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A Review of Prevalence, Antimicrobial Susceptibility Patterns and Molecular Characteristics of Methicillin-Resistant *Staphylococcus aureus* (MRSA) in the Caribbean

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Abstract

Methicillin-resistant *Staphylococcus aureus* (MRSA) is a major pathogen causing infections resulting in severe morbidity and mortality worldwide. To date, the true nature and extent of MRSA infections in the Caribbean are not well understood. This is a review of the limited studies in the Caribbean describing the prevalence, epidemiology, and molecular characteristics of MRSA in hospitalized and non-hospitalized patients. Relevant articles were searched and extracted from PubMed and Mendeley and a narrative review of the findings was constructed. An aggregate of 24 articles, from 1999 to 2020, was found from 10 of 27 countries. Majority of the studies were from Trinidad and Tobago (29%) and Jamaica (21%) while 50% were from Barbados, Dominican Republic, Martinique, Haiti, Cuba, St. Kits & Nevis, Guadeloupe, and Guyana. Approximately 75% of investigations were conducted on hospitalized patients versus 20% on outpatients. The data revealed geographical differences in the prevalence of MRSA within the Caribbean; 20% - 100% of *Staphylococcus aureus* clinical isolates from hospitalized patients and outpatients were resistant to methicillin, macrolides, and fluoroquinolones, but susceptible to several non-beta lactam antibiotics, due to the widespread occurrence of CA-MRSA clone ST8 SCC*mec* IV, PVL positive. There was moderate prevalence of ST72 SCC*mec* V (14% - 25%) in both hospital and community settings in a few of the countries while ST30 SCC*mec* IV, PVL positive, was moderately prevalent (27%) only in Dominican Republic. Also, there was moderate prevalence of HA-MRSA ST5 SCC*mec* II (18%) in community settings in the Dominican Republic and Martinique, but high prevalence of HA-MRSA ST239 SCC*mec* III (60%) in hospitalized patients in Cuba and Trinidad & Tobago. The epidemiologic profile of MRSA in both hospital and

community settings is changing in the Caribbean. Epidemiological studies on outpatient settings and the implementation of stringent hospital infection control measures are needed in the region.

Keywords

MRSA, Prevalence, Epidemiology, Molecular Characterization, Caribbean

1. Introduction

Antimicrobial Resistance (AMR) which occurs when microorganisms (bacteria, viruses, fungi, and parasites) become able to adapt and grow in the presence of antimicrobial agents that once impacted them is a significant threat to national, regional, and global public health systems [1] [2]. An infection with AMR leads to serious illnesses and prolonged hospital admissions, increases in healthcare costs, higher costs in second-line drugs, and treatment failures [1] [3] [4]. According to the US Centers for Disease Control and Prevention (CDC), antimicrobial resistance adds 20 billion dollars in direct healthcare costs in the United States, exclusive of the 35 billion dollars in loss of productivity annually [5]. Though there were uncertainties behind the estimates, a review projected that AMR could cause 10 million deaths a year by 2050 on a global scale [6].

One of the most well-known cases of AMR, Methicillin-resistant *Staphylococcus aureus* (MRSA), is a major nosocomial pathogen and a cause of community-acquired infections resulting in severe morbidity and mortality worldwide [7]. Methicillin resistance is mediated by PBP-2a, a penicillin-binding protein encoded by the *mec*A gene that permits the organism to grow and divide in the presence of methicillin and other beta-lactam antibiotics [8] [9]. The *mec*A gene is located on a mobile genetic element called staphylococcal chromosome cassette (SCC*mec*). To date, fourteen SCC*mec* types have emerged world-wide; SCC*mec* type I (1B), type II (2A), type III (3A), type IV (2B), type V (5C2), type VI (4B), type VII (5C1), type VIII (4A), type IX (1C2), type X (7C1), type XI (8E), type XII (9C2), type XIII (9A) and type XIV (5A) [10]. The increasingly prevalent community-associated MRSA (CA-MRSA) is genetically distinct from hospital-associated MRSA (HA-MRSA), by being resistant to fewer non-β-lactam antibiotics, carrying SCC*mec* types IV and V, and often Panton-Valentine leukocidin (PVL) genes that encode a *S. aureus* exotoxin that induces lysis of monocytes and neutrophil granulocytes [11].

The epidemiology of MRSA, both circulating clones and their antibiotic resistance profiles vary throughout regions and countries [12] [13]. The Caribbean region, composed of 13 independent countries and 15 dependencies (**Figure 1**), is a popular international tourist destination, especially, for Americans and Europeans [14] and this would have implications for the types of multiple drug resistant organisms. Increasingly, there are reports that returning international

Figure 1. The Caribbean map. (Source: https://www.freeworldmaps.net/caribbean/caribbean-map.jpg).

travelers with MRSA infections contracted strains specific to their country of vacation [15]. Similarly, frequent travel between Europe, Africa or North America to the Caribbean region appears to influence the local epidemiology of *S. aureus* infections [12]. The diversity in the socioeconomic conditions between individual countries in the Caribbean may lead us to assume that the epidemiology of MRSA might also differ between the countries. However, there was a need for a comprehensive assessment of the disparate data on the prevalence, antimicrobial susceptibility patterns and genotypes of MRSA in the Caribbean to help fill the global map of antimicrobial resistance. The present scholarly work sought to contribute to a review of the studies conducted in some English-speaking countries including Jamaica, Trinidad and Tobago, Barbados, St Kitts and Nevis, and the Dominican Republic, and a few French territories including Guadeloupe and Martinique, describing the prevalence, epidemiology, antimicrobial susceptibility patterns and molecular characteristics of MRSA in hospitalized and non-hospitalized patients.

