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Review

Determinants of methicillin-resistant *Staphylococcus aureus* (MRSA) prevalence in the Asia-Pacific region: A systematic review and meta-analysis

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ABSTRACT

Objectives: Published literature on methicillin-resistant *Staphylococcus aureus* (MRSA) in the Asia–Pacific region was reviewed to document the prevalence of MRSA in the region and to examine the impact of variability in study design on the reported MRSA prevalence data.
Methods: This review included studies reporting MRSA prevalence between 2000 and 2016. Studies were excluded if they did not contain complete information on antimicrobial susceptibility testing (AST) methods. Primary outcomes were the proportion of MRSA among *S. aureus* isolates (resistance proportion) or among individual samples (prevalence).
Results: A total of 229 studies in 19 countries/territories were included in the study. There was substantial heterogeneity in both outcomes (resistance proportion, $I^2 = 99.59\%$; prevalence, $I^2 = 99.83\%$), precluding pooled averages, and meta-regression analyses revealed that these variations were explained by country income status and participant characteristics but not by methodological differences in AST. Also, no significant secular changes in MRSA prevalence or resistance proportions in Asia-Pacific were found.
Conclusion: The resistance proportions and prevalence of MRSA infections in Asia-Pacific are comparable with those reported in other regions with no significant secular changes in the past decade. Country income status and characteristics of the sample population explained more variation in the reported resistance proportions and prevalence of MRSA than methodological differences in AST across locations in the region.

Contents

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1. Introduction

Antimicrobial resistance (AMR) is a major public-health concern globally. Methicillin-resistant *Staphylococcus aureus* (MRSA) is one of the most important pathogens worldwide, accounting for more than 80 000 severe infections in the USA alone in 2011 and for more than one-half of hospital-related *S. aureus* infections in most Asian countries [1,2]. In particular, the spread of MRSA infections from healthcare settings to various community settings over recent decades has raised considerable concern [3]. Whilst the prevalence of methicillin resistance among invasive *S. aureus* infections is reported to be on the decline in Europe and the USA [4,5], resistance remains common in Asia where self-medication with antibiotics is common [6].

The Asia-Pacific region is the most populous region in the world, with one-third of the world's population [7]. With rapid urbanisation, a significant proportion of people in this region live in high-density cities, which increases the risk of the development and spread of AMR [8]. Since the 1980s, detection of methicillin resistance in *S. aureus* in healthcare settings within Asia has increased significantly, with regional detection proportions ranging from 26% to 73% in 2011 [9]. This poses a significant health burden on healthcare systems in the region, especially in resource-limited countries where *S. aureus* infections frequently present as severe or invasive diseases [10]. Overall mortality from *S. aureus* blood infection was 48% in a study conducted in northeast Thailand [11], which is almost double the mortality rate reported in a similar study in the USA [12]. Although decreasing proportions of healthcare-associated MRSA (HA-MRSA) have been reported in Taiwan and Japan since 2000, community-associated MRSA (CA-MRSA) infections are increasingly detected in the region [13]. As MRSA remains an important cause of nosocomial and community-acquired infections in the region, and antimicrobial susceptibility patterns may differ between HA-MRSA and CA-MRSA strains, knowledge of their respective distributions in the population is important for the treatment and management of MRSA infections [14]. In addition to infections, there have also been increasing reports of MRSA carriage in various population groups in the region, including in young children and adults [6]. Whilst MRSA carriers do not experience clinical symptoms as a result of carriage, they may be at higher risk of MRSA infection especially in the event of hospitalisation or major invasive procedures [15]. Nevertheless, epidemiological trends in methicillin resistance among *S. aureus* isolates are difficult to determine in the absence of established and standardised common surveillance protocols in the region [16].

