Mupirocin-resistant *Staphylococcus aureus* in Africa: a systematic review and meta-analysis

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Abstract

**Background:** Mupirocin is widely used for nasal decolonization of *Staphylococcus aureus* to prevent subsequent staphylococcal infection in patients and healthcare personnel. However, the prolonged and unrestricted use has led to the emergence of mupirocin-resistant (mupR) *S. aureus*. The aim of this systematic review was to investigate the prevalence, phenotypic and molecular characteristics, and geographic spread of mupR *S. aureus* in Africa.

**Methods:** We examined five electronic databases (EBSCOhost, Google Scholar, ISI Web of Science, MEDLINE, and Scopus) for relevant English articles on screening for mupR *S. aureus* from various samples in Africa. In addition, we performed random effects meta-analysis of proportions to determine the pooled prevalence of mupR *S. aureus* in Africa. The search was conducted until 3 August 2016.

**Results:** We identified 43 eligible studies of which 11 (26%) were obtained only through Google Scholar. Most of the eligible studies (28/43; 65%) were conducted in Nigeria (10/43; 23%), Egypt (7/43; 16%), South Africa (6/43; 14%) and Tunisia (5/43; 12%). Overall, screening for mupR *S. aureus* was described in only 12 of 54 (22%) African countries. The disk diffusion method was the widely used technique (67%; 29/43) for the detection of mupR *S. aureus* in Africa. The *mupA*-positive *S. aureus* isolates were identified in five studies conducted in Egypt (n = 2), South Africa (n = 2), and Nigeria (n = 1). Low-level resistance (LmupR) and high-level resistance (HmupR) were both reported in six human studies from South Africa (n = 3), Egypt (n = 2) and Libya (n = 1). Data on mupR-MRSA was available in 11 studies from five countries, including Egypt, Ghana, Libya, Nigeria and South Africa. The pooled prevalence (based on 11 human studies) of mupR *S. aureus* in Africa was 14% (95% CI = 6.8 to 23.2%). The proportion of *mupA*-positive *S. aureus* in Africa ranged between 0.5 and 8%. Furthermore, the frequency of *S. aureus* isolates that exhibited LmupR, HmupR and mupR-MRSA in Africa were 4 and 47%, 0.5 and 38%, 5 and 50%, respectively.

**Conclusions:** The prevalence of mupR *S. aureus* in Africa (14%) is worrisome and there is a need for data on administration and use of mupirocin. The disk diffusion method which is widely utilized in Africa could be an important method for the screening and identification of mupR *S. aureus*. Moreover, we advocate for surveillance studies with appropriate guidelines for screening mupR *S. aureus* in Africa.

**Keywords:** Africa, Prevalence, Meta-analysis, Mupirocin, *Staphylococcus aureus*, Systematic review
Background

*Staphylococcus aureus* is a well-recognized human pathogen that is implicated in a wide array of superficial, invasive and toxigenic infections [1]. Meta-analyses of published studies have provided evidence that *S. aureus* nasal carriage is an important risk factor for subsequent infection among patients with surgical site infections and atopic dermatitis [2, 3]. Other high-risk groups include patients colonized with methicillin-resistant *Staphylococcus aureus* (MRSA) undergoing dialysis, and patients admitted in the intensive care unit [4, 5]. Consequently, infection prevention strategies such as nasal decolonization are employed to minimize the occurrence of staphylococcal infection and reduce the risk of transmission in healthcare settings [6, 7]. Mupirocin (2%) nasal ointment alone or in combination with 4% chlorhexidine (CHG) based body wash is considered as the main decolonization strategy for *S. aureus* carriage [8, 9]. Mupirocin is a naturally occurring antibiotic produced by *Pseudomonas fluorescens* that interferes with protein synthesis by competitive inhibition of the bacterial isoleucyl-tRNA synthetase (IRS) [10, 11]. It gained prominence in the mid-1990s for the eradication of *S. aureus* nasal carriage due to its effectiveness, safety and cost [12].

Mupirocin-resistant (mupR) *S. aureus* was first reported in the United Kingdom in 1987 [13]. Since then, it has been reported in several countries worldwide [14–17]. The emergence of mupR *S. aureus* has been associated with unrestricted policies and use of mupirocin for long periods in healthcare settings [8, 18]. Decolonization failure in patients with *S. aureus* carriage is associated with high-level mupirocin resistance (HmupR - minimum inhibitory concentration [MIC] ≥512 μg/ml), while that of low-level mupirocin resistance (LmupR – MIC: 8-64 μg/ml) is still unclear [7, 19]. LmupR is mediated through point mutation (largely V588F and V631F) in the native isoleucyl-tRNA synthetase (*ileS*) gene [20]. In contrast, HmupR is mainly attributed to the acquisition of plasmids with the *mupA* (or *ileS2*) gene encoding an additional IRS with no affinity for mupirocin [11, 21]. Another determinant for HmupR is the acquisition of a plasmid-mediated *mupB* gene [22].

There is no data summarizing reports on screening, prevalence, characterization, and geographic spread of mupR *S. aureus* in Africa. This systematic review evaluated published articles that assessed for mupirocin resistance in African *S. aureus* isolates. The findings from this systematic review highlight the need to develop an early warning system, including harmonized strategies for the prompt screening and identification of mupR *S. aureus* in Africa.

Methods

Literature search strategy

The relevant English articles from human and animal investigations were retrieved by three authors (YA, SA, and AS) from five electronic databases (EBSCOhost, Google Scholar, ISI Web of Science, MEDLINE, and Scopus). The search terms for each database are reported in Table 1. The literature search was concluded on 3 August 2016.

Eligible article identification

The identification of the eligible articles was conducted according to the guidelines for preferred reporting items for systematic reviews and meta-analyses (PRISMA) [23]. We defined an eligible article as a peer-reviewed publication that (i) included mupirocin in the antibiotic susceptibility testing of *S. aureus* isolates, and (ii) employed phenotypic ((disc diffusion, E-test, minimum inhibitory concentration (MIC), VITEK and other automated methods)), and/or molecular ((conventional or real-time polymerase chain reaction (PCR)) techniques. International multicentre studies that included African countries were also eligible for inclusion.

Data extraction and analysis

The relevant data were extracted from each of the eligible articles included in this systematic review. A study that analysed *S. aureus* isolates from another investigation but answered a different research question were both considered as one study (Table 2). We performed three levels of analysis (Fig. 1). First, to understand the characteristics and geographic spread of mupR *S. aureus* in Africa, studies that included mupirocin in the antibiotic susceptibility testing and employed phenotypic and/or molecular techniques were identified. Secondly, the prevalence of *S. aureus* with the *mupA* gene, isolates that expressed LmupR and HmupR, and mupR-MRSA in Africa were derived from each eligible study as follows:

\[
\text{MupA-positive } S. \text{ aureus} = \frac{\text{Number of MupA-positive } S. \text{ aureus isolates}}{\text{Total number of isolates screened with mupirocin}}
\]

\[
\text{S. \text{ aureus} that expressed LmupR} = \frac{\text{Number of } S. \text{ aureus isolates with LmupR}}{\text{Total number of isolates screened with mupirocin}}
\]

\[
\text{S. \text{ aureus} that expressed HmupR} = \frac{\text{Number of } S. \text{ aureus isolates with HmupR}}{\text{Total number of isolates screened with mupirocin}}
\]

\[
\text{MupR-MRSA} = \frac{\text{Number of mupR-MRSA isolates}}{\text{Total number of isolates screened with mupirocin}}
\]

Thirdly, to estimate the prevalence of mupR *S. aureus* in humans, studies that employed at least one of the screening methods with defined breakpoint for mupirocin resistance were included in the meta-analysis. The StatsDirect
statistical software version 3.0.165 (England: StatsDirect Ltd. 2016) was utilized to assess the heterogeneity of the eligible studies included in the meta-analysis (Cochran Q-test) [24], and to ascertain the inconsistency across the studies (I² statistic) [25]. The random effects model was used to determine the pooled prevalence of mupR S. aureus in Africa. The criterion for statistical significance for heterogeneity was set at alpha = 0.05. The risk of publication bias was assessed and visualized by a Funnel plot [26, 27].

