Prevalence, antimicrobial susceptibility and genotypic characteristics of *Staphylococcus aureus* in Tanzania: a systematic review

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Abstract

Background : Information about prevalence, antibiotic resistance and genotyping data of *Staphylococcus aureus* (*S aureus*) isolated from different infections and colonization, both in humans and animals is scarce in Tanzania. Given the wide range of infections *S aureus* can cause and the raise of methicillin resistant *S aureus* (MRSA) globally, this review was aimed at collecting local published data on the *S aureus* bacterium to better understand the epidemiology. **Methodology:** A systematic review of scientific studies reporting on prevalence, antibiotic resistance and genotyping of *S aureus* in human and animal infection and colonization was done. Literatures extracted from electronic databases such as PubMed and Google Scholar were screened for eligibility and relevant articles included into the review. The review is limited to literatures published in English, between the years 2010 and 2018. . **Results:** 39 studies conducted in 5 of the 9 administrative zones in Tanzania were reviewed to establish *S aureus* prevalence in human and animal infection and colonization. Prevalence in human ranged from 1 - 60%. Antibiotic resistance patterns of *S aureus* isolated from colonized humans showed higher resistance rates against erythromycin (49%), co-trimoxazole (38%) and tetracycline (28%) compared to report from other studies outside Africa. The review suggests an increased MRSA prevalence of up to 33% compared to 16% reported in previous years. Genotypic data reviewed suggested that MRSA predominantly belonged to ST88. *S aureus* prevalence in animal studies ranged from 33 - 49% whereas MRSA prevalence ranged from 4 - 35%. Generally low antibiotic resistance levels were reported in these studies with exception to penicillin (85%) and ampicillin (73%). Resistance against tetracycline reported at 30% collaborates the suggested overuse of the drug in livestock keeping in Tanzania. **Conclusion :** Prevalence of MRSA in Tanzania is rising although clear variations between different geographic areas could be observed. Non-susceptibility to commonly prescribed antibiotics in community associated *S aureus* is of concern. Research strategies to better understand the *S aureus* epidemiology by including genotypic characterisations, as well as strengthening antimicrobial resistance surveillance and antimicrobial stewardship are recommended.

Background

Antimicrobial resistance (AMR) is a global concern estimated to account for approximately 700,000 deaths each year (1). If no appropriate measures are taken to slowdown the progression of this epidemic it is estimated that by 2050 it will cost the world around 10 million lives per annum (1). The lack of development of new antimicrobial agents in the pipeline further emphasises the necessity to reduce dependency on antibiotics by implementing infection control strategies (1, 2).

According to the 2014 World Health Organization (WHO) report, most regions stated over 50% bacterial resistance against third generation antibiotics, particularly methicillin resistant *S. aureus* (MRSA) clones in hospitals (2). Furthermore in 2017, the WHO listed antibiotic resistant bacteria including *Staphylococcus aureus* (*S. aureus*) as a priority bacterium to guide research, discovery and development of new antibiotics (3). The report further recommended special attention to be directed towards the

identified resistant bacteria due to their ability to rapidly develop resistance against multiple antibiotic classes hence limiting therapeutic options (3).

S. aureus is an old bacterium discovered in the 18th Century, antibiotic resistance in the bacterium against penicillin was described in the 1950's, the penicillin-resistant staphylococci inactivates penicillin function by an enzyme called penicillinase or beta-lactamase which degrades the β -lactam ring in penicillin, thus altering the shape of penicillin and preventing its binding to the penicillin binding proteins (4). Following penicillin failure in treating *S. aureus* infections, methicillin was introduced. Methicillin was particularly effective upon its introduction into clinical therapy due to its ability to resist the action of β -lactamase. However, methicillin resistance in *S. aureus* was also reported only a year after its introduction. Strains of *S. aureus* resistant to methicillin or oxacillin or other β -lactam compounds are still termed MRSA, only to honour the historic role of methicillin that used to effectively treat staphylococcal infections, and it is to methicillin that the resistance was first described (5). Several terms are used to describe different MRSA strains associated with outbreaks in different settings based on strains' genomic background and level of virulence (6). MRSA strains associated with hospital-acquired infections are commonly abbreviated to HA-MRSA, while strains causing community-associated infection are abbreviated to CA-MRSA and those associated with livestock are abbreviated as LA-MRSA.

S. aureus, is both a commensal and potentially harmful pathogen in humans and animals. The bacterium can give rise to a variety of infections ranging from mild skin and soft tissue infections to more serious and complex diseases such as pneumonia, septicaemia, infective endocarditis and other deep-seated infections (e.g., osteomyelitis) in humans as well as mastitis and necrotic infections in a variety of animal hosts. *S. aureus* can also colonise the skin and approximately 30% of the population is found to be transiently colonised if nasal swabs are examined microbiologically.