Variations in published measures of methicillin resistance in *S. aureus* isolates also complicate the interpretability of MRSA detection data. Typically, levels of methicillin resistance in *S. aureus* within a selected population are measured using isolate-based screening in which resistance is measured as a proportion of MRSA detected among *S. aureus* that are successfully isolated from individual samples. This strategy is used by most established AMR surveillance networks, including the European Antimicrobial Resistance Surveillance Network (EARS-Net) and the Global Antimicrobial Resistance Surveillance System (GLASS) [17,18]. However, as more laboratory methods (e.g. screening agars) are made available for the detection of MRSA directly from clinical specimens, some studies today report methicillin resistance levels using a sample-based approach where resistance is measured as a proportion of MRSA detected from all clinical samples, including samples testing negative for *S. aureus*. Whilst the isolate-based and sample-based approaches measure methicillin resistance in *S. aureus* in different subsets of the population, MRSA resistance quantified by the two approaches is often compared with one another and described with non-standardised terms such as 'resistance', 'resistance rates', 'incidence' and 'prevalence' [19,20].

Therefore, in this systematic review, we sought to document methicillin resistance in *S. aureus* in the Asia-Pacific region based on published literature. Particular attention was paid to the surveillance metrics used, and the impact of variability in study participants, source of infection and laboratory methods on MRSA prevalence was examined.

2. Methods

2.1. Search strategy

This systematic review was conducted in accordance with the Preferred Reporting Items for Systematic Review and Meta-Analysis Protocols (PRISMA-P) guidelines [21]. Literature published to 5 December 2017 on methicillin resistance in *S. aureus* reported in 41 countries and regions in the Asia-Pacific region was systematically searched using the bibliographic databases PubMed and Embase (Appendix). Search results were catalogued using the bibliographic software Endnote v.X7 (Clarivate Analytics, Philadelphia, PA) and a database was generated to manage article screening and evaluation. In this review, the Asia-Pacific region refers to countries and regions that comprise Eastern Asia, Southeastern Asia and Oceania according to the definitions provided by the United Nations Statistics Division.

2.2. Study selection

Three reviewers (WWL, JYW and KN) independently screened the title, abstract and full-text of articles. Disagreements between reviewers were resolved by the decision of a fourth author (PW). Studies were included in this review if they were original studies that met all of the following conditions: (i) assessed methicillin resistance in *S. aureus* isolated from clinical specimens collected from populations in the Asia-Pacific region; (ii) assessed methicillin resistance in *S. aureus* isolates between 2000 and 2016; (iii) expressed antimicrobial resistance in proportion (%) of resistant organisms; (iv) written in English; and (v) had a full-text accessible to the review team (Appendix). Studies were excluded if they were: (i) randomised controlled trials, reviews, case studies, opinions or multiple publications of the same data set (only one publication per data set was included); (ii) studies that did not state laboratory methods or standards for antimicrobial susceptibility testing (AST); (iii) studies that did not specify individual drug or antibiotic names used for AST; (iv) studies that included data before the year 2000 that could not be disaggregated from later data; and (v) studies in which the study period was not clearly defined. The third exclusion criterion was not applicable to studies that assessed methicillin resistance in *S. aureus* through automated AST methods or by molecular and screening methods such as resistance gene identification with PCR and biochemical MRSA screening tests.

2.3. Data extraction

The following data were extracted from each included study using a standardised form: author and year of publication;

country; type of study; study period; sample population; participant age range; setting; source of infection; sampling site; sample size; laboratory methods; laboratory standards for AST; whether unique patient isolates were used to avoid duplication of samples; and proportion of *S. aureus* resistant to methicillin, cefoxitin, oxacillin or flucloxacillin out of total samples tested (prevalence) or out of *S. aureus* isolates tested (resistance proportion) (Appendix).

2.4. Data analysis

First, the overall search results (i.e. resistance proportions and prevalence of MRSA) for all countries with available data were described. In this review, 'MRSA prevalence' was defined as the proportion of MRSA among all tested samples and 'MRSA resistance proportion' was defined as the proportion of MRSA among all *S. aureus* isolates. Articles that reported resistance proportions and prevalence for different years, sampled populations or source of infections had individual entries recorded for each year, population subgroup (e.g. inpatients and outpatients recorded separately) and source of infection (e.g. hospital-associated infections are recorded separately from community-associated infections) or carriage. MRSA prevalence and resistance proportions were double arcsine-transformed [22] and were combined using a restricted maximum-likelihood (REML)-based random-effects model [23,24]. Statistical heterogeneity for MRSA prevalence and resistance proportions were assessed using the I^2 statistic, the value of which indicates the proportion of variation in reported estimates across studies that can be attributed to heterogeneity between these studies rather than chance [25,26]. Meta-regression analyses were conducted using multivariable mixed-effect models for studies that reported MRSA prevalence and resistance proportions, and reports on MRSA carriage were analysed separately from MRSA infections. Covariates of interest included country gross national income (GNI) per capita, study year, participant age group, AST method, sampling site and the use of unique patient isolates to avoid duplication of samples. The influence of sample population on the prevalence and resistance proportions of MRSA carriage, and of source of infection on the prevalence and resistance proportions of MRSA infections were also investigated. All data were visualised and analysed in R v.3.4.1 (R Development Core Team, Vienna, Austria) with the *metafor* package [27] as well as the Quantum GIS Geographic Information System v.2.18.7 (QGIS, Open Source Geospatial Foundation Project) [28].