Results

Eligible studies from electronic database search
We identified 43 reports (Table 1) of which 34 studies investigated only human samples. The remaining nine studies assessed samples from only animals (n = 5), human and environmental sources (n = 2), human and animal sources (n = 1), and cockroaches (n = 1). Most of the eligible studies (32/43; 74%) were obtained from EBSCOhost, ISI Web of Science, MEDLINE, and Scopus. The remaining studies (11/43; 26%) were obtained only through Google Scholar and consisted of studies conducted in Egypt [28–31], South Africa [32–34], Nigeria [35, 36], Ethiopia [37] and Kenya [38].

Table 1  Keywords used to identify eligible studies available in five biomedical databases

| Database | Search period | Search strategy |
|----------|---------------|-----------------|
| MEDLINE via PubMed | 1974 - August 2016 | (Staphylococcus aureus OR S. aureus) AND (Mupirocin) |
| EBSCOhost via Academic Search premier, Africa-Wide information and CINAHL | 1982 - August 2016 | (Algeria OR Angola OR Botswana OR Burkina Faso OR "Burkina Faso" OR Burkina Faso OR Upper Volta OR "Upper Volta" OR Burundi OR Cameroon OR Cape Verde OR "Cape Verde" OR Central African Republic OR Chad OR Comoros OR "Iles Comores" OR Iles Comores OR Comoro Islands OR "Comoro Islands" OR Congo OR Democratic Republic Congo OR "Democratic Republic of the Congo" OR Zaire OR Djibouti OR Egypt OR Equatorial Guinea OR "Equatorial Guinea" OR Eritrea OR Ethiopia OR Gabon OR Gambia OR Ghana OR Guinea OR Guinea Bissau OR "Guinea Bissau" OR Ivory Coast OR "Cote d’Ivoire" OR "Cote d’Ivoire" OR Kenya OR Lesotho OR Liberia OR Libya OR Libya OR Jamhuriya OR Jamahiriya OR Madagascar OR Malawi OR Mali OR Mauritania OR Mauritius OR "Ile Maurice" OR "Ile Maurice" OR Morocco OR Mozambique OR "Moçambique" OR Namibia OR Niger OR Nigeria OR Rwanda OR Sao Tome OR "Sao Tome" OR Senegal OR Seychelles OR Sierra Leone OR "Sierra Leone" OR Somalia OR South Africa OR "South Africa" OR Sudan OR South Sudan OR "South Sudan" OR Swaziland OR Tanzania OR Tanganyika OR Zanzibar OR Togo OR "Guinea pig* OR "Guinea pig* OR Aspergillus niger OR "Aspergillus niger OR Europe* OR America* OR Asia*) |
| ISI Web of Science | 1950 - August 2016 | (Staphylococcus aureus OR S. aureus) AND (Mupirocin) |
| Scopus from SciVerse | 1982 - August 2016 | (Staphylococcus aureus OR S. aureus) AND (Mupirocin) |
| Google Scholar** | Google Scholar** | Examples |

*The African countries were manually selected (as recommended by Scopus database) to exclude studies from other continents
**The Google Scholar search was conducted between July-September 2015

Screening and identification of mupR S. aureus in Africa
Only 12 of the 54 (22%) African countries reported data on screening for mupR S. aureus (Fig. 2). The first published article indicated that mupirocin had been in use in Africa, at least from the late 1980s [39]. Most of these studies (28/43; 65%) were conducted in Nigeria (10/43; 23%), Egypt (7/43; 16%), South Africa (6/43; 14%) and Tunisia (5/43; 12%) (Fig. 2). MupR S. aureus was mainly identified through the disk diffusion method (29/43; 67%).

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| ISI Web of Science | 1950 - August 2016 | (Staphylococcus aureus OR S. aureus) AND (Mupirocin) |
| Scopus from SciVerse | 1982 - August 2016 | (Staphylococcus aureus OR S. aureus) AND (Mupirocin) |
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Table 2 Characteristics of the 43 eligible studies on screening for mupirocin resistance in *Staphylococcus aureus* from various sources in Africa

| Region         | Country | Study Period | Setting Type | Sample Source Type | Method for testing resistance to mupirocin | Guideline (year of publication) | Published reports for detection of mupR  
S. aureus | Number of S. aureus isolates screened with mupirocin | Mupirocin resistant isolates | Reference |
|----------------|---------|--------------|--------------|--------------------|------------------------------------------|---------------------------------|----------------------------------|------------------------------------|--------------------------------|---------|
| North Africa   | Algeria | 2005–2007 C & H Human | Pus, venous catheter, tracheal aspirate, puncture fluid, blood, urine | Disk diffusion VITEK-2 | CLSI (NA) | – | 19 | 0 (0) | 0 (0) | – | – | [47] |
| Egypt          |         | 2005–2006 C & H Human | NA | Disk diffusion | NCCLS (2003) | – | 64 | 0 (0) | 0 (0) | – | – | [28] |
| Egypt          |         | 2008–2009 C & H Human | Skin and soft tissue, post-operative wound swab | Disk diffusion | CLSI (2007) | – | 386 | 1 (0.3) | NA | NA | – | [29] |
| Egypt          |         | 2007–2008 C Human | Pus, sputum, catheter, blood, urine, wound abcess | Broth dilution | CLSI (2005) | – | 21 | 0 (0) | 0 (0) | – | – | [58] |
| Egypt          |         | 2010 H Human | Sputum, blood, catheter, traumatic wound, urine | E-test | – | 86 | 30 (34.9) | 30 (34.9) | 25/5 | 2/3 (PCR) | [30] |
| Egypt          |         | 2012 H Human | Wound discharge, blood, body fluid aspirate, urine, faeces, sputum, nasal, throat, ear and genital swab | Disk diffusion Agar dilution | CLSI (2007) | – | 150 | 0 (0) | 0 (0) | – | – | [40] |
| Egypt          |         | 2012–2013 H Human | Nasal swab | Disk diffusion | CLSI (2011) | – | 39 | 3 (7.7) | 3 (7.7) | NA | – | [31] |
| Egypt          |         | 2013–2015 H Human | Pus & Wound swab | Disk diffusion | CLSI (2011) | – | 73 | 13 (17.8) | 13 (17.8) | 5/8 | 0/6 (PCR) | [52] |
| Libya          | NA      | Human | Skin swab | Disk diffusion | NA | – | 40 | 0 (0) | NA | – | – | [61] |
| Libya          | 2008–2009 H Human & Environment | NA | Disk diffusion BSAC (2008) | – | 86 | 13 (15.1) | 13 (15.1) | NA | – | [58] |
| Libya          | 2009 H Human | Nasal swab | Disk diffusion Agar dilution | BSAC (2008) | – | 109 | 5 (4.6) | 5 (4.6) | 4/1 | – | [57] |
| Morocco        | 2008–2009 H Human | Nasal swab | Disk diffusion | CA-SFM (2007) | – | 81 | 0 (0) | 0 (0) | – | – | [62] |
| Tunisia        | 2008–2009 C Human | Nasal swab | Disk diffusion | CLSI (2008) | – | 55 | 0 (0) | 0 (0) | – | – | [41] |
Table 2: Characteristics of the 43 eligible studies on screening for mupirocin resistance in *Staphylococcus aureus* from various sources in Africa (Continued)