High levels of MRSA have been reported across Africa, ranging between 43% and 72%, as reported in Cameroon, South Africa and Ethiopia (7). The vast majority of clinical *S. aureus*/MRSA data in Africa is associated with hospital acquired infection (HAI) affecting individuals with healthcare related risk such as recent hospitalization, surgery and underlying chronic diseases (8). Information on community acquired *S. aureus*/MRSA infections (CAI) causing diseases in people with no healthcare associated risk is also available on the continent even though to a lesser extent. Moreover very limited data on livestock acquired *S. aureus*/MRSA infections (LAI) whereby *S. aureus* clones of animal origins colonize or cause infections in humans have been published in Africa (7). Further information on the antibiotic resistant clones occurring in both human and animal are very limited, hindering comprehensive understanding of the epidemiology of the bacterium (9).

Tanzania, a developing country located along the East African coast, housing a population of about 57 million people, of which 36% is engaged in livestock keeping as the major source of livelihood. The potential for human-animal contact is very high, especially in tribes that co-habit with their animals such as Maasai people. The aim of this review is to summarize literatures reporting on the prevalence, antibiotic resistance of *S. aureus* in Tanzania. Furthermore reported genotypic characterization of *S.*

aureus will be reviewed to provide a more nuanced profile of *S. aureus* genetic diversity in colonization and infections both in animal and human hosts as well as their possible relationship.

Materials And Methods

Eligibility criteria

A systematic review of Tanzanian scientific studies reporting on prevalence, antimicrobial resistance and genotypic characterization of *S. aureus* from human and animal sources published between 2010 and 2018 was performed. Information sought for in the publication included commensal and clinical *S. aureus* recovered from different infections including invasive and non-invasive. Animal studies reporting on *S. aureus* recovered from animals and their products were also considered. All studies that recovered less than five *S. aureus* isolates in their studies as well as publications that were written in a language other than English were excluded from this review.

Information sources and search strategies

PubMed database was researched in November 2018 by a librarian using Boolean operators “AND” and “OR” to identify studies fitting our inclusion criteria. The following search terms were used “*Staphylococcus aureus* OR *S. aureus* AND antimicrobial susceptibility OR antibiotic resistance AND prevalence AND Tanzania.” Additionally search words such as “Molecular typing AND *S. aureus* AND antibiotic resistance AND Tanzania” and “*Staphylococcus aureus* OR *S. aureus* AND antimicrobial susceptibility OR antibiotic resistance AND prevalence AND Tanzania” were used in Google scholar to identify eligible articles. The bibliographies of all eligible documents were hand-searched for additional publications eligible for review.

Data extraction and appraisal process

The Joana Briggs Institute checklist was applied to appraise and review the quality of each study accessed by two independent reviewers. A data extraction form was designed to capture required information such as author, year of publication, study period, methodology, MRSA identification strategies, *S. aureus* and MRSA prevalence, antibiotic resistance patterns as well as genotypic information. Two reviewers were involved in the process whereby the first reviewer (TM) extracted the information and the second reviewer (TK) double checked the information to eliminate possible bias. All disagreement raised during the critical appraisal process were resolved through reviewers discussions. All extracted manuscripts were analyzed using reference manager ENDNOTEX7. This study followed the standardized scientific writing format of the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines. The study has not taken on any meta-analysis due to the heterogeneity of the studies under review; nevertheless mean resistance rates and prevalence were calculated to help present the results better.

Scope of the study

This review is limited to the prevalence, antibiotic resistance patterns and genetic typing information (i.e. resistance genes, virulence genes, Staphylococcus protein A (spa) typing and multilocus sequence typing) of *S. aureus* retrieved from human and animal hosts.

Results And Discussion.

PubMed search resulted in 16 eligible articles followed by an additional 8 articles included from the Googlescholar search. Rigorous reference list review supplemented another 14 eligible publications making a total of 39 (Figure 1).

Data concerning *S. aureus* prevalence, antimicrobial resistance and genotyping were extracted from studies performed in 5 zones of the 9 administrative zones in Tanzania. Table 1, describes the distribution of the published articles review in their consecutive zones. The majority of the publications reviewed were from regions in the eastern and lake zones (i.e. 43.6% and 30.8% respectively), showing lack of *S. aureus* researched data in the other parts of the country figure

Table 1: Distribution of the reviewed articles by zone in Tanzania.

Zone	Human	Animal	Human & Animal
Eastern Zone	14	2	1
Lake Zone	12	-	-
Northern Zone	5	1	-
Central	1	-	-
Zanzibar	2	1	-
Total	34	4	1

Majority of the publications were reported in the eastern and lake zones. *S. aureus* data of animal origin have been poorly represented throughout the country

Prevalence, antibiotic resistance and genotyping of *S. aureus* isolated from humans

S. aureus prevalence was reported in thirty three (33) human related studies, gave an account which ranged from 11 – 60 % as summarized in **Table 2**. Higher infection rates were typically observed in SSTI's nevertheless the bacterium was also implicated in other infections. Furthermore it was notably observed that *S. aureus* colonization ranged between 27% - 60% in the three zones that reported on colonization. Since most colonization studies involved healthy individuals these finding are indicative of the considerable circulation of community associated *S. aureus* in the country.