3. Results

3.1. Study characteristics

From the 9546 articles identified through the search of the PubMed and Embase databases, 7994 titles and abstracts were screened, of which 749 full-text articles were assessed and 229 articles that reported MRSA prevalence and resistance proportions in 19 of the 41 selected countries/territories in the Asia-Pacific region between years 2000 and 2016 were included in this review (Fig. 1). Most articles were excluded because they either did not report methicillin resistance ($n = 123$) or the methods and test

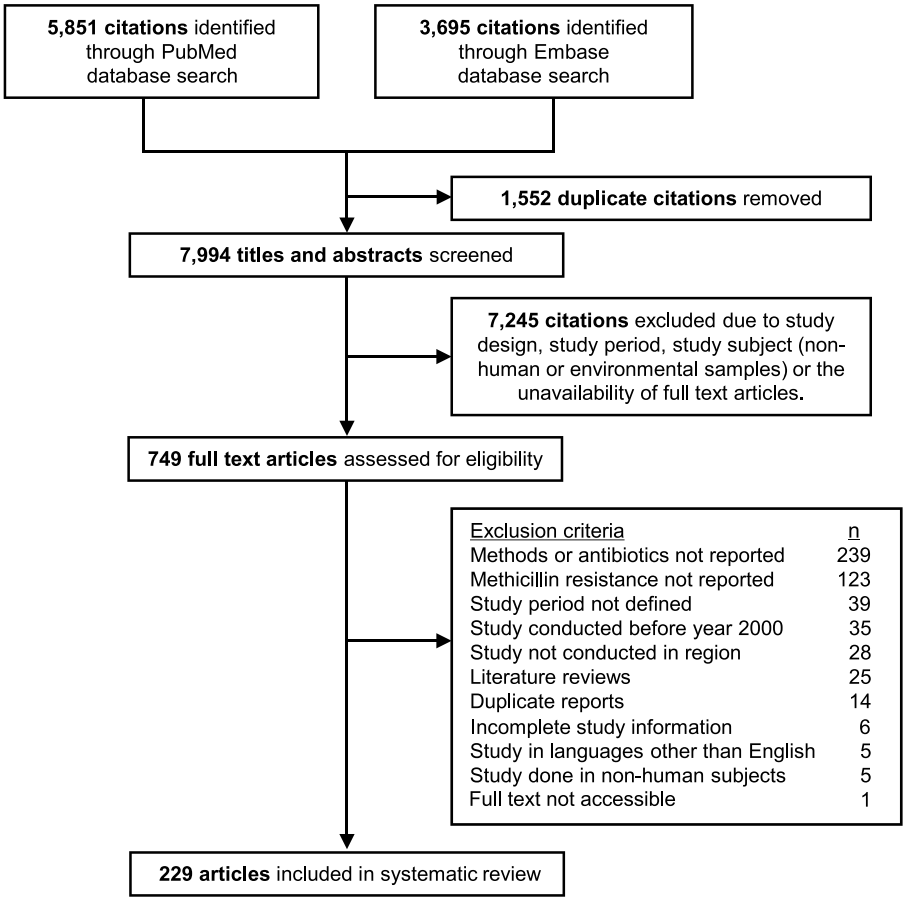

Fig. 1. Flow diagram of study selection.

Table 1
Summary of studies included in the analysis.