2. Methodology

According to the framework previously described [16] [17], the methods employed in this review corresponded with the Joanna Briggs Institute Reviewer's Manual guidelines [18]. We identified the research question, followed by relevant studies and consequently selecting them for data presentation. The search for peer-reviewed published articles conducted in PubMed and Mendeley were

limited to articles in English. An exploratory search of the literature was used to develop inclusion and exclusion criteria. The strategy used in searching the keywords combined "MRSA" OR "Methicillin-resistant *Staphylococcus aureus*" AND "Caribbean" with some other related terms such as "Wound infection" OR "SSTI" OR "staphylococcal skin and soft tissue infections" OR "Patients" OR "Surveillance" OR "Infection control" OR "Prevalence" AND "healthcare." Further articles were obtained using reference lists from several articles and manual searching.

This study included all types of observational studies. The relevant titles and abstracts were screened, and their full-text articles were included according to the eligibility criteria developed based on 1) region/country, 2) MRSA definitions (molecular or epidemiological), 3) study design, 4) study period and 5) settings. Articles that reported non-human isolates or did not provide a clear definition of clinical setting were excluded. Additional data extracted from each of the included studies consisted of the author, year of publication, number of patients and/or isolates of *S. aureus*, the type of the culture specimen and of staphylococcal infection, the percentage of MRSA to the total *S. aureus* isolates, molecular typing methods, the percentage of the MRSA SCCmec genotypes, the percentage of isolates positive for the Panton Valentine Leukocidin (PVL) toxin and antimicrobial resistant genes, the susceptibility of MRSA to the antibiotics tested in each study, and the status of infection control practices**.** The focus of this narrative review was to describe data on the percentage of MRSA to the total *S. aureus* isolates, assess their susceptibility to different antibiotics and document their genotypes.

3. Results

3.1. Synopsis of *Staphylococcus aureus* and MRSA Research Information from the Caribbean

The goal of surveillance in public health, to provide information to decrease morbidity and mortality, and to improve health, could be achieved through ongoing systematic collection, analysis, interpretation and dissemination of data regarding public health-related events. The surveillance system for MRSA in the Caribbean appears simple, most data are collected from a single or multiple, regional hospitals, primary health centers in the rural or urban communities with limited complex electronic system that receives and integrates data from the multiple sources. Out of 47 records identified during the literature screening process, an aggregate of 24 peer-reviewed publications met the search criteria, and were included in this review (**Table 1**), [11] [12] [19]-[38]. The publications, contributed by investigators from 10 countries (37%) of the 27 screened, ranged in dates from 1999 to 2020. The included studies were conducted in Trinidad and Tobago (n = 7), Jamaica (n = 5), Barbados (n = 2), Dominican Republic (n = 2), Martinique (n = 2), Haiti (n = 2), Cuba (n = 2), St. Kits & Nevis (n = 1), Guadeloupe (n = 1) and Guyana (n = 1).

Table 1. Summary of included studies.

Reference	Study period	Location	Study Design	Setting	Aims of study
[11]	2014-2015	Barbados	Prospective, observational	Hospital	To characterize S. aureus, MRSA in the Barbados healthcare system
	2013-2016			Community	
[12]	2004-2009	Martinique	Retrospective, observational	Hospital	To evaluate the possible relationship between human migration and local MRSA epidemiology
	2010-2011	Martinique Guadeloupe Tobago Trinidad Jamaica	Retrospective, observational	Hospital	
[16]	2008	Cuba	Prospective, observational	Hospital	To investigate the molecular epidemiology of MRSA isolates from four major Cuban hospitals
[20]	2002	Manchester, southern Jamaica	Prospective, observational	Hospital & Community	To assess the antimicrobial susceptibility patterns and prevalence of methicillin resistance among S. aureus isolates from hospital and community sources in southern Jamaica
[21]	2013 to 2017	Queen Elizabeth Hospital, Barbados	Retrospective cohort study	Hospital; Screening for colonization	To investigate the prevalence of MRSA and CRKP colonization and infection in the patients of the ICU and HDU units at the Queen Elizabeth Hospital, Barbados
[22]		Jamaica	Retrospective, cross-sectional	Hospitalized patients (with skin and soft tissue infections)	To compare the carriage of virulence determinants and antibiotic resistance phenotypes between MRSA and MSSA isolates and examine their virulence potential using the nematode, *C. elegans*
[23]	2004-2007	Manhattan, New York City	Prospective, observational	Community	To assess the potential for horizontal transmission of S. aureus ST398 and evidence for identical strain profiles between USA and Dominican Republic
		Dominican Republic	Retrospective	Hospital	
[24]	2007-2008	Dominican Republic	Retrospective, observational	Community	To characterize S. aureus isolates from the DR and contrast this with S. aureus from Martinique
		Martinique	Retrospective, observational	Community	
[25]	2014	Haiti	Prospective, observational	Hospital	To determine incidence and independent risk factors for SSI after CS, as well as pathogens associated with infections
[26]	1999-2004	Trinidad	Retrospective, observational	Hospital and Community	To characterize MRSA isolates of S. aureus recovered from different sources in Trinidad
[27]	2011-2012	Kingston and St. Andrew metropolis, Jamaica	Retrospective observational	Hospital	To characterize MRSA isolates from patients admitted to public hospitals in the Kingston and St. Andrew metropolis