| Region     | Country | Study Period | Setting | Sample Source Type | Method for testing resistance to mupirocin | Guideline (year of publication) | Published reports for detection of mupR S. aureus | Number of S. aureus isolates screened with mupirocin | Mupirocin resistant isolates | Published reports for detection of mupR S. aureus | Reference |
|------------|---------|--------------|---------|-------------------|-------------------------------------------|---------------------------------|-----------------------------------------------|-------------------------------------------------|--------------------------------|-----------------------------------------------|-----------|
| Tunisia    | 2003–2005 | C | Human | Nasal swab | Phoenix Automated Microbiology System | CA-SFM (2006) | – | 64 | NA | NA | – | – | [59] |
| Tunisia    | 2013 | H | Human | Wound abscess | Disk diffusion | CA-SFM (2013) | – | 8 | NA | NA | – | – | [60] |
| Tunisia    | 2010 | C | Animal (Sheep) | Nasal swab | Disk diffusion | CLSI (2010) | – | 73 | 0 (0) | 0 (0) | – | – | [42] |
| Tunisia    | 2010 | C | Animal (Donkeys) | Nasal swab | Disk diffusion | CLSI (2010) | – | 50 | 0 (0) | 0 (0) | – | – | [43] |
| West Africa | Ghana | 2011–2012 | H | Human | Nasal swab | Disk diffusion | EUCAST (2012) | – | 105 | 1 (0.9) | 0 (0) | 0/1 | – | [54] |
| Ghana | 2011–2012 | C | Human | Nasal swab | Disk diffusion | EUCAST (2012) | – | 124 | 0 (0) | 0 (0) | – | – | [57] |
| Ghana | 2010–2013 | C & H | Human | NA | Broth microdilution | EUCAST (NA) | – | 30 | 4 (13.3) | 4 (13.3) | 4/0 | 0/0 (DNA microarray) | [53] |
| Ghana | 2012–2013 | C | Human | Nasal & Wound swab | VITEK-2 | EUCAST (NA) | – | 91 | 0 (0) | 0 (0) | – | – | [58] |
| Nigeria* | NA | NA | Human | NA | Disk diffusion | NA | – | 1 | 0 (0) | 0 (0) | – | – | [80] |
| Nigeria* | 2002–2004 | H | Human | Wound, blood, ear, eye, urine | Disk diffusion | – | Udo et al., (1999) | 200 | 1 (0.5) | 0 (0) | 0/1 | 0/1 (PCR) | [53] |
| Nigeria | 2006 | C | Human | Nasal swab | Disk diffusion | CLSI (2005) | – | 101 | 12 (11.9) | NA | NA | – | [44] |
| Nigeria | 2007 | H | Human | NA | Disk diffusion | CLSI (NA) | – | 96 | 0 (0) | 0 (0) | – | – | [44] |
| Nigeria* | NA | H | Human | Wound swab, blood, urine, endotracheal aspirate | Disk diffusion | E-test | NCCLS (2003) | – | 1 | 1 | 0 (0) | 0/1 | 0/1 (PCR) | [45] |
| Nigeria | 2009 | H | Human | Wound, sputum, semen, nasal swab | Broth microdilution | DIN 58940 (2004) | – | 68 | 0 (0) | 0 (0) | – | – | [63] |
| Nigeria | 2010 | H | Human | NA | VITEK-2 | – | – | 51 | 0 (0) | 0 (0) | – | – | [64] |
| Nigeria | 2009–2011 | H | Human | Aspirate, blood, ear, eye, vaginal discharge, sputum, wounds, urine, nasal swab | Disk diffusion | CLSI (NA) | – | 62 | 0 (0) | 0 (0) | – | – | [49] |
| Region         | Country          | Study Period  | Setting          | Sample Source  | Type                | Method for testing resistance to mupirocin | Guideline (year of publication) | Published reports for detection of mupR S. aureus | Number of S. aureus isolates screened with mupirocin | Mupirocin resistant isolates | Published reports for detection of mupR S. aureus | Reference |
|----------------|------------------|---------------|------------------|----------------|---------------------|--------------------------------------------|---------------------------------|------------------------------------------------|-------------------------------------------------|----------------------------------|-------------------------------------------------|-----------|
|                |                  |               |                  |                |                     |                                            |                                 |                                                | Number (%) | Number MRSA (%) | Number LmupR/HmupR | Number mupA gene + LmupR/HmupR (Method) |
| Nigeria        | 2010–2011        | H             | Human            | NA             |                     | VITEK-2                                     | EUCAST (NA)                     | 290                                              | 0 (0)                  | 0 (0)                                  | –                                  | [65]      |
| Nigeria        | 2008–2010        | C             | Animal (Bats)    | Faecal swab    |                     | Disk diffusion                             | –                               | 107                                              | 0 (0)                  | 0 (0)                                  | –                                  | [66]      |
| Nigeria        | 2006–2007        | C & H         | Animal (Bovine) & (Ovine) | Nasal & skin swab |                     | Disk diffusion                             | –                               | 173                                              | 0 (0)                  | 0 (0)                                  | –                                  | [35]      |
| Nigeria        | 2012             | C             | Human            | Animal         | Nasal swab Milk     | Disk diffusion                             | CLSI (2008)                     | 10 Humans 77 Animals                          | 33 (37.9)   | NA                      | 0/33                               | – [36]   |
| Central Africa | Gabon            | 2009          | C & H            | Human          | Nasal, axilla, inguinal swab | Disk diffusion                             | CLSI (2008)                     | 5                                                | 0 (0)                  | 0 (0)                                  | –                                  | [69]      |
| São Tomé & Príncipe | 2010–2012   | H             | Human            | Nasal swab     |                     | Disk diffusion                             | BSAC (NA)                      | 55                                               | 0 (0)                  | 0 (0)                                  | –                                  | [70]      |
| East Africa    | Ethiopia         | NA            | H & R            | Cockroach      | Cockroach Body surface/Gut | Disk diffusion                             | Jorgenson et al., (1999)       | 17                                               | 17 (100)   | NA                      | NA                                  | – [37]   |
| Kenya          | 2011             | H             | Human            | Nasal and axillary skin swab |                     | VITEK-2                                    | CLSI (2012)                     | 86                                               | 0 (0)                  | 0 (0)                                  | –                                  | [71]      |
| Kenya          | 2011–2013        | H             | Human            | Pus, blood, urine |                     | VITEK-2                                    | CLSI (2010)                     | 731                                              | 0 (0)                  | 0 (0)                                  | –                                  | [72]      |
| Kenya          | NA               | C             | Animal (Cameleon) | Raw camel milk |                     | Disk diffusion                             | Broth microdilution             | 47                                               | 0 (0)                  | 0 (0)                                  | –                                  | [38]      |
| South Africa   | South Africa     | 1996          | H                | Human          | Wound, urine, skin and blood | Disk diffusion                             | NCCLS (2001)                    | 236                                              | 5 (2.1)                | NA                      | NA                                  | – [46]    |
| South Africa** | 2001–2003        | H             | Human            | Wound, sputum, blood |                     | Disk diffusion                             | –                               | 227                                              | 16 (7.0)               | 15 (6.6)                              | 14/2                      | 0/2 (PCR) | [50]      |
| South Africa   | 2005–2006        | H             | Human            | Blood, pus & skin wound, cerebrospinal fluid | Disk diffusion                             | E-test                          | –                               | 248                                              | 123 (49.6)             | 123 (49.6)                           | 117/6                                 | – [32]    |
| South Africa** | NA               | H             | Human            | Wound swab, blood, urine, endotracheal aspirate | Disk diffusion                             | E-test                          | NCCLS (2003)                    | –                               | 16                                               | 16 (100)               | 14 (87.5)                             | 14/2                      | 0/2 (PCR) | [45]      |
| South Africa   | 2013             | H             | Human            | Tissue, blood, cerebrospinal fluid, wound swab | Disk diffusion                             | VITEK-2                         | CLSI (2012)                     | –                               | 997                                              | 277 (27.8)             | NA                      | 43/234                      | 0/5 (Real time PCR) | [33]      |
Table 2 Characteristics of the 43 eligible studies on screening for mupirocin resistance in *Staphylococcus aureus* from various sources in Africa (Continued)

| Region          | Country | Study Period | Setting Source Type | Sample Type | Method for testing resistance to mupirocin | Guideline (year of publication) | Published reports for detection of mupR S. aureus | Number of S. aureus isolates screened with mupirocin | Mupirocin resistant isolates | Reference |
|-----------------|---------|--------------|---------------------|-------------|------------------------------------------|---------------------------------|-----------------------------------------------|--------------------------------------------------|---------------------------------|-----------|
| South Africa    | 2010–2012 | H | Human | Blood | Microscan (MIC Panel Type 33) | CLSI (2015) – | – | 2709 | 236 (8.7) | 202 (7.5) | NA – | [51] |
| South Africa    | 2009–2010 | H | Human & Environment | Nasal & hand swab, dialysate fluid, surface swab, air samples | VITEK-2 | – | – | 13 | 4 (30.8) | 4 (30.8) | 0/4 – | [34] |

KEY: mupR S. aureus: mupirocin resistant *Staphylococcus aureus*; LmupR low-level mupirocin resistance, HmupR high-level mupirocin resistance, mupA mupirocin resistance gene, MIC Minimum inhibitory concentration, BSAC British Society for Antimicrobial Chemotherapy, CA-SFM Comité de l’Antibiogramme de la Société Française de Microbiologie, CLSI Clinical and Laboratory Standards Institute, DIN 58940 Deutsches Institut für Normung DIN 58940, EUCAST European Committee on Antimicrobial Susceptibility Testing, NCCLS National Committee for Clinical Laboratory Standards, PCR Polymerase Chain Reaction; – Not determined, NA Not available, H Hospital, C Community, R Restaurant

*Separate reports that analyzed the same isolates but answered different questions (considered as one single study) in Nigeria; **: Separate reports that analyzed the same isolates but answered different questions (considered as one single study) in South Africa.