	No. of studies
Total no. of articles included	229
Publication year	
2000–2006	19
2007–2011	59
2012–2017	151
	No. of observations
Total no. of observations included[a]	346
Study setting	
Healthcare	311
Community	25
Healthcare and community (mixed)	4
Animal/livestock-related	6
No. of study sites	
Single site	209
2–10 sites	63
>10 or multiple sites	74
Sample population	
Inpatient	146
Outpatient	53
Healthy participants	53
Mixed	66
Not reported	28
Age group of study participants	
Children (0–17 years)	39
Adults (18–64 years)	129
Older adults (≥65 years)	30
All ages/not reported	148
Source of infection	
Hospital-associated	53
Community-associated	60
Hospital- and community-associated	147
Carriage	83
Livestock-associated	3
Measure of antimicrobial resistance	
Resistance proportion[b]	293
Prevalence[c]	216
Laboratory method	
Agar dilution	10
Automated system	53
Broth dilution	70
Chromogenic agar	21
Disk diffusion	156
Etest	3
Oxacillin agar test	2
PCR and/or molecular typing methods	12
Mixed	19
Antibiotics tested[d]	
Cefoxitin	75
Methicillin	15
Oxacillin	226
Flucloxacillin	10
More than one antibiotic tested	26
Not applicable	45
Sampling site	
Blood only	47
Respiratory tract only	75
Skin/wound only	24
Mixed sites	175
Not reported	25

[a] The total number of articles included in this study differs from the total number of studies (observations) included because some articles included data for more than one country, year, sample population or study setting.
[b] Resistance proportion is defined as the proportion of methicillin-resistant *Staphylococcus aureus* (MRSA) out of the total *S. aureus* isolates subjected to susceptibility testing for methicillin resistance.
[c] Prevalence is defined as the proportion of MRSA out of the total number of specimens collected or patients recruited in the study.
[d] Antibiotics used for susceptibility testing are not recorded for studies that used automated antimicrobial susceptibility testing methods or genotyping and screening methods such as resistance gene identification with PCR and biochemical (chromogenic) MRSA screening tests.

antibiotics used in AST ($n = 239$). Detailed study characteristics are available in the Appendix. Of the 229 included articles, 210 were published in or after the year 2007 (Table 1). As MRSA prevalence and resistance proportions for different years, sample populations and sources of infection in the same study were recorded as separate observations, 346 observations or data points were included in this review.

There were more reports of methicillin resistance as a proportion of MRSA among *S. aureus* isolates ($n = 293$) than among individual samples ($n = 216$). Most observations were results from studies conducted in healthcare settings ($n = 311$), among inpatients ($n = 146$) and in single sites ($n = 209$). More than 75% of the observations recorded in this review were reports of MRSA infections ($n = 263$) and the remaining observations were of MRSA carriage ($n = 83$). A substantial number of studies were conducted in adults (43%), whilst 33% of the studies included samples or isolates from individuals from all ages.

Almost one-half (45%) of included observations used the disk diffusion method for AST, and oxacillin was used as the test antibiotic in approximately two-thirds of these observations. Over one-half of all included observations assessed AMR of *S. aureus* isolated from various body sites, and the most common sampling sites were the respiratory tract (22%), blood (14%) and skin or wound (7%). Types of samples collected from the respiratory tract included sputum, nasal swabs and throat swabs, and samples collected from the skin or wound included pus and swabs taken from sites such as the axilla and groin.

3.2. Estimates of MRSA prevalence and resistance proportions

The most observations (prevalence and resistance proportions) between the years 2000 and 2016 were reported from mainland China ($n = 74$), Taiwan ($n = 64$), Australia ($n = 62$), South Korea ($n = 30$), Japan ($n = 30$), Hong Kong ($n = 20$) and Thailand ($n = 15$). Twelve locations reported fewer than 10 observations each (Fig. 2). Overall, the prevalence of MRSA infections in the 19 locations ranged from 0% to 73% between the years 2000 and 2016 (Fig. 3). The resistance proportions of MRSA infections ranged from 0% to 98.4% for the same period. The prevalence and resistance proportions of MRSA carriage ranged from 0–39.1% and 0–88.9% respectively. However, these proportions varied considerably between locations (Table 2).