The publication under review showed that *S. aureus* was isolated in a number of infections including SSTI's, bloodstream, otitis media, respiratory tract and urinary tract infections (Figure 3) staying true to characteristically causing a wide range of infections. It was also evident how various vulnerable populations such as children, elderly and immune compromised individual were at risk of *S. aureus* infections/colonization. This observation emphasises the necessity to establish a reliable and sustainable surveillance system to monitor the *S. aureus* bacterium countrywide.

Table 2: Human related studies investigating *S. aureus* in different conditions and populations across Tanzania

S.No	Prevalence <i>S. aureus</i> % (n)	Prevalence MRSA % (n)	Population	Source of <i>S. aureus</i> isolates	Location	Reference
1	41.4% (157)	37.6% (59)	Health care workers adults male and female from June 2016 -October 2016.	Nasal carriage	Dar es Salaam (Eastern zone)	Joachim A et al 2018 (11)
2	NR	11.8% in ICU patients and 2.1% in ICU HCW.	ICU patients (male and female of all age groups) and ICU HCW from October 2012 - March 2013	Nasal carriage	Dar es Salaam (Eastern zone)	Geofrey A et al 2015 (12)
3	34.5% (89) in swabs collected on admission. 20% (4) in swabs collected 48hrs after admission	24.7% (22) from samples on admission, and 50% (2) in samples collected after 48hrs.	Patients admitted to emergency or medical ward aged 5 and above.	Nasal carriage	Dar es Salaam (Eastern zone)	Joachim A et al 2017 (13)
4	40% (114)	8.3% (12)	Healthy children <5yrs From April 2010 - June 2010	Nasal carriage	Dar es Salaam (Eastern zone)	Moyo S et al 2014 (14)
5	Overall 23.2% (223), where by 26.2% (95),detected in children with acute respiratory infection and 21.4% (128) were detected in children without acute respiratory infection	NR	ages 2 to 10, with axillary temperature of $\leq 38^{\circ}\text{C}$ Dar es Salaam from April to August 2008(DSM) and June to December 2008 (Ifakara)	Nasal carriage	Dar es Salaam and Morogoro (Eastern zone)	Chochua et al 2016 (15)
6	13.2% (138)	NR	Healthy children <5yrs born after mass distribution of Azithromycin for trachoma control. Study was conducted in 2014	Nasal carriage	Kilosa, Morogoro (Eastern zone)	Bloch EM et al 2017 (16)
7	22% (22)	0%	100 nasal swabs from healthy individuals with no epidemiological connection were collected within urban and peri urban Morogoro Municipalities	Nasal carriage	Morogoro (Eastern zone)	Katakweba et al 2016 (17)

8	13.2% (245)	23.3% (57)	Male and female of all age groups who were subjected to microbiology testing between January 2005 and December 2009 (Retrospective study).	Bacteremia	Dar es Salaam (Eastern zone)	Moyo S et al 2010 (18)
9	28% (12)	NR	Male and female sickle cell anemic patients of all age groups seeking health care at MNH from January 2006-December 2008	Bacteremia	Dar es Salaam (Eastern zone)	Makani J et al 2015 (19)
10	In blood 36.5% (27), and in pus swabs 52.3% (132)	NR	Neonates aged 3 - 26 days suspected with neonatal sepsis. Study duration October 2009 - January 2010	Bacteremia and wound swabs	Dar es Salaam (Eastern zone)	Mhada T et al 2012 (20)
11	12.2% (18)	44.4% (8)	100 participants (male and female aged 18-80) with clinical evidence of Surgical site infection. Duration from September 2011 to February 2012	Wound infections	Dar es Salaam (Eastern zone)	Manyahi Jet al 2014 (21)
12	71.4% (132)	0.8% (1)	Skin and soft tissue infections patients of all age groups	Wound infections	Bagamoyo (Eastern zone)	Kazimoto T et al 2018 (22)
13	48.3% (131)	NR	Asymptomatic otitis media (OM)-associated bacteria found in patients living with HIV	Ear colonization	Morogoro (Eastern zone)	Mwabete KD et al 2018 (23)
14	The overall carriage rate of S. aureus was 21.0 % (66). 47 % (31) were from preclinical students while 53 % (35) from clinical students	1.5% (1)	Healthy students (clinical and Pre clinical) aged 18 and above. Study duration February to June 2013	Nasal carriage	Mwanza (Lake zone)	Okamo B et al 2016 (24)
15	21.5%	28% (9)	300 neonates with clinical neonatal sepsis	Bacteremia	Mwanza (Lake zone)	Kayange N et al 2010 (25)
16	14.8 (8)	50% (4)	402 malnourished under five children.	Bacteremia	Mwanza Lake zone	Ahmed M et al 2017 (26)

			Study duration September 2012- January 2013.			
17	13.7% (29)	79% (23)	Patients of all age groups and gender with lower limb ulcers seen at the surgical ward or outpatient department from November 2010-April 2012	Wound infection	Mwanza (Lake zone)	Mbunda F et al 2012 (27)
18.	8.9%(18)	44.4% (8)	Patients of all age groups with chronic lower limb ulcers seen at the surgical ward.300 wound infection were swabbed between November 2011 and February 2012	Wound infection	Mwanza (Lake zone)	Moremi et al 2014 (28)
19	28.6% (18)	19% (3)	65 patients of all age groups who underwent major surgery at BMC between July 2009 and June 2010	Surgical site wound infection	Mwanza (Lake zone)	Mawalla et al 2011 (29)
20	27.3% (6)	16.7% (1)	Woman aged 14 to 44 who have developed surgical site infections after having undergone a caesarean section. 345 woman were swabbed between October 2011 and February 2012	Surgical site wound infection	Mwanza (Lake zone)	Mpogoro et al 2014 (30)

Antibiotic resistance in human originated isolates.