Reference [45] is recorded in Nigeria and South Africa, but the isolates were derived from studies in Nigeria [53] and South Africa [50], respectively.

Other published reports applied for the detection of mupR S. aureus in Africa

1. Jorgenson JH, Turnidge JD, Washington JA. Dilution and disc diffusion method. In: Murray PR, Baron EJ, Pfaller MA, Tenover FC, Yolken RH, editors. Manual of Clinical Microbiology, 7th edition. American Society for Microbiology, Washington DC, 1999. p. 1526–1543. Adapted from NCCLS: National Committee for Clinical Laboratory Standards 1997. Approved Standard M2-A6; National Committee for Clinical Laboratory Standards 1999. Approved Standard M100-S9.

2. Kresken M, Hafner D, Schmitz FJ, Wichelhaus TA. Prevalence of mupirocin resistance in clinical isolates of *Staphylococcus aureus* and *Staphylococcus epidermidis*. Results of the antimicrobial resistance surveillance study of the Paul-Ehrlich Society for Chemotherapy, 2001. Int J Antimicrob Agents, 2004; 23:577–81. The widely accepted breakpoints: ≤4 mg/l (susceptible), 8–256 mg/l (low-level resistance) and ≥512 mg/l (high-level resistance) was utilized in this study.

3. Udo EE, Farook VS, Mokadas EM, Jacob LE, Sanyal SC. Molecular fingerprinting of mupirocin-resistant methicillin-resistant *Staphylococcus aureus* from a burn unit. Int J Infect Dis, 1999;3:182–7. Growth within a 14-mm zone of inhibition with the 5 μg mupirocin disk detected low-level resistance, while growth to the edge of the 200 μg mupirocin disk indicated high-level resistance.

4. Udo EE, Al-Sweih N, Mokadas E, Johny M, Dhar R, Gomaa HH, Al-Obaids I, Rotimi VO. Antibacterial resistance and their genetic location in MRSA isolated in Kuwait hospitals, 1994–2004. BMC Infect Dis, 2006;6:168. The widely accepted breakpoints:<4 mg/l (susceptible), 8–256 mg/l (low-level resistance) and ≥512 mg/l (high-level resistance) was utilized in this study.
Institute (CLSI), previously known as National Committee for Clinical Laboratory Standards (NCCLS), were broadly used in Africa (Table 2). However, a number of studies [28, 29, 31, 33, 36, 40–46] utilized the disk diffusion method with CLSI guidelines that had no zone diameter breakpoint for mupirocin. Moreover, some studies [47–49] did not provide information on the year of publication of the CLSI guidelines. MupR S. aureus was reported in six African countries including South Africa [32–34, 46, 50, 51], Egypt [29–31, 52], Nigeria [36, 44, 53], Ghana [54, 55], Libya [56, 57] and Ethiopia [37] (Fig. 2; Table 2). The mupA-positive S. aureus was detected in five studies from Egypt [30, 52], South Africa [33, 50] and Nigeria [53]. LmupR and HmupR were both reported in six human studies conducted in South Africa [32, 33, 50], Egypt [30, 52] and Libya [57]. The
Table 3: Prevalence of mupirocin-resistant *S. aureus* from various sources in Africa based on phenotypic and molecular methods

| MupA-positive *S. aureus* | Country | Source | Number positive/Total tested (%) | Phenotypic | Molecular | Guidelines or reports | Reference |
|--------------------------|---------|--------|---------------------------------|------------|-----------|----------------------|----------|
|                          | Egypt   | Human  | 5/86 (5.8)                      | Agar Dilution: √, Broth microdilution: –, Disk diffusion: –, E-test: –, Microscan system: √ | PCR Microarray: √ | BSAC: –, CLSI: –, EUCAST: –, Other reports: – | [30]     |
|                          | Egypt   | Human  | 6/73 (8.2)                      | Agar Dilution: √, Broth microdilution: –, Disk diffusion: –, E-test: –, Microscan system: – | PCR Microarray: √ | BSAC: –, CLSI: –, EUCAST: –, Other reports: – | [52]     |
|                          | Nigeria | Human  | 1/200 (0.5)                     | Agar Dilution: –, Broth microdilution: √, Disk diffusion: –, E-test: –, Microscan system: – | PCR Microarray: – | BSAC: –, CLSI: –, EUCAST: –, Other reports: – | [53]     |
|                          | South Africa | Human  | 2/227 (0.9)                   | Agar Dilution: √, Broth microdilution: –, Disk diffusion: –, E-test: –, Microscan system: – | PCR Microarray: – | BSAC: –, CLSI: –, EUCAST: –, Other reports: – | [50]     |
|                          | South Africa | Human  | NA                             | Agar Dilution: –, Broth microdilution: √, Disk diffusion: –, E-test: –, Microscan system: – | PCR Microarray: – | BSAC: –, CLSI: –, EUCAST: –, Other reports: – | [33]     |

| LmupR *S. aureus* | Country | Source | Number positive/Total tested (%) | Phenotypic | Molecular | Guidelines or reports | Reference |
|-------------------|---------|--------|---------------------------------|------------|-----------|----------------------|----------|
|                    | Egypt   | Human  | 25/86 (29.1)                    | Agar Dilution: –, Broth microdilution: √, Disk diffusion: –, E-test: –, Microscan system: – | PCR Microarray: √ | BSAC: –, CLSI: –, EUCAST: –, Other reports: – | [30]     |
|                    | Egypt   | Human  | 8/73 (11.0)                     | Agar Dilution: √, Broth microdilution: –, Disk diffusion: –, E-test: –, Microscan system: – | PCR Microarray: – | BSAC: –, CLSI: –, EUCAST: –, Other reports: – | [52]     |
|                    | Ghana   | Human  | 1/105 (1.0)                     | Agar Dilution: –, Broth microdilution: √, Disk diffusion: –, E-test: –, Microscan system: – | PCR Microarray: √ | BSAC: –, CLSI: –, EUCAST: –, Other reports: – | [54]     |
|                    | Libya   | Human  | 1/109 (0.9)                     | Agar Dilution: √, Broth microdilution: –, Disk diffusion: –, E-test: –, Microscan system: √ | PCR Microarray: √ | BSAC: –, CLSI: –, EUCAST: –, Other reports: – | [57]     |
|                    | Nigeria | Human  | 1/200 (0.5)                     | Agar Dilution: –, Broth microdilution: √, Disk diffusion: –, E-test: –, Microscan system: – | PCR Microarray: – | BSAC: –, CLSI: –, EUCAST: –, Other reports: √ | [53]     |
|                    | Nigeria | Human  | 1/101 (11.9)                    | Agar Dilution: –, Broth microdilution: √, Disk diffusion: –, E-test: –, Microscan system: √ | PCR Microarray: – | BSAC: –, CLSI: –, EUCAST: –, Other reports: √ | [44]     |
|                    | Nigeria | Human & Animal | 33/87 (37.9)            | Agar Dilution: –, Broth microdilution: –, Disk diffusion: –, E-test: –, Microscan system: – | PCR Microarray: √ | BSAC: –, CLSI: –, EUCAST: –, Other reports: √ | [36]     |
|                    | South Africa | Human  | 2/227 (0.9)                   | Agar Dilution: –, Broth microdilution: √, Disk diffusion: –, E-test: –, Microscan system: – | PCR Microarray: – | BSAC: –, CLSI: –, EUCAST: –, Other reports: √ | [50]     |
|                    | South Africa | Human  | 6/248 (2.4)                   | Agar Dilution: –, Broth microdilution: √, Disk diffusion: –, E-test: –, Microscan system: – | PCR Microarray: – | BSAC: –, CLSI: –, EUCAST: –, Other reports: √ | [32]     |
|                    | South Africa | Human  | 234/997 (23.5)          | Agar Dilution: –, Broth microdilution: √, Disk diffusion: –, E-test: –, Microscan system: – | PCR Microarray: √ | BSAC: –, CLSI: –, EUCAST: –, Other reports: – | [33]     |