3.3. Factors that influence the prevalence and resistance proportions of MRSA carriage and infections

A high degree of statistical heterogeneity was indicated in estimates of the MRSA prevalence and resistance proportion (prevalence, $I^2 = 99.83\%$; resistance proportion, $I^2 = 99.59\%$) using a REML-based random-effects model. Meta-regression analyses were conducted to assess the potential association between the reported prevalence and resistance proportions of MRSA carriage and infections and study variables [including country grouped by income status (GNI per capita), study year, participant age group, AST method, sample population, source of infection, sampling site and use of unique patient isolates to avoid duplication of samples]. Factors showing a statistically significant association with MRSA carriage or infections are presented in Tables 3 and 4, including country grouped by income status (GNI per capita), study year and sample population groups.

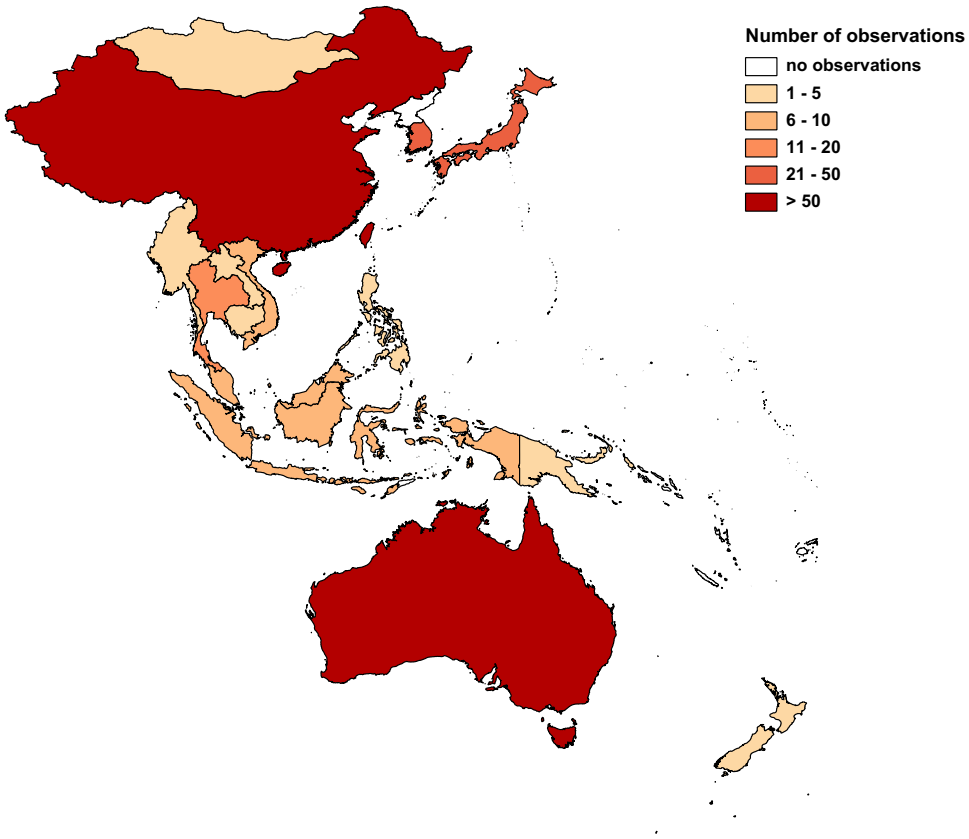

Fig. 2. Number of observations reported for methicillin-resistant *Staphylococcus aureus* (MRSA) prevalence and resistance proportions in selected locations in the Asia-Pacific region (2000–2016).

Meta-regression results show non-significant ($P > 0.05$) temporal increases in the prevalence and resistance proportions of MRSA carriage and the resistance proportions of MRSA infections during the study period (2000–2016). However, temporal increases in the prevalence for MRSA infections were statistically significant. In studies that reported MRSA carriage, a significantly higher prevalence of MRSA was found in older adults compared with children (aged <18 years) and a significantly lower prevalence was found in outpatients and healthy participants compared with inpatients (Fig. 4). GNI per capita was associated with increases in the prevalence of MRSA carriage and infections. However, this association was not significant for resistance proportion of MRSA carriage, and the association was significantly negative in the resistance proportion of MRSA infection. In studies that reported MRSA infections, there were no statistically significant associations between the age group of participants and MRSA prevalence or resistance proportions. However, a lower prevalence of MRSA infections was found in upper-middle- and lower-middle-income countries compared with high-income countries. Generally, lower prevalence and resistance proportions of MRSA infections were reported in community-associated or livestock-associated infections compared with hospital-associated infections, although no statistically significant association was shown between the prevalence of MRSA infections and the source of infection.