Continued

[28]	2013-2014	Trinidad	Prospective, observational	Hospital	To obtain overview on MRSA and MSSA clinical isolates and characterize them by microarray hybridization and by multi locus sequence typing (MLST)
[29]	2016	Northern region of Trinidad and Tobago	Retrospective, observational	Rural Community	To delineate the SCCmec type and toxin genes, and genes mediating antibiotic resistance in MRSA isolates
[30]	2011	Cuba	Retrospective, observational (Epidemiological analysis)	Hospital	To characterize MRSA isolates recovered from Cuban hospitals by a variety of methods
[31]	2012	Haiti	Cross-sectional analysis	Community	To describe the molecular epidemiology of nasal carriage isolates of S. aureus.
[32]	2017-2018	St. Kitts	Prospective, observational	Hospital	To determine the prevalence of antimicrobial resistance among *S. aureus* isolates and to reveal the frequency and population structure of MRSA in St. Kitts and Nevis
[33]	2013	Trinidad and Tobago	Prospective, observational	Hospital	To assess the prevalence of MRSA in patients hospitalized in the surgical wards of, and determine associated risk factors
[34]	2008	Jamaica	Prospective, observational	Hospital	To determine the prevalence of MRSA and characterize the isolates at the University Hospital of the West Indies (UHWI)
[35]	1997-1998	Trinidad	Prospective, observational	Hospital Community	To determine the prevalence of MRSA isolated from hospital and community practices and their anti-microbial resistance profiles
[36]	2005-2006	Trinidad	Prospective, observational	Hospital	To investigate the prevalence of mupirocin resistance among clinical isolates of MRSA at SFGH
[37]	2000-2001	Trinidad and Tobago	Retrospective	Hospital	To delineate and document the clonal relatedness of all MRSA clinical isolates
[38]	2013	Guyana	Prospective	Hospital	To determine the prevalence and molecular characteristics of MRSA isolates

The Caribbean researchers used cohort studies, choosing equally between prospective and retrospective study designs [39] as dictated by their budgets, availability of resources and relative access to patients' samples. For the prospective study designs, hospital and/or community clinical specimens included high vaginal swabs, urine, skin and soft tissue swabs, surgical and burn wounds, pus/abscess, respiratory tract, blood, bone, nasal cavity swabs and catheters submitted by pa-

tients or subjects being investigated for staphylococcal colonization or infections [11] [20] [29] [32] [33] [34]. For the retrospective study designs, investigators conducted cohort analysis of patients admitted to the major hospitals over a given period (years) as part of surveillance programs established to screen surgical and burn wounds, nasal, groin, and axilla for colonization with *Staphylococcus aureus* and prevalence of MRSA [21] [26] [37]. The main outcomes of interest in the studies were the rate of MRSA in *S. aureus* in hospital and/or community settings, country or regional capabilities including phenotypic characterization through antimicrobial susceptibility testing, distribution of major MRSA genotypes through various molecular genotyping methods, detection of toxin and antibiotic resistance genes, and infection control practices.

3.2. The Prevalence of MRSA in the Caribbean

An overview of the peer-reviewed articles that reported on the prevalence of MRSA in the Caribbean is shown in **Table 2**. The number of *S. aureus* or MRSA isolated from clinical samples and characterized in the included studies ranged from 16 to 1997. The results show that majority (75%) of the investigations were conducted on cultures of hospitalized patients' samples [12] [16] [21] [23] [26] [28] [31] [32] [33] [34] [35] [37]. A few studies investigated only cultures obtained from clinical samples obtained from outpatients [24] [29], or from cultures of samples obtained from hospitalized patients and outpatients [11] [21] [27].

The results show that between 12.8% and 60% of Caribbean *S. aureus* isolates from samples collected from infected, hospitalized patients are MRSA [12] [16] [21] [23] [26] [28] [31] [32] [33] [34] [35] [37]. Interestingly. the prevalence of MRSA differed across the Caribbean countries and territories (**Table 2**). Even though the mean MRSA prevalence reported in hospitalized patients was characteristically < 21% in Barbados [11], Dominican Republic [25] and Trinidad and Tobago [27], the percentage of MRSA isolates ranged from 39% in Martinique [25], 45% in Jamaica [21] and St Kitts and Nevis [33], to 51% in Guyana [39], and 59% in Cuba [16]. Similarly, while the MRSA prevalence in the samples cultured from outpatients was 20% in the Dominican Republic [25], percentage of MRSA isolates in this patient group were, 39% and 45%, respectively, in Martinique [25], and Trinidad & Tobago [28].

Most of the MRSA isolates from hospitalized patients were associated with surgical wounds, and infections of skin and soft tissue, respiratory tract and urinary tract, age (peak range of 60 - 69 years), gender, ethnicity, duration of hospital stay, co-morbidities such as diabetes mellitus and hypertension, previous penicillin use or previous surgery [11] [12] [16] [21] [22] [25] [27] [31] [34] [35] [39]. However, prevalence of MRSA isolates in clinical samples collected from outpatients, though, associated with gender, diabetes, hypertension or asthma, some considerable proportion of the subjects tended to be healthy, students or those who participated in physical contact sports [11] [30] [33].