The primary method for establishing *S. aureus* antibiogram in the reviewed work was done phenotypically by the use of the *Kirby-Bauer* disk diffusion test along with Clinical Laboratory Standard Institute (CLSI) guidelines. *Kirby-Bauer* is a test for antimicrobial susceptibility of bacteria, based on the size of inhibition zones of bacterial growth in a lawn culture around disks impregnated with the antimicrobial drug (44). This method has been reported to have inherent shortcomings such as being highly dependent on experimental conditions that may affect end results (45). With this fact in mind the *Kirby Bauer* antibiogram results would have to be confirmed by another test of a different principle such as genomic based method to prevent over reporting of resistance, particularly in the confirmation of MRSA and VRSA

S.No	Prevalence <i>S. aureus</i> % (n)	Prevalence MRSA % (n)	Population	Source of <i>S. aureus</i> isolates	Location	Reference
21	29.2% (7)	NR	162 patients of all age group and gender who underwent major limb amputations at BMC between March 2008 and February 2010. 24 of the participants had surgical site infections out of which different bacteria were recovered as the cause of infection.	Surgical wound infection	Mwanza (Lake zone)	Chalya et al 2012 (31)
22	59.3%	NR	All patients of all age groups and gender presenting with animal related injuries at the BMC between September 2007 and August 2011. Postoperative wound infection was the most commonest complication reported lead by <i>S aureus</i> infections	Surgical site wound infections	Mwanza (Lake zone)	Gilyoma et al 2013 (32)
23	Overall prevalence 16.1 (25) out of which 28% (7) were isolated in HIV positive patients and 72%(18) in HIV negative patients	NR	The study was done to compare magnitude of bacterial resistance to cotrimoxazole/other antimicrobials among isolates from HIV infected patients on cotrimoxazole prophylaxis and those not on prophylaxis and non-HIV patients attending BMC between January and October 2012	Urine and wound swabs	Mwanza (Lake zone)	Marwa et al 2015 (33)
24	18.2% (34)	41.2% (14)	301 patients aged more than one year who presented with ear discharge for more than 6 weeks and tympanic membrane perforation at the ENT department between October 2013 and March 2014 were recruited into the study	Ear infection	Mwanza (Lake zone)	Mushi et al 2016 (34)
25	Overall 22.8% (100) Blood 80% (80) Pus swabs 18% (18)	Only 78 were subjected to AST.34.6%	A total of 3330 microbiological culture results scripts representing non-repetitive specimens reported between June 2013 and	Bacteremia, wound infection, urinary tract infection and	Mwanza (Lake zone)	Moremi et al 2016 (35)

	Other infections 2% (2)	(27) were MRSA	May 2015 were retrieved and analyzed for pathogens and their susceptibility patterns using STATA-11 software.	pulmonary infection		
26	55.3% (68)	NR	Primary school children (aged 6-15) from 4 schools in Moshi municipality assessed/self-reported respiratory tract infection symptoms. The community based study was conducted between January and March 2014.	Nasal and Trought swabs	Moshi Northen zone	Ngocho et al 2015 (36)
27	66% (103) at 6 weeks, 36% (47) at 3 months and 24% (33) at 6 months. 38% (17) mothers were colonized by S aureus parallel to their children.	NR	Children born to HIV positive mothers attending RCH clinics to establish prevalence and influence of nasal pharyngeal bacterial colonization on children. Nasal swabs from children were taken at 6 weeks (n=156), 3 (n=136) and 6 (n= 130) months consecutively. Mothers (45) of the infants were also swabbed at 3 and 6 month visits(Study duration 2005-2009	Nasal carriage	Moshi Northen zone	Kinabo et al 2013 (37)
28	16% (23)	NR	Patients presenting with SSI, infected diabetic wounds, infected wounds due to trauma, and patients with other infected wounds admitted in surgical ward (study duration July 2013 to June 2014)	Wound infections	Moshi (Northen zone)	Kassam et al 2017 (38)
29	9.3% (35) of which 82.9 (29) were from wound infections, 11% (4) from blood samples and 6% (2) from sputum samples	Only 22 isolates were subjected to AST. 27.3% (6) were MRSA	People admitted to the medical or surgical wards at KCMC between 2013 and 2015. The study collected stool, sputum, blood and wound/pus samples from patients of all age groups to describe causative agents of different infections.	Wound infection Blood infection Bronchial infection	Moshi (Northen zone)	Kumburu et al 2017 (39)
30	9.1% (6)	NR	A total of 867 patients aged between 2 and 5 with fever above 37 ⁰ C were	Urinary tract infection	Tanga (Korogwe)	Mahende et al