4. Discussion

Methicillin resistance in *S. aureus* has been documented in the Asia-Pacific region since the 1960s shortly after methicillin became available for clinical use. Whilst there has been an increase in published studies on methicillin resistance in *S. aureus* especially after the mid-2000s, there are substantial variations in approaches to measure resistance across the studies included in this review. As noted in previous narrative reviews, most studies are hospital-based, single-institution studies conducted predominantly in better-resourced countries in East and Southeast Asia [6,13].

Although a pooled average MRSA prevalence or resistance proportion could not be reliably estimated in the current review owing to the substantial statistical heterogeneity across the included studies, the range of resistance proportions for MRSA infections and prevalence for MRSA carriage recorded in locations where data were available was consistent with previous reports [6,9]. Most of the resistance proportions of MRSA infections reported in the Asia-Pacific region in this study (range: 0–98.4%) were comparable with resistance proportions reported in Europe (19.7–21.5%) [18,30] and the Middle East (12.4–30%) [31] and lower than those reported in the USA (29–43.2%) [32,33] and Africa (16–55%) [19]. East Asian locations reported the highest resistance proportions (>40%) in the region, followed by Southeast Asian locations (20% and 30%). MRSA prevalences reported in the Asia-Pacific region are similar to those reported in other regions and are typically between 1% and 25% [34,35].

On average, positive but mostly non-significant secular trends in MRSA prevalence and resistance proportions for MRSA infections or carriage in the past 16 years were observed even when between-country differences and methodological variation such as laboratory methods and sampling sites were considered. As there is no consensus or a most appropriate metric to report levels of methicillin resistance in *S. aureus* infections or carriage, resistance proportions and prevalence of MRSA infections and carriage can be compared inappropriately. By definition, the prevalence of MRSA in a population, usually measured with sample-based approaches, will be lower than the resistance proportion among *S. aureus* isolates (usually measured with isolate-based strategies) as the former