Table 2. MRSA percentage in *Staphylococcus aureus*.

Reference	Study period	Inclusion criteria	No. of *S. aureus*	No. of MRSA (%)	MRSA clone
[12]	2004-2009	Hospitalized patients' skin and soft tissue samples had cultures obtained (Martinique)	Data not reported	69	**Martinique** CC8-MRSA-IV "Lyone" (50.7%) CC8-MRSA-IV "UK-EMRSA" (7.2%) ST8-MRSA-IV "USA300" (7.2%) ST8-MRSA-IV ACME− (1.45%) WA-MRSA-62 PVL− (1.45%) ST239-MRSA-III "Brazillian" (1.45%) ST72-MRSA-IV "USA700" (1.45%) CC59 ST59-MRSA-V (1.45%) CC5 ST5-MRSA-I "Geraldine" (13%) CC5-MRSA-IV "pediatric" (4.3%) CC5-MRSA-IV "pediatric" PVL− (1.45%) CC80-MRSA-IV PVL− "European CA-MRSA" (10%)
	2010-2011	Hospitalized patients' skin and soft tissue samples had cultures obtained (Trinidad, Tobago, Jamaica, Guadeloupe)	Data not reported	16	**Jamaica** ST8-MRSA-IV "USA300" (6.25%) ST5/ST225-MRSA-II New York-Japan (12.5%) Trinidad ST8-MRSA-IV "USA300" (6.25%) ST239-MRSA-III "Brazillian" (18.75%) CC5-MRSA-IV "pediatric" (6.25%) Tobago ST8-MRSA-IV "USA300" (12.5%) ST239-MRSA-III "Brazillian" (12.5%) WA-MRSA-62 PVL− (6.25%) Guadeloupe ST8-MRSA-IV "USA300" (6.25%) WA-MRSA-62 PVL− (6.25%) CC5 ST5-MRSA-I "Geraldine" (6.25)
[11]	2014-2015	Hospitalized patients' blood, bone, ear, fluids, surgical drains, tissue, urine and wounds had culture obtained	Data not reported	100	CA-MRSA PVL+ (76%) CA-MRSA PVL− (14%) HA-MRSA, PVL+ (9%) HA-MRSA, PVL− (1%)
	2013-2016	Outpatients' convenience samples from wounds, nasal, penile and vaginal had culture obtained	Data not reported	193	CA-MRSA, PVL+ (95.9%) CA-MRSA, spa+, mecA+ (4.1%) CA-MRSA, spa+, mecA+ resistant to vancomycin (2.07%)
[19]	2008	Hospitalized patients' surgical wounds, bronchial/tracheal aspirations, blood, skin, abdominal drainage and chest tissue biopsy had culture obtained	68	40 (58.9)	Spa-types t149 (60%) CC8 t008 (20%), PVL+ t037 (15%), t4088 (2.5) t2029 (2.5%)

Continued

[20]	2002	Hospitalized patients' urine, high vaginal swabs, blood, wound and abscess swabs, had culture obtained	39	18 (46)	No genotypic characterization reported.
		Outpatients' urine, high vaginal swabs, blood, wound and abscess swabs, had culture obtained	41	0 (0)	
[23]	Study period not reported	Hospitalized patients' skin and soft tissue had culture obtained	102	56 (55)	Data from SCCmec typing study not reported. 35 virulence-associated genes examined.
[24]	2007-2008	Outpatients' skin and soft tissue, ear, conjunctiva, and urinary tract samples had cultures obtained (Dominican Republic)	112	22 (20%)	MRSA SCCmec IV (82%) MRSA PVL+ (45%) MRSA SCCmec V (18%) Spa-CC665/ST30 PVL+ (27%) Spa-CC148/ST72 (23%) Spa-CC002/ST5 (18%) MSSA (80%) MSSA PVL+ (46%) Spa-CC665/ST30 PVL+ (33%) Spa-CC002/ST5 (7.8%) Spa-CC002/t571/ST398 (7.8%) t008 USA300 MSSA (3.3%) Spa-CC008/ST8 (6.6%)
		Outpatients' skin and soft tissue, blood, lung, and urinary tract samples had cultures obtained (Martinique)	143	56 (39%)	MRSA MRSA PVL+ (8.9%) ST8 spa t304 SCCmec IVc PVL− (49%) spa-CC0044/ST80 (13%) spa-CC002/ST5 (18%) spa-CC008 t008 USA300 (12.5%) MSSA (61%) MSSA PVL+ (10.3%) spa-CC1096/ST152 (15%) spa-CC571/ST398 (10%)
[25]	2014	Hospitalized patients' post-surgery wound sites had culture obtained	Data not reported	4	No genotypic characterization data reported.
[27]	2011-2012	Hospitalized patients' wounds, sputum, urine and catheter tip, ear and nasal swabs, and knee aspirate had culture obtained	Data not reported	61	SCCmec typing confirmed in only 34 isolates. SCCmec type IV (85%) SCCmec type II (9%) SCCmec type III (3%) SCCmec type I (3%)