			enrolled between January and October 2013. 373 urine samples were collected and 66 tested positive for UTI. All <i>S. aureus</i> isolates were recovered from UTI patients		(Northern zone)	2014 (40)
31	17% (17)	NR	Children aged 0-12yrs dismissed from the hospital with pneumonia diagnosis. 100 children were enrolled in the attempt to characterize etiology of community acquired pneumonia. (study duration August 2014- April 2015)	Blood infection	Itigi (Central zone)	Caggiano et al 2017(41)
32	11.3% (9)	0%	Febrile adults and children seeking care at the Mnazi mmoja hospital between March 2012- April 2013	Blood infection	Zanzibar	Onken et al 2015 (42)
33	6.3% (5)	0%	Febrile patients seeking outpatient health care at 3 different district hospitals (Wete, Chake chake, and Mkoani) on Pemba island between March 2009 to December 2010	Blood infection	Zanzibar	Thriemer et al 2012 (43)

strains. In this review, four studies had MRSA confirmed genotypically which showed 100% agreement with the phenotypic *Kirby-Bauer* disk diffusion test. This agreement between the methods should encourage the use of the *Kirby-Bauer* disk diffusion test as an antibiotic sensitivity monitoring strategy in the country, since it is the most available and affordable method in our settings.

Twenty two (22) studies contributed information on antibiotic susceptibility of *S. aureus* bacteria. MRSA in most cases was identified by resistance against ceftazidime, however one study used methicillin as their identification drug. As summarized in Table 3, extremely high resistance rates against β -lactams i.e. penicillin (87 - 99%) and ampicillin (67 - 91%) were observed.

S. aureus colonization is considered being a risk factor for eventual infection as well as a potential source of spread of resistant strains. Examination of colonization strains is therefore key in understanding the epidemiology of *S. aureus* infection/diseases. This review discovered that the antibiotic resistance patterns in colonization strains showed uncharacteristically high resistance to commonly used antibiotics compared to studies reported in Europe and Asia. In den Heijer et al 2013's report about antibiotic resistance of commensal *S. aureus* across Europe described resistance rates lower than 20% against erythromycin, gentamicin, tetracycline and co-trimoxazole (46). Similar low resistance rates were reported in some parts of Asia with an exception of tetracycline which was slightly higher than 30% (47).

This review on the other hand recorded higher mean resistance rates of 49%, 38% and 28% against erythromycin, co-trimoxazole and tetracycline respectively. Further resistance against gentamicin was significantly higher than recorded in other parts outside Africa (46, 47).

Resistance pattern in clinical *S. aureus* observed in this review were in accordance with other reports around Africa (48, 49). As in many parts recorded resistance against β lactams was high, further markedly resistance rates ranging from 44-50% against erythromycin, gentamicin, co-trimoxazole and clindamycin were also described in this review. The affected antibiotics are readily available in the community and also commonly used for empirically treatment of different cases of bacterial suspected infections. A notable presence of resistance against these antibiotics is an indication of their failure in treatment and a need for broader class antibiotics which are expensive and not accessible for most Tanzanians.

MRSA prevalence reported in different studies in this review was between 19-33% which seems to have risen in the last 10 years. Abdulgader et al 2015 in the review of MRSA prevalence on the African continent categorized Tanzania as belonging to countries with low MRSA prevalence ranging from 6-16% between the years 2001-2009 (50). This abrupt increase should be taken seriously by which more research efforts should be directed towards understanding and preventing further spread of these strains in order to safe guard much needed antibiotics

Table 3: Antimicrobial resistance rates of *S. aureus* in humans

<i>Antibiotic (N*)</i>	<i>Resistance rates in S. aureus isolates from humans colonization. References (% range)</i>	<i>Mean resistance (n/N*) (%)</i>
Penicillin(267)	(11-13) (96 -100)	(263/267) (99%)
Ampicillin (151)	(17, 24, 36) (84-100)	(133/151) (88%)
Tetracycline (223)	(12, 14, 17, 24) (9-95)	(63/223) (28%)
Erythromycin (244)	(11, 12, 24) (19-100)	(119/244) (49%)
Gentamicin (382)	(11, 13, 14, 17, 36) (9-34)	(99/382) (26%)
Co-trimoxazole (314)	(11, 12, 14, 17) (14-66)	(118/314) (38%)
Ciprofloxacin (233)	(13, 14) (4-11)	(15/233) (6%)
Clindamycin (178)	(11, 12) (9-76)	(30/178) (14%)
Cefoxitin (388)	(11, 12, 14, 24) (2-100)	(93/388) (24%)
	<i>Resistance rates in S. aureus isolates from invasive (blood-born) infections. References (% range)</i>	
Penicillin (46)	(25, 42, 43) (23-80)	(40/46) (87%)
Ampicillin (27)	(20) (85)	(23/27) (85%)
Erythromycin (37)	(25, 43) (20-66)	(23/37) (62%)
Gentamicin (27)	(20) (56)	(15/27) (56%)
Co-trimoxazole (46)	(25, 42, 43) (22-60)	(23/46) (50%)

Two publications gave an account on genetic characterization of MRSA(39, 51). The observed MRSA were dominated by ST88, however sequence types ST8, ST1719, ST 1820, and ST239 were also reported. None of the MRSA were *pvl* positive consistent with the findings by Abdulgader et al 2015 who suggested that Africa is predominated by *pvl* negative MRSA belonging to ST88 (50).