| HmupR *S. aureus* | Country | Source | Number positive/Total tested (%) | Phenotypic | Molecular | Guidelines or reports | Reference |
|-------------------|---------|--------|---------------------------------|------------|-----------|----------------------|----------|
|                    | Egypt   | Human  | 5/86 (5.8)                      | Agar Dilution: −, Broth microdilution: –, Disk diffusion: –, E-test: –, Microscan system: – | PCR Microarray: – | BSAC: –, CLSI: –, EUCAST: –, Other reports: – | [30]     |
|                    | Egypt   | Human  | 13/73 (17.8)                    | Agar Dilution: √, Broth microdilution: –, Disk diffusion: –, E-test: –, Microscan system: – | PCR Microarray: – | BSAC: –, CLSI: –, EUCAST: –, Other reports: – | [52]     |
|                    | Ghana   | Human  | 4/30 (13.3)                     | Agar Dilution: –, Broth microdilution: –, Disk diffusion: –, E-test: –, Microscan system: – | PCR Microarray: √ | BSAC: –, CLSI: –, EUCAST: –, Other reports: √ | [55]     |
|                    | Libya   | Human  | 13/86 (15.1)                    | Agar Dilution: √, Broth microdilution: –, Disk diffusion: –, E-test: –, Microscan system: – | PCR Microarray: – | BSAC: –, CLSI: –, EUCAST: –, Other reports: – | [56]     |
|                    | Libya   | Human  | 5/109 (4.6)                     | Agar Dilution: √, Broth microdilution: –, Disk diffusion: –, E-test: –, Microscan system: – | PCR Microarray: – | BSAC: –, CLSI: –, EUCAST: –, Other reports: √ | [57]     |
|                    | Nigeria | Human & Animal | 33/87 (37.9)            | Agar Dilution: –, Broth microdilution: –, Disk diffusion: –, E-test: –, Microscan system: – | PCR Microarray: – | BSAC: –, CLSI: –, EUCAST: –, Other reports: – | [36]     |
|                    | South Africa | Human  | 15/227 (6.6)                   | Agar Dilution: –, Broth microdilution: –, Disk diffusion: –, E-test: –, Microscan system: – | PCR Microarray: √ | BSAC: –, CLSI: –, EUCAST: –, Other reports: √ | [50]     |
Table 3: Prevalence of mupirocin-resistant *S. aureus* from various sources in Africa based on phenotypic and molecular methods (Continued)

| Mupirocin resistance | Country    | Source                  | Number positive/Total tested (%) | Phenotypic | Molecular | Guidelines or reports | Reference |
|----------------------|------------|-------------------------|----------------------------------|------------|-----------|----------------------|-----------|
|                      |            |                         |                                  | Agar       | Broth     | Disk                 | Microscan  | VITEK     | PCR      | Microarray | BSAC | CLSI | EUCAST | Other reports |
|                      |            |                         |                                  | Dilution   | microdilution | diffusion | E-test               | system     | PCR       |  |       |       |                       |           |
|                      |            |                         |                                  |           |            |         |       |                       |           |           |       |       |       |                       |           |
|                      |            |                         |                                  |           |            |         |       |                       |           |           |       |       |       |                       |           |
| South Africa         | Human      | Human                   | 123/248 (49.6)                  | –          | –         | √        | –                   | –         | –         | –   | –     | –    | √                | [32]     |
| South Africa         | Human      | Human                   | 202/2709 (7.5)                  | –          | –         | –        | –                   | –         | –         | √   | –     | –    | –                | [51]     |
| South Africa         | Human & Environment | 4/13 (30.8)            | –                                  | –          | –         | –        | –                   | √         | –         | –   | –     | –    | –                | [34]     |

**KEY:** BSAC British Society for Antimicrobial Chemotherapy, CLSI Clinical and Laboratory Standards Institute, EUCAST European Committee on Antimicrobial Susceptibility Testing, NA Not Available, PCR Polymerase Chain Reaction, √: test was performed, -: test was not performed.

*aThe widely accepted breakpoints: ≤ 4 mg/l (susceptible), 8–256 mg/l (low-level resistance) and ≥ 512 mg/l (high-level resistance) was utilized in this study: Kresken M, Hafner D, Schmitz FJ, Wichelhaus TA. Prevalence of mupirocin resistance in clinical isolates of *Staphylococcus aureus* and *Staphylococcus epidermidis*. Results of the antimicrobial resistance surveillance study of the Paul-Ehrlich Society for Chemotherapy, 2001. Int J Antimicrob Agents, 2004, 23:577–81.

A growth within a 14-mm zone of inhibition with the 5 μg mupirocin disk detected low-level resistance, while growth to the edge of the 200 μg mupirocin disk indicated high-level resistance according to: Udo EE, Farook VS, Mokadas EM, Jacob LE, Sanyal SC. Molecular fingerprinting of mupirocin-resistant methicillin-resistant *Staphylococcus aureus* from a burn unit. Int J Infect Dis, 1999;3:82–7.

*bThe widely accepted breakpoints: ≤ 4 mg/l (susceptible), 8–256 mg/l (low-level resistance) and ≥ 512 mg/l (high-level resistance) was utilized in this study: Udo EE, Al-Sweih N, Mokaddas E, Johny M, Dhar R, Gomaa HH, Al-Obaid I, Rotimi VO. Antibacterial resistance and their genetic location in MRSA isolated in Kuwait hospitals, 1994–2004. BMC Infect Dis, 2006;6:168.
mupR-MRSA isolates were identified in South Africa [32, 34, 50, 51], Egypt [30, 31, 52], Libya [56, 57], Ghana [55] and Nigeria [36] (Table 3). MupR-MRSA was not reported from MRSA isolates recovered from studies conducted in Egypt [28, 58], Tunisia [59, 60] and Algeria [47]. An assessment of data on mupR S. aureus at the regional level is described as follows (Fig. 3).

**North Africa**
Seventeen eligible studies were recorded from this region, including Egypt [28–31, 40, 52, 58], Tunisia [41–43, 59, 60], Libya [56, 57, 61], Algeria [47] and Morocco [62]. MupR S. aureus was reported in six studies conducted in two North African countries: Egypt [29–31, 52] and Libya [56, 57]. PCR detection of the mupA gene was performed in only two studies conducted in Egypt [30, 52]. In addition, one of the reports identified two mupA positive MRSA that exhibited LmupR [30]. MupR S. aureus was not detected in Tunisia [41–43, 59, 60], Algeria [47], and Morocco [62].

**West Africa**
S. aureus resistance to mupirocin was investigated in Nigeria [35, 36, 44, 48, 49, 53, 63–66] and Ghana [54, 55, 67, 68]. Only two studies from Ghana reported on mupR S. aureus [54, 55]. In Nigeria, three studies (including two from only human sources and one from both animal and human samples, respectively) reported on S. aureus isolates that demonstrated HmupR [36, 44, 53].

**Central Africa**
MupR S. aureus was not detected in studies conducted in Gabon [69], and São Tomé and Príncipe [70].

**East Africa**
In this review, we identified four eligible studies conducted in Kenya [38, 71, 72] and Ethiopia [37]. A report on the role of cockroaches as potential vectors of foodborne pathogens in Ethiopia identified 17 mupR S. aureus isolates [37]. All the S. aureus isolates (one animal and two human studies) from Kenya were susceptible to mupirocin [38, 71, 72].

![Fig. 3 Geographic distribution of mupirocin-resistant (mupR) Staphylococcus aureus in Africa. Countries (in green) in which mupR S. aureus have been investigated but not reported. Countries (in red) in which mupR S. aureus have been investigated and reported.](image)
Southern Africa
The six studies reported in this geographical area were from South Africa and consisted of two single centre studies [34, 46] and four multicenter studies [32, 33, 50, 51]. MupR S. aureus was identified in all the reports, while mupA-positive S. aureus isolates were noted in only two studies [33, 50].