Continued

		Hospitalized patients' surgical and burn wounds, pus/abscess, upper respiratory tract and urine had culture obtained	1997	416 (20.8)	No genotypic characterization data reported.
[26]	1999-2004	Outpatients' surgical and burn wounds, pus/abscess, upper respiratory tract and urine had culture obtained	433	35 (8.1)	No genotypic characterization data reported
[28]	2013-2014	Hospitalized patients' clinical samples had culture obtained	294	45 (15.31)	MRSA ST239 SCCmec III (60%) ST8 SCCmec IV (37.78%); PVL +, "USA300" SCCmec V (2.22%); ACME− positive "Staphylococcus argenteus" lineages (2.38%) MSSA PVL− positive CC8-MSSA (20.41%) "African" PVL− positive CC152-MSSA (9.52%) PVL− positive CC30-MSSA (8.84%)
[29]	2016	Outpatients' anterior nares and wound swabs had culture obtained	36	16 (44.4)	SCCmec IV (75%); PVL + SCCmec V (25%)
[30]	2011	Hospitalized patients' skin lesion, surgical wounds, blood and bronchial secretions had culture obtained	Data not provided.	87	ST8 t008 SCCmec IVa (67.8%) PVL+, ACME+ ST8 t008 SCCmec IVa (13.8%) PVL+, ACME− ST8 t008 SCCmec IVa (1.2%) PVL−, ACME− ST8 t211 IVa (3.6%) PVL+, ACME+ ST72 t13567 SCCmec V (12.6%) PVL−, ACME− ST72 t13567 SCCmec V (1.2%) PVL+, ACME−
[31]	2012	Hospitalized patients' and staff's anterior nares had cultures obtained	16	4 (25%)	t148, CC72, SCCmec IV (50%) t002, CC5, SCCmec II (25% t002, CC5, SCCmec IV (25%)
[32]	2017-2018	Hospitalized patients' samples from pus, nasal cavity, wounds, catheters, blood, skin urine had cultures obtained	119	54 (45.4%)	ST8 SCCmec IV (88%) "USA300-NAE lineage" ST5 (2.9%) ST4080 (2.9%) ST30-MRSA-V (1.5%)
		Hospital staffs' nasal samples had cultures obtained	33	15 (42.42%)	ST72 (1.5%) ST121 (1.5%) ST134 (1.5%)
[33]	2013	Hospitalized patients' surgical wounds had culture obtained	38	15 (39.5)	No genotypic characterization reported

Continued

[34]	2008	Hospitalized patients' skin and soft tissue, respiratory tract, the urinary tract and blood had culture obtained	471	33 (7)	No genotypic characterization reported
[36]	2005-2006	Hospitalized patients' skin and soft tissue, urine, lungs and nares	Data not reported	188	No genotypic characterization reported

3.3. Antimicrobial Susceptibility Patterns of Clinical MRSA Isolates

Treatment of MRSA infections has remained problematic in the Caribbean region because of the organism's resistance to many antimicrobial agents. Routine characterization of the clinical MRSA isolates through antimicrobial susceptibility testing and analyses, in the most instances, using the Kirby-Bauer disc diffusion method on Müller-Hinton agar [40] has been reported in approximately 50% of the studies to guide empirical treatment of mild or moderate infections [12] [21] [25] [27] [28] [30] [31] [32] [33] [35] [36]. In a study reported from Trinidad [27], involving MRSA isolates (n = 451) from clinical samples collected from hospitalized patients between 1999 and 2004, all the organisms were fully sensitive to vancomycin, while the greatest resistance was against erythromycin (86.7%) clindamycin (75.3%), tetracycline (78.7%) and ciprofloxacin (59.1%). However, the MRSA strains were less resistant to gentamicin (44.7%), chloramphenicol (17.3%) and trimethoprim-sulfamethoxazole (13%) [27].

In a study reported from Jamaica [21], all MRSA isolates (n = 80) collected from samples of hospitalized and community patients in 2002 were susceptible to vancomycin. Overall, 77.5% of the isolates were resistant to at least one antibiotic, and 10% of isolates were resistant to gentamicin, ciprofloxacin, tetracycline, chloramphenicol, and erythromycin. Sixty percent of the isolates were resistant to penicillin G, 22.5% each to trimethoprim-sulfamethoxazole and oxacillin, and 13.8% to tetracycline. More isolates from hospital sources were resistant to the antimicrobials evaluated (except for gentamicin). Notably, 82% of hospital isolates were resistant to penicillin, compared to 39% of community isolates. Further, all isolates resistant to oxacillin were from hospital sources [21]. In another study of hospitalized patients reported from Jamaica in 2010 [34], MRSA isolates (n = 33), again, showed sensitivity to vancomycin, but variable resistance to erythromycin (94%), clindamycin (52%), gentamicin (33%) and tetracycline (27%). However, resistance to trimethoprim-sulfamethoxazole and minocycline was 12% and 6%, respectively [34].