Even though some important information was apparent in this review data concerning MSSA and MRSA genotyping is still limited, Kumburu et al 2018 for example was the only one who reported on other virulence factors apart from *pvl*/hence still lacking knowledge on other important factors associated to the bacteria circulating in our communities. Furthermore genotypic characterization studies predominantly focused on screening for the *mecA* gene the β -lactam associated resistance gene, neglecting other resistant markers for other commonly used antibiotic in the country. Nurjadi et al 2014 whilst researching on trimethoprim resistance genes in *S. aureus* isolated from different countries determined that 100% of the Tanzanian isolated in the study which were phenotypically trimethoprim resistant in fact harboured a trimethoprim conferring resistant gene (52). This emphasises the need for research efforts to be directed towards researching a wider range of resistance causing genes in *S. aureus* to get comprehensive resistance profile data.

Most *pvl*/positive MSSA clones associate with skin infections identified in this review belonged to ST152 which concurs with the findings from other African based studies (53).

Table 4: *S. aureus* genetic diversity as described by the reviewed publications

Author	Host	Sample type	Resistant gene	Virulence factor	spa Type	MLST
Moremi et al 2012 (51)	Human	Wound, pus, nasal swabs (24 MRSA strains from previous studies)	<i>mecA</i> (100%)	pvl (16.7%)	t7231, t690 t064, t104, t1855,t7237 t186, t667	ST88, ST1719, ST8,ST1820
Kumburu et al 2018 (39)	Human	Blood, Sputum, wound/pus	<i>mecA</i> (33.3%)	pvl (16.7%) ,txt (6.7%) both in non <i>mecA</i> isolates	ND	ST-8, ST-1, ST-152, ST1719, ST15, ST1847, ST188, ST22, ST239, ST30, ST5, ST580, ST6, ST97
Katakweba et al 2016 (17)	Human	Nasal swabs	<i>mecA</i> and <i>mecC</i> (None detected)	NS	t714, t148, t084, t002, t223, t314, t311, t015, t451, t690, t1849, t2030, t10779*	ST15, ST18, ST72, ST22, ST5, ST121, ST231, ST45, ST8
Katakweba et al 2016 (17)	Pig	Nasal swab	<i>mecA</i> and <i>mecC</i> (None detected)	NS	t131	ST80
Katakweba et al 2016 (17)	Dog	Nasal swabs	<i>mecA</i> and <i>mecC</i> (None detected)	NS	t084, t127, t223, t314, t267, t508, t1476	ST15,ST18, ST1, ST22, ST121,
Nurjadi et al 2014 (52)	Human	Nasal, SSTI swabs	<i>dfrA</i> , <i>dfrG</i> and <i>dfrK</i> .	NS	ND	ND

			<i>dfrG</i> detected by 37% *			
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ND: Not done, **NS:** Not screened

Prevalence, antibiotic resistance and genotyping of *S. aureus* isolated from animals.

Studies reporting on prevalence, antimicrobial resistance and genetic characteristics of *S aureus* in animals published between 2010 and 2018 in Tanzania were few. Only 5 studies were included in this review, scantily representing a small area in the country. Three publications reported on *S. aureus* prevalence in milk samples, one study described prevalence in milk and cow nasal swabs and the last study reported on *S. aureus* prevalence in pig and dog nasal swabs.

Prevalence of *S aureus* in Animals

As indicated in table 5 most examined specimen in animals was milk. Prevalence of *S. aureus* varied in different geographic area. Kashoma et al 2018 and Mohammed et al 2018 reported the highest prevalence at 49% and 41% in Morogoro respectively (54, 55). Suleiman et al 2018 (56) did not fall far back when observing a prevalence of 37% describing subclinical mastitis in cows on Unguja Island. The lowest prevalence of 33% was recorded in a study aiming at assessing raw milk quality in Arusha and Meru district(57). Generally prevalence of *S. aureus* seems to be much lower in swabs taken from nasal cavities as shown by Kashoma et al 2018 who swabbed cows observed a prevalence of 28% whereas Katakweba et al 2016(17) observed a prevalence of 4% and 11% in pig and dog nasal swabs respectively.

MRSA detection in milk associated studies varied tremendously ranging from 4- 35% (54, 55), even though both studies reporting on this data were conducted in Morogoro township. Furthermore, Kashoma et al 2018 reported MRSA prevalence of 16% isolates recovered from cow nasal cavities, whereas no MRSA was detected by Katakweba et al 2016 in pigs and dogs nasal swabs.