Prevalence of mupR S. aureus in Africa
The random-effects pooled prevalence of mupR S. aureus in Africa is 14% (95% CI = 6.8 to 23.2%). This was calculated based on 11 heterogeneous human studies (Figs. 4 and 5) conducted in South Africa [32, 33, 50, 51], Ghana [54, 55], Egypt [30, 52], Libya [56, 57] and Nigeria [53]. In Africa, the proportion of S. aureus isolates with the mupA gene, and those that expressed LmupR and HmupR ranged between 0.5 and 8%, 4 and 47%, 0.5 and 38%, respectively. The frequency of mupR-MRSA isolates ranged between 5 and 50% (Table 3).

Association of MupR S. aureus with mupirocin use in Africa
There is no data on the use of mupirocin as an agent for S. aureus decolonization and its association with mupR S. aureus in Africa.

MupR S. aureus and biofilm production
A report from Egypt noted that mupR-MRSA were moderate to strong biofilm producers [52].

MupR S. aureus and co-resistance to other antibiotics
In this systematic review, two studies (conducted in Egypt and South Africa) showed that mupR S. aureus was associated with multi-drug resistance [30, 33].

Molecular characterization of mupR S. aureus in Africa
Only three studies provided molecular data on mupR S. aureus in Africa [45, 54, 55]. A report provided evidence of a 35 kb (non-conjugative) and 41.1 kb (conjugative) plasmid encoding mupA in S. aureus isolates from Nigeria and South Africa [45]. It also described an MRSA clone that demonstrated LmupR in South Africa. LmupR was also identified among MRSA isolates assigned with ST36, ST88, and ST789 in Ghana [55]. A cross-sectional S. aureus study identified a methicillin susceptible S. aureus (MSSA) strain with HmupR from a 51-year-old hospital staff in Ghana [54]. Molecular characterization indicated that the strain (spa type t4805) was PVL-positive.

Discussion
This is the first systematic review on mupR S. aureus in Africa and clearly showed the paucity of data on the continent. Nevertheless, this study indicated a high prevalence ((14% (95% CI = 6.8 to 23.2)) of mupR S. aureus in Africa. These observations support the need for mupR S. aureus surveillance data to provide information on its epidemiology and clinical significance in Africa. It is noteworthy that Google Scholar was valuable in the identification of several eligible studies [28–38].

Fig. 4 Bias assessment (Funnell) plot for studies assessing rates of mupi-rocin-resistant Staphylococcus aureus in Africa. Random effects (DerSimonian-Laird). Pooled proportion = 0.139303 (95% CI = 0.067511 to 0.23165). Bias indicators, Begg-Mazumdar: Kendall’s tau = 0.2 P = 0.4454, Egger: bias = 4.771137 (95% CI = −2.517874 to 12.060148) P = 0.1728, Harbord: bias = 2.014783 (92.5% CI = −5.90181 to 9.931377) P = 0.6208.
observed that 26% (11/43) of the eligible studies were identified from African journals which were not indexed in commonly used electronic databases. Google Scholar has been considered as a useful supplement with other electronic databases for systematic review search [73] including recent meta-analyses of published studies on S. aureus in Africa [74, 75].

The phenotypic methods for the screening and identification of mupR S. aureus include disc diffusion (two-disc strategy: 5 μg and 200 μg), agar dilution, broth micro-dilution and E-test [19]. In this study, the disk diffusion method and the CLSI (formerly NCCLS) guidelines were strategies mainly applied to detect mupR S. aureus in Africa. However, we observed certain inconsistencies [28, 29, 31, 33, 36, 40–42, 44–46] applied the disk diffusion method with the CLSI guidelines that had no breakpoint values for mupirocin. The 2017 CLSI guidelines recommend the use of the 200 μg disk to differentiate between HmupR and the absence of HmupR (i.e. no zone = HmupR; any zone = absence of HmupR) [76].

The 200 μg disk with a different breakpoint (Susceptible ≥30 mm, Resistance < 18 mm) is also endorsed for the differentiation between HmupR and the absence of HmupR in the latest versions (accessed 28th May, 2018) of the European Committee for Antimicrobial Susceptibility Testing (EUCAST) and Comité de l’antibiogramme de la Société Française de Microbiologie (CA-SFM) [77, 78]. The breakpoint values for the detection of LmupR and differentiation from HmupR are not provided in these documents (CA-SFM, CLSI, and EUCAST). Despite this limitation, the disk diffusion method in conjunction with any of these guidelines could at least be valuable for the preliminary screening and identification of HmupR S. aureus in Africa. MRSA decolonization failure is of clinical significance as it is often attributed to persistence or re-colonization associated with isolates exhibiting HmupR, while that of LmupR is not clear [7, 19, 79]. In this review, the prevalence of S. aureus that exhibited LmupR, HmupR and mupR-MRSA in Africa was predicted on a range of methods using different guidelines. We suggest that surveillance data from Africa is established on harmonized guidelines to enhance quality assurance and comparison at the continental and global level.

We noted a prevalence of mupR-MRSA ranging between 5 and 50% in Africa (Table 3). This is of serious concern. Specifically, the relationship between mupirocin resistance and MRSA has important consequences on infection control measures and effectiveness of decolonization strategies [8]. MupR-MRSA could limit the choices available for the control and prevention of healthcare-associated MRSA infections (7, 8). Therefore, surveillance studies are important to investigate the emergence and spread of mupirocin resistance in
hospital settings in Africa. This is important among patients at high risk of MRSA infections, including patients in the dermatology, dialysis and the Intensive Care Units. In addition, there is the need for more data on the molecular characterization of mupR S. aureus in Africa [45, 54, 55]. For instance, whole genome sequencing (WGS) will assist in understanding the transmission dynamics of mupR S. aureus in Africa. Moreover, WGS data will allow comprehensive investigation of the genetic basis for LmuR mutation (which is largely due to V588F and V631F in the native gene (ileS)) and mupB-positive S. aureus in Africa.

Language bias was the main limitation of this systematic review as we did not include studies published in French, Portuguese, Arabic and Spanish.

Conclusions
This study showed the need for more epidemiological data to understand the transmission, burden and risk factors associated with mupR S. aureus in Africa. In addition, there is a need for data on administration and use of mupirocin in community and hospital setting in Africa. This is important in antibiotic stewardship to mitigate the emergence and spread of mupR S. aureus in Africa. Finally, this systematic review highlighted the need for harmonized guidelines to facilitate the comparison of data on mupR S. aureus from Africa.

Abbreviation
HmupR: High-level mupirocin resistance; LmupR: Low-level mupirocin resistance; MIC: Minimum inhibitory concentration; MRSA: Methicillin-resistant Staphylococcus aureus; MSSA: Methicillin-susceptible S. aureus; mupR: Mupirocin-resistant; PCR: Polymerase chain reaction; PVL: Panton Valentine Leucocidin; S. aureus: Staphylococcus aureus; ST: Sequence type

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Availability of data and materials
All supporting materials (Figures and Tables) are included in the manuscript.

Authors’ contributions
AOS conceived the project. YOA, SMA and AOS extracted the data and reviewed the articles. MOA and AOSA wrote the initial draft of the manuscript. AOS, SMA, YOA, and MK wrote the subsequent draft. All the authors reviewed and agreed on the final version of the manuscript before submission for publication.