In a study reported from Barbados [11] antimicrobial susceptibility testing revealed that all hospital-associated MRSA isolates (n = 100) were resistant to ceftriaxone and ciprofloxacin, and 90% of isolates were resistant to erythromycin. All isolates were sensitive to vancomycin, rifampin, gentamicin, linezolid

and trimethoprim-sulfamethoxazole; 82% were sensitive to clindamycin, with 2% inducible clindamycin resistance [11]. In the same study from Barbados, of the community-associated MRSA isolates (n = 193) evaluated, nine, or 4.7%, gave D-zones for clindamycin induction. A total of 94.3% susceptibility was recorded to trimethoprim-sulfamethoxazole. A susceptibility to vancomycin of 97.4% was observed; clindamycin susceptibility averaged 89.6%. All isolates were resistant to the β-lactam antibiotics and macrolides. However, for 4.2% of 193 MRSA isolates, four were resistant to vancomycin, whilst one isolate was resistant to cotrimoxazole, ciprofloxacin and vancomycin, and six isolates were resistant to clindamycin [11].

In a study conducted on hospitalized patients and community subjects from St Kitts & Nevis in 2019 [32], the prevalence of MRSA accounted for 46% (70/152) of the isolates. The highest rates of resistance to non-β-lactam agents were observed for daptomycin (97.1%), erythromycin (91.3%), levofloxacin (75.4%), moxifloxacin (73.9%), whereas lower proportions of resistant isolates were seen for tetracycline (10.1%), tobramycin (10.1%), gentamicin (4.3%), fusidic acid (4.3%), clindamycin (2.9), mupirocin (2.9%) and rifampicin (1.4%). All the MRSA isolates were susceptible to ceftaroline, linezolid, teicoplanin, telavancin, trimethoprim/sulfamethoxazole and vancomycin [32].

3.4. Molecular Typing of Clinical MRSA Isolates

In the last decade, six molecular typing methods have been utilized in the molecular characterization of MRSA to monitor geographic spread of one or several clones among countries in the Caribbean region [11] [12] [19] [24] [27]-[32]. These molecular techniques included pulsed field gel electrophoresis (PFGE) after *Sma*I digestion [37], multi-locus sequence typing (MLST) [19] [25] [28], whole genome sequencing-MLST [27], multiplex polymerase chain reaction (PCR) to detect 16SrRNA, *mec*A, the staphylococcal chromosomal cassette (SCC) *mec* types, spa types, presence of exotoxins, Panton-Valentine Leukocidin (PVL) and LukAB, and the arginine catabolic mobile element (ACME) [11] [24] [27] [29] [30] [38], microarray hybridization [12] [28], and Multiple Locus Variable-number Tandem Repeat Analysis (MLVA) [27]. Each of these genotyping methods varies regarding the equipment, cost, and expertise required, and their ability to discriminate among related isolates is not the same [10] [41]. Notwithstanding, the sequence-based techniques are specific and sensitive enough to distinguish MRSA strains based on the genes encoding the staphylococcus protein A, the SCCmec types, the PVL, and ACME [41].

Molecular typing of clinical MRSA isolates was established in approximately 60% of the studies reviewed [11] [12] [19] [24] [27]-[32]. Only 15% of the studies reported the genotypes of Methicillin sensitive *S. aureus* (MSSA) isolates from either hospitalized or community patients [24] [28]. More than a third of the studies did not report on the MRSA genotypes [20] [22] [25] [26] [33] [34] [36]. The clonal results of the MRSA isolates from clinical samples collected

from patients in hospital and community settings in the Caribbean region (**Table 2**), [11] [12] [19] [24] [27]-[32] are described below.

CA-MRSA clones

There was a wide-spread occurrence of the North American epidemic or endemic ST8 MRSA SCC*mec* IV, PVL positive, (CA-MRSA, USA300) clone in the clinical samples of hospitalized patients studied in several countries including Barbados [11], St Kitts & Nevis [32], Trinidad & Tobago [28] [29], Jamaica [27], Cuba [30], Dominican Republic and Martinique [24]. A similar ST8 MRSA SCC*mec* IV, PVL positive, prevalence frequency was shown in the clinical samples of outpatients studied in Barbados [11], Trinidad & Tobago [29], Dominican Republic and Martinique [24]. However, there was occurrence of geographical differences in the prevalence of most other MRSA clones in the region. Of particular interest, was the prevalence of CC8-MRSA-IV, "Lyone" clone, CC8-MRSA-IV "UK-EMRSA" clone, and European-CA-MRSA clone in a study of clinical samples of hospitalized patients from Martinique [12]. Another CA-MRSA clone, ST72 SCC*mec* V was moderately prevalent [25%] in the clinical samples of outpatients reported from Dominican Republic [24], Trinidad & Tobago [29], but rarely observed in outpatients from Barbados [11] and Martinique [24]. ST72 SCC*mec* V was moderately prevalent [14%] in hospitalized patients studied in Cuba [30] and Haiti [31], of extremely low frequency (1.5% to 2.22%) in Trinidad & Tobago [28], and St Kitts & Nevis [32], but rare in Jamaica [27]. ST30 MRSA SCC*mec* IV was moderately prevalent (27%) in the samples of outpatients studied in Dominican Republic [24)] but not reported in community patients studied in Martinique [24], Trinidad & Tobago [29], and Barbados [11]. ST30 MRSA SCC*mec* IV was rare (1.5%) in hospitalized patients reported from St Kitts & Nevis but it was not observed in hospitalized patients' studies from Jamaica [27], Cuba [30], Haiti [31], and Barbados [11]. Similarly, spa-CC0044-ST80 SCC*mec* IV was moderately prevalent (13%) in the clinical samples of outpatients studied from Martinique [24] but rare in both hospital and community settings in the other Caribbean countries with published surveillance data (**Table 2**).