Table 5: *S. aureus* prevalence in Animal related samples

S.No	Prevalence <i>S aureus</i> % (n)	Prevalence MRSA % (n)	Population	Source of <i>S aureus</i> isolates	Location	Reference
1	Milk: 49% (49) Cow nasal swabs : 28% (37)	Milk: 35% (17) Cow nasal swabs: 16% (6)	The study was carried out in 3 dairy farms (A, B and C) that belonged to Sokoine University of Agriculture. All farms were located within the same climatic zone. All 3 farms carried out mixed animal farming	Milk samples and cow nasal swabs	Morogoro (Eastern zone)	Kashoma et al 2018 (55)
2	41% (48)	4% (3)	The study involved 18 of the 29 Wards within Morogoro Municipality. In each of the selected Wards, sales points and local shops where raw milk is sold were randomly selected. A total of 117 milk samples. The study was conducted between January and June 2015	Milk samples	Morogoro (Eastern zone)	Mohammed et al 2018 (54)
3	37% (217)	NR	Study conducted between January - July 2014 on Unguja Island to establish prevalence of subclinical mastitis in smallholder dairy cows and pattern of antimicrobial susceptibility of major mastitis pathogens.	Milk samples	Unguja (Zanzibar)	Suleiman et al 2018 (56)
4	33% (30)	NR	105 milk samples from smallholder dairy farmers, milk vendors and retailers were taken within Arusha City and Meru District to assess the quality of raw milk and stakeholders' awareness on milk-borne health risks and factors for poor milk hygiene.	Milk samples	Arusha city and Meru district (Northern zone)	Ngasala et al 2015 (57)
5	Pig nasal swabs 4% (4) Dog nasal swabs 11% (11)	Pig swabs: 0% Dog nasal swabs: 0%	100 pigs and 100 dogs dwelling in urban and peri urban Morogoro Municipality	Nasal swabs	Morogoro (Eastern zone)	Katakweba et al 2016 (17)

NR: Not reported

Table 6: Antibiotic resistance in animals

<i>Antibiotic (N*)</i>	<i>Resistance rates in different studies in Animals. (References) (range%)</i>	<i>Mean resistance (n/N*) (%)</i>
Penicillin(265)	(54, 56) (72-88)	(225/265) (85%)
Ampicillin (99)	(17, 55) (62-100)	(72/99) (73%)
Tetracycline (364)	(17, 54-56) (16-73)	(110/364) (30%)
Erythromycin (301)	(55, 56) (5-23)	(28/301) (9%)
Gentamicin (99)	(17, 55) (6-25)	(4/99) (4%)
Co-trimoxazole (132)	(54, 55) (22-40)	(42/132) (32%)
Vancomycin (132)	(17, 54, 55) (2-11)	(10/132) (8%)
Amoxicillin (217)*	(56) (47)	(102/217) (47%)
Cephalexin (217)*	(56) (30)	(64/217) (30%)
Oxacillin (147)	(17, 54, 55) (0-34)	(25/147) (17%)
Cefoxitin (132)	(54, 55) (4-17)	(13/132) (10%)

*Reported in one study only

Antibiotic resistance in animal originated *S aureus* isolates

Four studies described resistance in *S. aureus* using different antibiotic pallets which included cephalexin, gentamicin, kanamycin, neomycin, tetracycline, streptomycin, amoxicillin, cephalexin, clindamycin, vancomycin, ampicillin, co-trimoxazole, oxacillin, and cefotixin. This review however focused on the most reported antibiotics in this area as indicated in Table 6.

Most of the reviewed studies reported low antibiotic resistance levels with exception of penicillin and ampicillin which showed mean resistances rates of 85% and 73% respectively. Suleiman et al 2018 also further observed resistance against amoxicillin and cephalexin at a rate of 47% and 30%, which was unfortunately not reported by any of the other reviewed studies. Oxy-tetracycline has been stated as being the most over used antibiotic in the livestock keeping business in Tanzania (58). The mean resistance rates against oxacillin (17%) and tetracycline (30%) observed in this review are indicative of the effects of previously reported overuse.

MRSA detection in all studies was confirmed by resistance against cefoxitin and/or oxacillin, whereby mean resistance rates of 10% and 17% were observed respectively. An average of 8% resistance against vancomycin was observed, reported in 3/5 studies as described in

Table 6.

Genotypic characterisation of animal originated *S. aureus* isolates

Genotypic data were retrieved from 2 of the 5 studies reviewed. In both, real time- PCR (qPCR) was used to confirm *S. aureus* as well as screening for *mecA* resistance conferring gene. Katakweba et al 2016 additionally screened for *mecC* a recently discovered *mecA* homologue said to have the potential to be mis-categorized as Methicillin sensitive *S. aureus* (MSSA). None of the two resistance conferring genes were detected in Katakweba's study, however *S. aureus* was confirmed in 4 pigs and 11 dog samples respectively. Further *spa* typing of the pig originating MSSA characterized them as *spa* type t131 associated with ST80. Additionally isolates of dog origin were characterized as *spa* types t314 (ST121), t084 (ST15 and ST18) and t223 (ST22) all of which were also identified in human nasal isolates reported in the same study.

