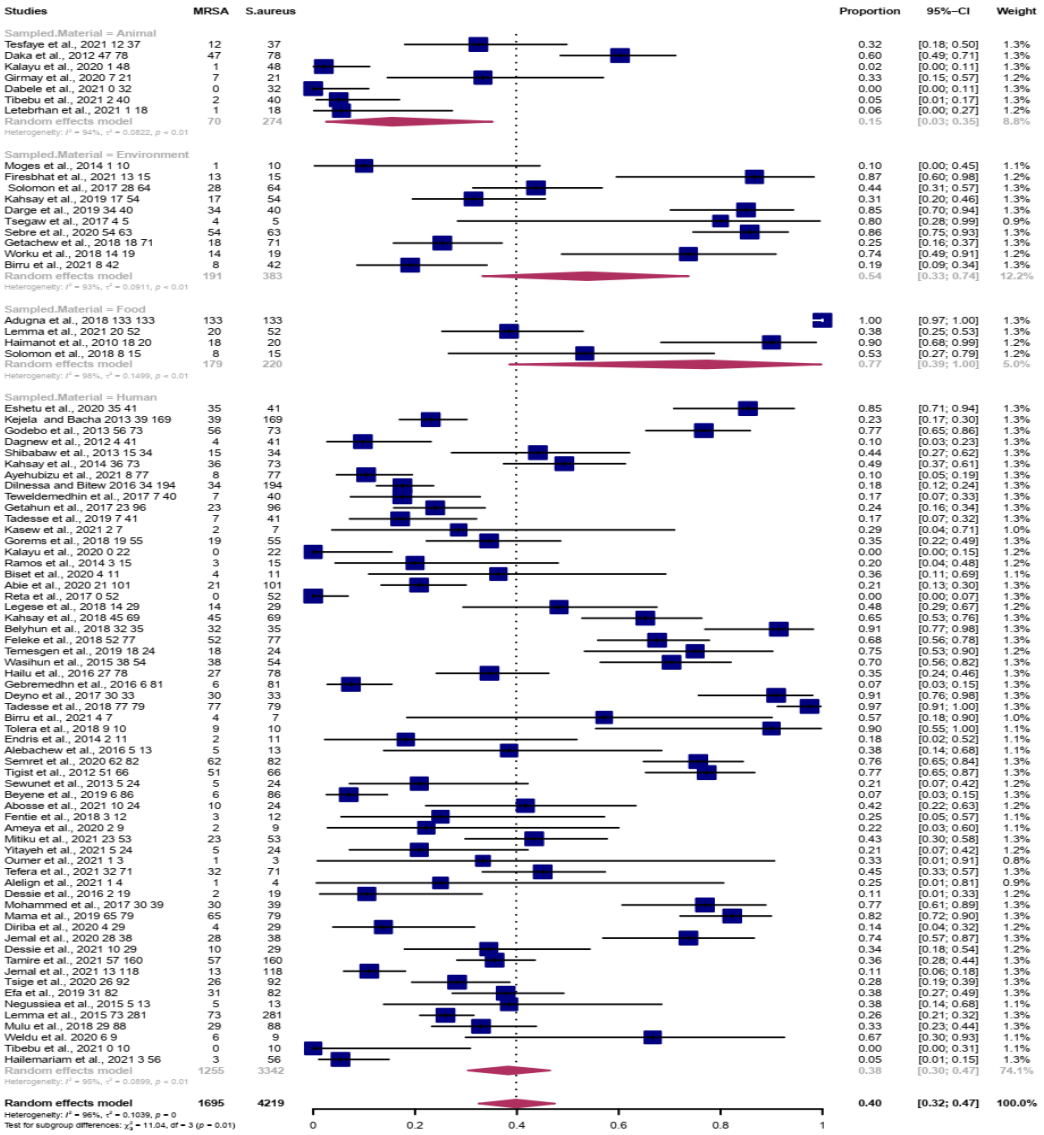

Figure 5: Forest Plot of the Subgroup Analysis Based on Sampled Materials

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-τ2-was-0.0859-with I2=95%-in patients and 0.0597 with I2 =93%.

Publication Bias

As determined from funnel plot (Figure 6) 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.

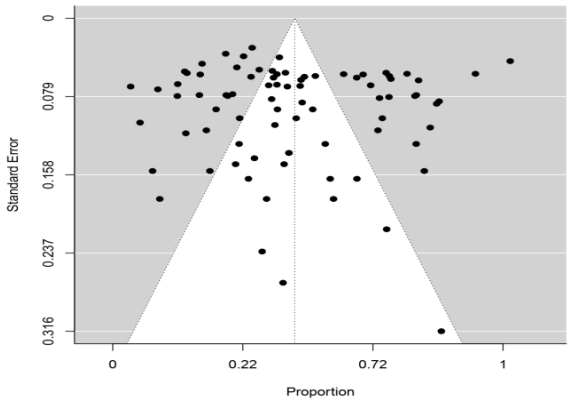

Figure 6: Funnel Plot of the Publication Bias of the of the Meta Analysis

3.5. 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 3.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).