HA-MRSA clones

According to the results shown in **Table 2**, ST239-MRSA-III, a common cause of hospital-acquired MRSA, was highly prevalent (60%) in the clinical samples of hospitalized patients studied in Trinidad & Tobago [28], but was of considerably low occurrence (1.45% - 3%) in the clinical samples of hospitalized patients reported from Jamaica [27] and Martinique [12]. ST5 MRSA SCC*mec* II (New York-Japan) clone had low prevalence (3% - 12.5%) in the clinical samples of hospitalized patients in the reports from St Kitts & Nevis [32] and Jamaica [27], and moderately prevalent (18%) in the samples of outpatients from Martinique and Dominican Republic [24]. CC5-ST5-MRSA-SCC*mec* 1 "Geraldine" clone was of low prevalence (3% - 13%) in the samples of hospitalized patients studied in Jamaica [27], Guadeloupe and Martinique [12].

3.5. Detection of Toxin and Antimicrobial Resistant Genes

In a population structure study on several MRSA clones (n = 45) from Trinidad and Tobago in 2014 [28], the common antimicrobial resistance markers reported were the beta-lactamase operon (*bla*Z/I/R; in 86.39% of isolates), *erm* (A) (in 9.86%, mostly ST239-MRSA-III), *msr* (A)/*mph* (C) (in 8.16% and 7.14%, respectively; mostly associated with "USA300") and *aph*A3/*sat* (in 15.31%, largely associated with ST239-MRSA-III and "USA300"). The gentamicin/tobramycin resistance gene *aac*A-*aph*D occurred in 9.52% of isolates that all belonged to ST239-MRSA-III or "USA300". A gene associated with mupirocin resistance, *mup*A, was detected in 17.78% of MRSA isolates. Other resistance markers; *van*A (vancomycin resistance) and *cfr* (linezolid resistance) were not found [28].

Similarly, a separate study conducted on outpatients in the rural communities from the same country (Trinidad & Tobago) in 2018 showed the presence of the *erm*A gene in 31% (5/16) MRSA isolates tested, but none of them tested positive for the *erm*C and *van*A genes, respectively [29]. Majority (62.5%, 10/16) of the MRSA isolates from the outpatients possessed the *pvl* gene, whereas 25% (4/16) possessed the alpha hemolysin (*hla*) gene. None of the MRSA isolates possessed the *tst*1 gene, 18.8% (3/16) possessed both virulence genes, *pvl* and *hla* [29]. Nearly all the MRSA (ST8, 88%) isolates from hospitalized patients and community subjects from a study reported in 2019 from St Kitts & Nevis [32] carried genes encoding resistance to streptomycin [*ant* (6)-Ia], amikacin and other aminoglycosides [*aph* (3')-III], fosfomycin (*fos*D), macrolides, lincosamides and streptogramins [*mph* (C) and *mrs* (A)], and penicillin (*bla*Z). Additionally, genes encoding resistance to trimethoprim (*dfi*G) and phenicols (*cat*) were found in four and one isolate, respectively [32].

3.6. MRSA Infection Control Practices

MRSA infection prevention and control practices are well known, and they include effective personal hygiene, proper wound care, optimum laundry and cleaning or disinfection of high-touch or soiled surfaces [26]. However, the successful application of these practices is dependent on the knowledge, attitudes and practices of health care workers in the local or regional, major hospitals in the Caribbean. In Trinidad and Tobago, lack of effective infection control programs has been associated with poor level of knowledge, attitudes and practices among healthcare workers [42], limited resources, competing priorities, and other barriers [33]. Stringent MRSA infection control measures, on the other hand, appeared to have been set up in Barbados, which accounted for the rare prevalence of HA-associated MRSA infections in the community [11].

4. Discussion

Peer-reviewed published studies on the epidemiology of MRSA in the Caribbean remain scanty, and the true nature and extent of MRSA infections in the region are not well characterized. To our knowledge, this is the first extensive review of

available peer-reviewed articles on MRSA prevalence, characteristics and clonal distributions in the Caribbean. Twenty-four studies on MRSA prevalence in different hospital and outpatient settings in 10 different Caribbean countries were analyzed. The majority (75%) of the investigations were conducted on cultures of hospitalized patients' samples while a few studies investigated only cultures obtained from clinical samples obtained from outpatients or from cultures of samples obtained from hospitalized patients and outpatients. The MRSA isolates from hospitalized patients, clinical samples collected from outpatients, subjects who tended to be healthy, students or those who participate in physical contact sports were from major sites of MRSA colonization and infections consistent with previous reports in humans [43] [44] [45] [46].

The mean MRSA prevalence reported in hospitals and outpatients was characteristically < 21% in Barbados, Dominican Republic, Trinidad and Tobago, however, the percentage of MRSA isolates ranged from 39% in Martinique, 45% in Jamaica, St Kitts and Nevis, to 51% in Guyana, and 59% in Cuba. The heterogeneity in MRSA prevalence across the Caribbean is similar to previous reports of MRSA in Latin America which ranged from 6% in Central America to 80% in some South American countries [47], between 25% and 50% in most parts of Africa [48], or 25% - 60% in the Mediterranean European countries [49]. These different MRSA prevalence rates among different countries may be attributed to disparities in patient populations, the biological characteristics of the *S. aureus* strains, widespread antimicrobial use, differences in infection control practices and/or impact of regional or intercontinental travel of healthcare personnel and tourists [12] [15] [33] [50]. In a specific investigation, comparing the characteristics of MRSA clones in the French (Guadeloupe and Martinique) and non-French territories (Jamaica and Trinidad and Tobago), it has been shown that the differences in the major clones in each country most closely reflected those found in the home countries of tourists or healthcare workers and the frequency of visits to the islands [12].