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References
1. Lowy FD. Staphylococcus aureus infections. N Engl J Med. 1998;339:520–32.
2. Levy P, Ollivier M, Drancourt M, Raoult D, Argenson JN. Relation between nasal carriage of Staphylococcus aureus and surgical site infection in orthopedic surgery: the role of nasal contamination. A systematic literature review and meta-analysis. Orthop Traumatol Surg Res. 2015;99:45–51. https://doi.org/10.1016/j.otsr.2013.03.030.
3. Totté JE, van der Feltz WT, Hennekam M, van Belkum A, van Zuuren EJ, Pasmans SG. Prevalence and odds of Staphylococcus aureus carriage in atopic dermatitis: a systematic review and meta-analysis. Br J Dermatol. 2016;175:687–95. https://doi.org/10.1111/bjd.14566.
4. Zacharioudakis IM, Zervou FN, Ziakas PD, Mylonakis E. Meta-analysis of methicillin-resistant Staphylococcus aureus colonization and risk of infection in dialysis patients. J Am Soc Nephrol. 2014;25:2131–41. https://doi.org/10.1681/ASN.2013091028.
5. Ziakas PD, Anagnostou T, Mylonakis E. The prevalence and significance of methicillin-resistant Staphylococcus aureus colonization at admission in the general ICU setting: a meta-analysis of published studies. Crit Care Med. 2014;42:433–44. https://doi.org/10.1097/CCM.0000000000000312.
6. Wertheim HF, Melles DC, Vos MC, van Leeuwen W, van Belkum A, Verbrugh HA, Nouwen JL. The role of nasal carriage in Staphylococcus aureus infections. Lancet Infect Dis. 2005;5:751–62. https://doi.org/10.1016/S1473-3099(05)70295-4.
7. Septimus EJ, Schweizer ML. Decolonization in prevention of health-care associated infections. Clin Microbiol Rev. 2016;29:201–22. https://doi.org/10.1128/CMR.00049-15.
8. Poovelikunnel T, Gethin G, Humphreys H. Mupirocin resistance: clinical implications and potential alternatives for the eradication of MRSA. J Antimicrob Chemother. 2015;70:2681–92. https://doi.org/10.1093/jac/dkv169.
9. Global Guidelines for the prevention of surgical site infection. World Health Organization, Geneva. 2016. http://www.who.int/gpsc/sa-prevention-guidelines/en/ Accessed 15 June 2017.
10. Fuller AT, Mellow G, Woolford M, Banks GT, Barrow KD, Chain EB. Pseudomonic acid: an antibiotic produced by Pseudomonas fluorescens. Nature. 1971;234:416–7.
11. Gilbert J, Perry CR, Slocombe B. High-level mupirocin resistance in Staphylococcus aureus: evidence for two distinct isoleucyl-tRNA synthetases. Antimicrob Agents Chemother. 1993;37:32–4.
12. Perl TM, Gelub JE. New approaches to reduce Staphylococcus aureus nosocomial infection rates: treating S. aureus nasal carriage. Ann Pharmacother. 1998;32:57–16.
13. Rahman M, Noble WC, Cookson B. Mupirocin resistant Staphylococcus aureus. Lancet. 1987;330:387–8. https://doi.org/10.1016/S0140-6736(87)92398-1.
14. Hughes J, Stabler R, Gaunt M, Kanadag T, Desai N, Betley J, Ioannou A, Ayyee A, Hearn P, Marbach H, Patel A, Otter JA, Edgeworth JD, Tosas AO. Clonal variation in high- and low-level phenotypic and genotypic mupirocin resistance of MRSA isolates in south-East London. J Antimicrob Chemother. 2015;70:3191–9. https://doi.org/10.1093/jac/dkv248.
15. Boswidi SS, Udo EE, Al-Sbewi N. Shifts in the clonal distribution of methicillin-resistant *Staphylococcus aureus* in Kuwaiti hospitals: 1992-2010. PLoS One. 2016;11:e0162744. https://doi.org/10.1371/journal.pone.0162744.

16. Hayden MK, Lolans K, Haffner-Kruger K, Avery TR, Kleinman K, Li H, Kaganov RE, Lankiewicz J, Moody J, Septimus E, Weinstein RA, Hickok J, Nemigian J, Perlin JB, Pratt R, Huang SS. Chlorhexidine and mupirocin susceptibility of methicillin-resistant *Staphylococcus aureus* isolates in the REDUCE-MRSA trial. J Clin Microbiol. 2016;54:2735–42. https://doi.org/10.1128/JCM.01706-16.

17. Gostev V, Kuglov A, Kalinogorskaya O, Dmitrenko O, Khokhlova O, Yamamoto T, Lobzin Y, Ryabchenko I, Sidorenko S. Molecular epidemiology and antibiotic resistance of methicillin-resistant *Staphylococcus aureus* circulating in the Russian Federation. Infect Genet Evol. 2017;53:189–94. https://doi.org/10.1016/j.ijmge.2017.06.006.

18. Hetem DJ, Bonten MJ. Clinical relevance of mupirocin resistance in *Staphylococcus aureus*. J Hosp Infect. 2013;85:249–56. https://doi.org/10.1016/j.jhin.2013.09.006.

19. Svendsen JM, Wong B, Simor AE, Thomson RB, Ferraro MJ, Hardy DJ, Hindler J, Hetem DJ, Bonten MJ. Clinical relevance of mupirocin resistance in *Staphylococcus aureus* and antibiotic resistance of methicillin-resistant *Staphylococcus aureus* in Maidauguri, Nigeria. Adv Anim Vet Sci. 2013;1:59–64.

20. Nair-siyama IB, Okon KO, Adamu NB, Askira UM, Isyama TK, Adamu SG, Mohammed A. Methicillin-resistant *Staphylococcus aureus* (MRSA) colonization rate among ruminant animals slaughtered for human consumption and contact persons in Maidauguri, Nigeria. Afr J Microbiol Res. 2014;8:2643–9. https://doi.org/10.5897/AJMR2014.6855.

21. Tachelle B, Eru K, Gebre-Michael T, Ashenifi M. Cockroach-associated food-borne bacterial pathogens from some hospitals and restaurants in Addis Ababa, Ethiopia. Distribution and antibiograms. JRTPH. 2006;5:34–41.

22. Seah C, Alexander DC, Louie L, Simor A, Low DE, Longtin J, Melano RG. A multicenter study to determine disk diffusion and broth microdilution criteria for prediction of high- and low-level mupirocin resistance in *Staphylococcus aureus*. J Clin Microbiol. 2010;48:2469–75. https://doi.org/10.1128/JCM.00340-10.

23. Antonio M, McFerran N, Pallen MJ. Mutation affecting the Rossman fold of isoleucyl-tRNA synthetase are correlated with low-level mupirocin resistance in *Staphylococcus aureus*. Antimicrob Agents Chemother. 2002;46:438–42. https://doi.org/10.1128/AAC.46.2.438-442.2002.

24. Hodgson JE, Cernoch SP, Dyke KG, Morris R, Sylvester DR, Gross MS. Molecular characterization of the gene encoding high-level mupirocin resistance in *Staphylococcus aureus* J2B70. Antimicrob Agents Chemother. 1994;38:1205–8. https://doi.org/10.1128/AAC.38.5.1205-1208.1994.

25. Huggins JPT, Thompson SG, Deeks JJ, Altman DG. Measuring inconsistency in meta-analyses. BMJ. 2011;342:1. https://doi.org/10.1136/bmj.d4002.

26. Seeh S, Alexander DC, Louie L, Simor A, Low DE, Longtin J, Melano RG. MupM, a new high-level mupirocin resistance mechanism in *Staphylococcus aureus*. Antimicrob Agents Chemother. 2012;56:1916–20. https://doi.org/10.1128/AAC.00325-11.

27. Moher D, Liberati A, Tetzlaff J, Altman DG. PRISMA group. Preferred reporting items for systematic reviews and meta-analyses: the PRISMA statement. PLoS Med. 2009;6:e1000097. https://doi.org/10.1371/journal.pmed.1000097.

28. Cochran WG. The combination of estimates from different experiments. Biometrics. 1954;10:1–29.

29. Huggins JPT, Thompson SG, Deeks JJ, Altman DG. Measuring inconsistency in meta-analyses. BMJ. 2001;327:557–60. https://doi.org/10.1136/bmj.327.7414.557.

30. Egger M, Smith GD, Schneider M, Minder C. Bias in meta-analysis detected by a simple, graphical test. BMJ. 1997;315:629. https://doi.org/10.1136/bmj.315.7109.629.

31. Melake N, Zakaria AS, Ibrahim NH, Salama M, Mahmoud AZ. Prevalence of MRSA in skin and nasal swabs from South African university students. PLoS One. 2016;11:e0153710. https://doi.org/10.1371/journal.pone.0153710.

32. Perovic O, Iyaloo S, Kularatne R, Lowman W, Bosman N, Wadula J, Seetharam, S, Duse A, Mbelle N, Bamford C, Davood H, Mahabere Y, Bhola P, Abrahams S, Singh-Moodley A. Prevalence and trends of *Staphylococcus aureus* in a tertiary care hospital in KwaZulu-Natal, South Africa. South Afr J Infect Dis. 2015;3:06–10.