Table 2: Pooled Multidrug resistance rates of MRSA strains

	Tesfaye *et al.*, (2021)	Daka *et al.*, (2021)	Kejela-and Bacha (2013)	Kahsay *et al.*,(2014)	Dilnessa and Bitew .(2016)	Tadesse*et al.*,(2019)	Solomon *et al.*,(2017)	Abie *et al.*,(2020)	Legese *et al.*,(2018)	Kahsay *et al.*, (2018)	Kahsay *et al.*,(2019)	Deyno *et al.*,(2017)	Tadesse *et al.*,(2018)	Alebachew *et al.*,(2016)	Adugna *et al.*,(2018)	Lemma *et al.*, (2021)	Haimanot *et al.*,(2010)	Mitiku *et al.*,(2021)	Mama *et al.*,(2019)	Tsige *et al.*,(2020)	Efa *et al.*,(2019)	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
Oxy TTC.	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
Doxy-cy.							4			9			45							8			0.31-	0.11-	0.54
Tri-matho.		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

Antimicrobial resistance is a natural process in which an antimicrobial agent previously used against a microbe is no longer effective. The resistant microorganisms can survive or even grow in the presence of an antimicrobial concentration at levels of sufficient to inhibit or kill non-resistant microorganisms of the same species [9]. As the result, drug resistance-of microorganisms has been becoming the top issue of the world. *Staphylococcus areus*-is one of such pathogens which is losing susceptibility to the most effective antibiotics such as methicillin and vancomycin. Furthermore, studies have reported that, methicillin resistant *S. aureus* (MRSA) is the most resistant to other antibiotics including penicillin, ampicillin, amoxicillin, tetracycline and other third generation antibacterial agents (8, 15). MRSA was initially considered as the one of the health care associated pathogens. However, since the past ten years, the prevalence of the community based MRSA has been determined significantly increasing in the environment of different countries (WHO, 2017).

Different types of MRSA strains have been distinguished based on epidemiological groupings. Even if the cut points are ambiguous, the three substrians of-MRSA, hospital associated MRSA (HA-MRSA) (or sometimes called Health Care Associated MRSA (HCA-MRSA)), Community Associated MRSA (CA-MRSA) (Mohammed and Nigatu, 2015; Eshetie et al., 2016) and livestock Associated MRSA (LA-MRSA) (GFMH , 2015) have been

frequently reported so far. HA-MRSA infections are acquired in health care settings and associated with particular-risk factors including prolonged hospitality and antibiotic treatments, surgical interventions and close contact with MRSA infected individuals. CA-MRSA emerges in the community without hospitalization as a risk factor. It spreads due to close contact in sport settings, schools, day care centers, military settings and prisons. The livestock associated MRSA colonizes different food animal and may cause infections in humans (Mohammed and Nigatu, 2015). It is expected to be transmitted to human through direct contact with animals, environmental contamination, as well as eating or handling contaminated foods (Tarekgne, 2016).

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 Eshetie et al., (2016) and Sarrafzadeh et al.,(2021) 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. Our result is also less than the analysis of Deyno et al (2017) which reported the pooled prevalence of MRSA among *S.auresu* in Ethiopia as 47%.-However, it is coincided with the report of Khanala et al.,(2021) who reported the pooled prevalence of MRSA among *S.aureus* as (38.2%). According to the assessment of WHO (2014), the resistance rate of *S.auresus* to methicillin exceeds 50% in the community and hospitals in WHO regions and ranged between .-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% [8].

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.,(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 Samutela *et al*., (2021) 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. However, it is higher than the previous report by Lozano *et al*., (2016) who reported-the prevalence of animal associated MRSA among *S. aureus* in different African countries including Ethiopia as ranged-between 0 and 3%. 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 (Paterson *et al.*, 2014) and can jump between hosts. These species may act as carriers of MRSA originating from humans (so called "humanosis") (Morgan, 2008). Moreover, bovine and human MRSA strains are indistinguishable by phenotyping and genotyping methods providing evidence for MRSA transmission between human and cattle (Hata *et al*., 2010). 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 (Crespo-Piazuelo and Lawlor, 2021).

Apart from its ability to resist antibiotics,-the concern of *S.aureus* to be burden in public and animal health arises from its adaptation to diversity of environmental conditions (Pournajaf *et al*.,2014). 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. Researchers indicated that there might be cross contamination of MRSA between the carriers and their environments to pose health care associated MRSA infections, and they recommended the disinfection of the rooms and associated materials (Hasson *et al*.,2017; Nkuwi *et al*.,2018).-

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 (Abebe *et al*.,2020).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. Researchers insisted that 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 (Tsepo *et al.*,2016).

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 such as (4 Eshetie *et al,*2016) and (Gebremariam *et al*.,2014) have also documented that MRSA strains were found to be too highly resistant to most of the above mentioned antibiotics. It is obvious that MRSA strains are able to express beta-lactam hydrolyzing enzymes so called betalactamases or capable of modifying penicillin binding proteins (Tenover.,2006) so that MRSA strains are capable of inactivating the beta-lactam agents such as penicillin, ampicillin, cephalosporins, and carbapenems. 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 gene (Ardic *et al.*,2006). 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 (Enright *et al.*,2002). 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.

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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