This review study revealed changes in the molecular epidemiologic profile of MRSA clone in both hospital and community settings in the Caribbean. The prevalence of CA-MRSA ST8 SCC *mec* V, PVL+ among hospitalized patients ranged between 20% and 100% in Trinidad & Tobago, Dominican Republic, Martinique, Jamaica, St Kitts & Nevis, Barbados, and Cuba. This result is consistent with reports of continued expansion of CA-MRSA among hospitalized patients in the United States [51], Europe [52], Asia [53] [54], Africa [48] and Latin America [55], indicating the invasion of these strains into hospitals and they may replace the classical HA-MRSA strains due to their unique characteristics and faster growth patterns [11].

This study also showed that the prevalence of HA-MRSA (SCC*mec* type I and/or SCC*mec* type II) in hospitalized patients ranged between 3% to 10% in several of the Caribbean countries with the exceptions of Cuba, Trinidad & Tobago that registered HA-MRSA (ST239 SCC*mec* III) prevalence of 60%. The high prevalence of SCC*mec* type III among hospitalized patients has implica-

tions in terms of use of alternative antimicrobial treatments in the face of significant resistance to most old beta-lactam and non-beta lactam antibiotics, and the serious requirement for effective infection control to prevent spread between hospitalized patients or spread of the HA-MRSA clone to the community [56]. However, notably, there were no reports of HA-MRSA isolates in samples of outpatients from Barbados, Trinidad & Tobago and Cuba, though, reports of moderate HA-MRSA (ST5 SCCmec II) (18%) prevalence rate in the clinical samples of outpatients in the Dominican Republic and Martinique suggest that this MRSA hospital strain has spread to the community, in the two countries. The spread of HA-MRSA isolates to the community, has been demonstrated previously through the presence of SCC*mec* types I, II and III in CA-MRSA isolates from Taiwan (China), Korea, Hong Kong (China), Philippines, Thailand and Vietnam [56].

In addition to most β-lactams, MRSA strains are variably resistant to several antimicrobial agents, including fluoroquinolones, macrolides, lincosamides, rifampin and tetracyclines [8] [57] [58]. Resistance to trimethoprim-sulphamethoxazole, glycopeptides (vancomycin, teicoplanin), oxazolidinones (linezolid, tedizolid), daptomycin, tigecycline and the new cephalosporin, ceftaroline remains uncommon [57]. Consistent with the clonal results of the MRSA isolates from clinical samples from patients in hospital and community settings analyzed in this review study, the antimicrobial susceptibility patterns indicate wide-spread occurrence of CA-MRSA with demonstrated high resistance to β-lactam agents, macrolides and fluoroquinolones, however, with significant susceptibility to vancomycin, trimethoprim-sulphamethoxazole, clindamycin, gentamicin, rifampin and tetracycline. Similarly, the prevalence of HA-MRSA in hospitalized patients in several of the Caribbean countries with surveillance data is reflected by the antibiograms of such clones that were mostly resistant to all β-lactam antibiotics and non-β-lactam antibiotics evaluated except vancomycin and trimethoprim-sulphamethoxazole.

The major limitation of this work is that it is based on passive surveillance in the Caribbean countries that presented their findings through peer-reviewed publications. There may be additional data in grey literature or government databases from the same or other countries and territories in the region that are excluded from unfettered access and robust assessment. Second, since most of the clinical samples processed for MRSA were from hospitalized patients in the countries reporting these studies, there may have been an underestimation of the actual community prevalence of MRSA in the review study populations since there were no reports of routine sampling of patients for microbiological analyses.

5. Conclusion

In conclusion, the data from peer-reviewed articles evaluated for this report indicate the occurrence of geographical differences in the prevalence of MRSA clones within the Caribbean region. The review ascertained that a high propor-

tion of clinical isolates from patients in the hospital and community settings of the reporting Caribbean countries were resistant to methicillin, macrolides, and fluoroquinolones, but susceptible to tetracyclines, gentamicin, clindamycin, and trimethoprim-sulphamethoxazole, due to the widespread occurrence of epidemic/endemic CA-MRSA clone ST8 SCCmec IV, PVL positive, USA300. Also, there was moderate prevalence of ST72 SCCmec V clones in both hospital and community settings in a few of the countries while ST30 SCCmec IV, PVL positive, was moderately prevalent in only one country with published research article. The moderate prevalence of HA-MRSA ST5 SCCmec II in community settings, and the high prevalence of HA-MRSA ST239 SCCmec III circulating in hospitalized patients in two countries are concerning. Future epidemiological studies which also focus on the populations outside of healthcare facilities in various countries could assist in the assessment of the burden of infections with MRSA in community settings. The implementation of stringent hospital infection control measures could substantially reduce the burden of MRSA on the healthcare systems in the Caribbean.

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Conflicts of Interest

The authors declare that this research does not have any commercial or financial affiliations that may be regarded as a potential conflict of interest.

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