33. Bannai PH, Ariensona AT. Prevalence and antimicrobial susceptibility patterns of bovine and ovine *Staphylococcus aureus* isolates in Maidauguri, Nigeria. Adv Anim Vet Sci. 2013;1:59–64.

34. Niranjan IS, Parak P, Okon KO, Adamu NB, Askira UM, Isyama TK, Adamu SG, Mohammed A. Methicillin-resistant *Staphylococcus aureus* (MRSA) colonization rate among ruminant animals slaughtered for human consumption and contact persons in Maidauguri, Nigeria. Afr J Microbiol Res. 2014;8:2643–9. https://doi.org/10.5897/AJMR2014.6855.

35. Shittu et al. Antimicrobial Resistance and Infection Control (2018) 7:101
 aureus bacteraemia in hospitalized patients in South Africa, 2010-2012: laboratory-based surveillance mapping of antimicrobial resistance and molecular epidemiology. PLoS One. 2015;10:e0154529. https://doi.org/10.1371/journal.pone.0154529.

52. Barakat GI, Nabil YM. Correlation of mupirocin resistance with biofilm production in methicillin-resistant Staphylococcus aureus from surgical site infections in a tertiary Centre, Egypt. J Glob Antimicrob Resist. 2016;4:16–20. https://doi.org/10.1016/j.jgar.2015.11.010.

53. Shittu A, Lin J, Kowalowe D. Antimicrobial susceptibility patterns of Staphylococcus aureus and characterization of MRSA in southwestern Nigeria. Wounds. 2006;18:77–84.

54. Egyir B, Guardabassi L, Nielsen SS, Larsen J, Addo KK, Newman MJ, Larsen AR. Molecular characterization and antimicrobial susceptibility of methicillin-resistant Staphylococcus aureus strains from Ghana include USA300. J Glob Antimicrob Resist. 2015;3:26–30. https://doi.org/10.1016/j.jgar.2014.11.006.

55. Egyir B, Guardabassi L, Almgazeli MH, Eltamalli AK, Amr SG, Aghila ES, Abouzeed YM. Misidentification of methicillin-resistant Staphylococcus aureus. (MRSA) in hospitals in Tripoli, Libya. Libyan J Med. 2010;5:5230. https://doi.org/10.4304/ljm.v5i0.5230.

56. Ahmed MO, Eltamalli AK, Amr SG, Abuzveda AR, Abouzeed YM. Isolation and screening of methicillin-resistant Staphylococcus aureus from healthcare workers in Libyan hospitals. EMHL. 2012;18:37–42.

57. Finan Y, Yosita Y, Eman Y, Yamanoto T. Molecular characterization of Pantone-Valentine Leukocidin-positive community-acquired methicillin-resistant Staphylococcus aureus isolates in Egypt. Microbiol Res. 2010;165:152–62. https://doi.org/10.1016/j.micres.2009.03.005.

58. Ben Nejma MB, Mastouri M, Jrad BBH, Nour M. Genotyping of methicillin resistant Staphylococcus aureus using inpatients and hospital staff at Korle Bu teaching hospital, Ghana. J Glob Antimicrob Resist. 2013;1:189–93. https://doi.org/10.1016/j.jgar.2013.05.006.

59. Ben Nejma MB, Merghni A, Mastouri M. Characterization of Staphylococcus aureus nasal carriage among patients and health care workers in Sano Tomé and Principe. Microb Drug Resist. 2014;20:57–66. https://doi.org/10.1089/mdr.2013.0136.

60. Aiken AM, Mutuku IM, Sabat AJ, Akkerboom V, Mwangi J, Scott JAG, Morpeth SC, Friedrich AW, Grundmann H. Carriage of Staphylococcus aureus in Thika level 5 hospital, Kenya: a cross-sectional study. Antimicrob Resist Infect Control. 2014;3:22. https://doi.org/10.1186/2047-919X-3-22.

61. Omuse G, Kabera B, Revath G. Low prevalence of methicillin resistant Staphylococcus aureus as determined by an automated identification system in two private hospitals in Nairobi, Kenya: a cross sectional study. BMC Infect Dis. 2014;14:669. https://doi.org/10.1186/1471-2148-14-669.

62. Haddaway NR, Collins AM, Coughlin D, Kirk S. The role of Google scholar in evidence reviews and its applicability to Grey literature searching. PLoS One. 2015;10:e0138237. https://doi.org/10.1371/journal.pone.0138237.

63. Eshetie S, Tarekegn F, Moges F, Amsalu A, Birhan W, Huruy K, Methicillin resistant Staphylococcus aureus in Ethiopia: a meta-analysis. BMC Infect Dis. 2016;16:689. https://doi.org/10.1186/1471-2175-16-689.

64. Deyno S, Fekadu S, Astatkie A. Resistance of Staphylococcus aureus to antimicrobial agents in Ethiopia: a meta-analysis. Antimicrob Resist Infect Control. 2017;6:65. https://doi.org/10.1186/s12879-017-0243-7.

65. Aiken AM, Mutuku IM, Sabat AJ, Akkerboom V, Mwangi J, Scott JAG, Morpeth SC, Friedrich AW, Grundmann H, Carriage of Staphylococcus aureus in Thika level 5 hospital, Kenya: a cross-sectional study. Antimicrob Resist Infect Control. 2014;3:22. https://doi.org/10.1186/2047-919X-3-22.

66. Haddaway NR, Collins AM, Coughlin D, Kirk S. The role of Google scholar in evidence reviews and its applicability to Grey literature searching. PLoS One. 2015;10:e0138237. https://doi.org/10.1371/journal.pone.0138237.

67. Eshetie S, Tarekegn F, Moges F, Amsalu A, Birhan W, Huruy K, Methicillin resistant Staphylococcus aureus in Ethiopia: a meta-analysis. BMC Infect Dis. 2016;16:689. https://doi.org/10.1186/1471-2175-16-689.

68. Omuse G, Kabera B, Revath G. Low prevalence of methicillin resistant Staphylococcus aureus as determined by an automated identification system in two private hospitals in Nairobi, Kenya: a cross sectional study. BMC Infect Dis. 2014;14:669. https://doi.org/10.1186/1471-2148-14-669.

69. Wayne CLSI. 2017.

70. The European Committee on Antimicrobial Susceptibility Testing. Breakpoint tables for interpretation of MICS and zone diameters. Version 8.1, 2018. http://www.eucast.org. Accessed 28th May, 2018.

71. Comité de l’antibiogramme de la Societe Francaise de Microbiologie – recommendations 2018 v1.0 mai. http://www.sf-microbiologie.org. Accessed 28th May, 2018.

72. Hurdle JG, O’Neill AJ, Mody L, Chopra I, Bradley SF. In vivo transfer of high-level mupirocin resistance from Staphylococcus epidermidis to methicillin-resistant Staphylococcus aureus associated with failure of mupirocin prophylaxis. J Antimicrob Chemother. 2005;56:1166–8.

73. Shittu AO, Lin J, Morrison D, Kowalowe DO. Isolation and molecular confirmation of a multiresistant catalase-negative Staphylococcus aureus in Nigeria. J Infect. 2003;46:203–4. https://doi.org/10.1016/j.jinf.2002.11.006.

74. Eshetie S, Tarekegn F, Moges F, Amsalu A, Birhan W, Huruy K, Methicillin resistant Staphylococcus aureus in Ethiopia: a meta-analysis. BMC Infect Dis. 2016;16:689. https://doi.org/10.1186/1471-2175-16-689.

75. Deyno S, Fekadu S, Astatkie A. Resistance of Staphylococcus aureus to antimicrobial agents in Ethiopia: a meta-analysis. Antimicrob Resist Infect Control. 2017;6:65. https://doi.org/10.1186/s12879-017-0243-7.

76. CLSI. Clinical and Laboratory Standard Institute (CLSI). Performance standards for antimicrobial susceptibility testing: 27th edition. CLSI supplement M100. Wayne, CLSI 2017.

77. Afari PT, Asiedu S, Ofori-Boateng DD. Challenges in the investigation of Community-acquired methicillin-resistant Staphylococcus aureus (CA-MRSA) in urban Ghana. J Globantimicrob Res. 2017;8:101. https://doi.org/10.1016/j.jgar.2017.08.010.