In the study by Mohammed et al 2018, both coagulase positive (n=46) and coagulase negative (n=2) *S. aureus* were detected in their milk samples. *mecA* gene was detected in 2 coagulase positive and one coagulase negative *S. aureus* isolate making this study the first in Tanzania to report on coagulase negative *S. aureus* harboring the *mecA* gene. Of the 3 MRSA isolates detected in the study only the coagulase negative *S. aureus* isolate was able to be characterized as *spa* type t2603, whereas the other two MRSA's were *spa* un- typable.

S. aureus is one of the leading causes of bovine mastitis which explains the fact that the majority of publications included in this review concerning *S. aureus* in animals addressed the pathogen in clinical and sub-clinical mastitis or in regards to milk production quality. This has been instrumental in the reviews failure to make a link in describing animals and/or humans as potential *S. aureus* reservoir for each other, as well as the effect of such in both public and animal health. Very few studies on genomic *S. aureus* characterisation were available for review and did not suffice in showing such linkage.

Limitations

The data from this review cannot be generalized as true prevalence, antibiotic resistance patterns or genotypic characterization of *S. aureus* bacterium in Tanzania. High inter-study variations such as type of specimen analysed, objective of studies, time frame as well as methods employed including criteria set for resistance/MRSA confirmation may have influenced the outcome.

Methods used to genetically characterise *S. aureus* in this review were very divergent from simple PCR to whole genome sequencing. The data collected in these methods had different focuses which made comparing the results between studies difficult. Since the main objective in characterizing *S. aureus* or any other bacteria for that matter is understanding the genetic similarities and differences in conferring antibiotic resistance, strain type as well as and virulence factors, it would therefore be useful to have a common guideline that allowing inter laboratory comparability to gather more reliable and holistic data meant to guide treatment and infection prevention strategies in the country.

Conclusion

Information about prevalence, antibiotic susceptibility and genotypic characteristics of *S aureus* in Tanzania still remains scarce. It is evident that the majority of the publications included in this review are from research institutions or tertiary hospitals affiliated to universities with health related focuses hence most information could be derived from three focal points MNH in Dar es Salaam, BMC Mwanza and , KCMC Moshi respectively.

According to the Tanzania National Bureau of Statistics the focal regions represented in this review earn higher income per capital compared to the zones whereby no information could be gathered. This implies that most of the data obtained for review is based in relatively well to do regions (59). No published data between 2010 and 2018 on the epidemiology of *S aureus* was available for the southern, southern highlands, south western highlands as well as the western parts of the country, which is home to some of the most impoverished regions in Tanzania..

It is known that poverty struck areas also face other challenges as poor healthcare facilities and access, lack of basic needs such as food, proper housing and sanitation, which in turn leaves the population ridden by different infectious diseases. Furthermore since the income gained by the poor is mainly for subsistence, the tendency to resort to self-treatment and or consulting traditional healer is very high (60) all of which are known indicators associated with driving antibiotic resistance (61).

It is therefore imperative to emphasize the need to further gather information about the epidemiology (susceptibility patterns and genotypic characterization) of all bacteria of public health and animal health importance in Tanzania to gain a comprehensive description of the burden of the bacteria as well as enable proper strategies guiding empirical infections treatment and management in the country.

Abbreviations

AMR; Antimicrobial resistance, AST; Antibiotic susceptibility testing, BMC; Bugando Medical Centre, CAI: Community acquired Infection, CLSI; Clinical Laboratory Standard Institute, CNS; Coagulase negative Staphylococcus, HAI; Hospital Acquired Infection, HCW; Healthcare workers, ICU; Intensive care unit, KCMC; Kilimanjaro Christian Medical Centre; LAI; Livestock acquired infections, MLST; Multilocus sequence typing, MNH; Muhimbili National Hospital, MRSA; Methicillin resistant Staphylococcus aureus, MSSA; Methicillin sensitive Staphylococcus aureus, ND; Not done, NR; Not reported, NS; Not Screened, OM; Otitis media, RCH; Reproductive and child health, Spa; Staphylococcus protein A, SSI; Surgical Site infection, SSTI's; Skin and soft tissue infections, ST; Sequence type, UTI; Urinary tract infection, WHO: World Health Organization

Declarations

Ethics approval and consent to participate

Not applicable.

Consent for publication

Not applicable.

Availability of data and materials

Not applicable.

Competing interests

The authors declare that they have no competing interests.

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Authors' contributions

TSM, TSK and JM participated in the literature search; TSM and TSK played equal part in the reviewing process of this work. TSM prepared the first draft of the manuscript. All authors read and approved the final manuscript

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Figures

Figure 1

PRISMA diagram for a systematic review examining prevalence, antimicrobial resistance and genotyping characteristics of *S. aureus* in Tanzania

Figure 2

Tanzania administrative zones. Modified map adopted from Suleiman 2018 (10)

Figure 3

Distribution of *S. aureus* prevalence in colonization and different infections from humans isolates based on reviewed publications in Tanzania. Regional variations in prevalence of different infections could be observed. *S. aureus* blood was more prevalent in the lake zone compared to other regions. Collectively the review revealed that *S. aureus* was most frequently implicated in association with skin and soft tissue infections. Prevalence in colonized people in all reported regions was generally normal with exception to the northern zone where the prevalence was uncharacteristically high.

Supplementary Files

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