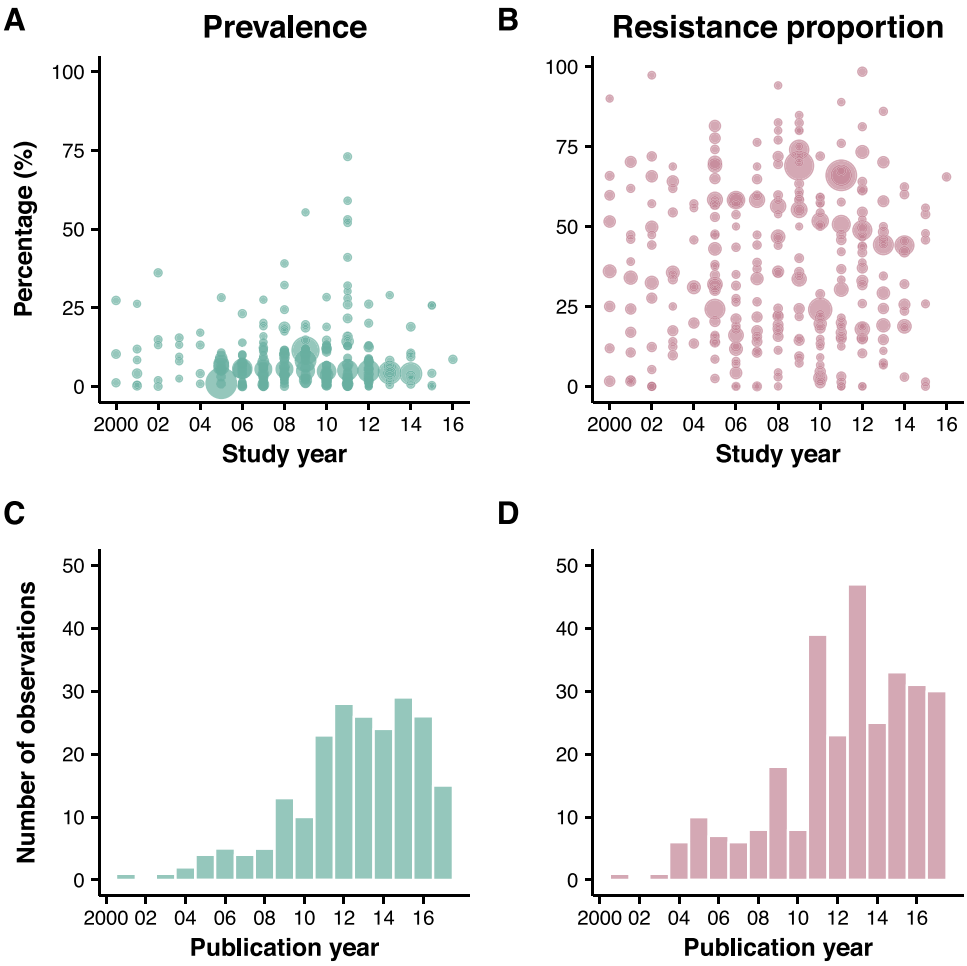

Fig. 3. Methicillin-resistant *Staphylococcus aureus* (MRSA) prevalence and resistance proportions reported in Asia-Pacific by year of study and the number of observations or data points by year of publication. (A) MRSA prevalence, defined as the proportion of MRSA among all tested samples, reported in selected countries between the years 2000 and 2016. For studies that report prevalence for more than one year, the midpoint of the study is reported as the study year. Bubble sizes reflect the study sample size for each observation. (B) MRSA resistance proportion, defined as the proportion of MRSA among all *S. aureus* isolates, reported in selected countries between the years 2000 and 2016. For studies that report the proportion for more than one year, the midpoint of the study is reported as the study year. Bubble sizes reflect the study sample size for each observation. (C) Number of observations or data points of MRSA prevalence in selected countries in 2000–2017. (D) Number of observations or data points of MRSA resistance proportions in selected countries in 2000–2017.

Table 2
Reported methicillin-resistant *Staphylococcus aureus* (MRSA) prevalence and resistance proportions by country (2000–2016).

Country	Prevalence (%) (range)		Resistance proportion (%) (range)	
	Infections[a]	Carriage	Infections[a]	Carriage
American Samoa	8.0[b]	–[c]	17.4[b]	–
Australia	2.2–26.0	1.21–16.00	7.25–82.50	3.10–50.00
Cambodia	–	3.50–4.10	–	–
China	0.50–55.30	0–10.50	2.62–98.40	0–47.83
Hong Kong	0.22–28.00	0.52–39.06	2.00–84.80	1.12[b]
Indonesia	–	6.04–9.33	–	0–21.43
Japan	0.70–41.00	0.78–30.20	24.35–72.00	14.81–88.89
South Korea	0.58–73.00	0–36.10	10.59–81.44	0–71.92
Laos	0	–	0–7.30	–
Malaysia	1.01–32.00	0–2.10	7.90–60.00	0–6.67
Mongolia	–	–	8.8[b]	–
Myanmar	0.15–2.97	–	4.35–38.73	–
New Zealand	0.50–9.00	8.2[b]	1.54–2.94	14.6[b]
Papua New Guinea	2.6[b]	–	75.0[b]	–
Philippines	59.0[b]	–	30.10–80.00	–
Singapore	4.80–52.00	1.79–20.20	70.0[b]	–
Taiwan	0–29.00	0.60–32.20	0–97.30	5.26–77.03
Thailand	0–53.00	0–3.60	0–71.40	0–6.67
Vietnam	0–3.00	7.90–8.59	0–90.00	65.5[b]

[a] Infections include hospital-associated, community-associated, mixed (hospital- and community-associated) and livestock/animal-associated MRSA infections.
[b] Only one observation recorded.
[c] – indicates no data available.

Table 3
Variables potentially associated with the prevalence and resistance proportion of methicillin-resistant *Staphylococcus aureus* (MRSA) carriage identified in the meta-regression analysis.

	Prevalence		Resistance proportion	
	β	95% CI	β	95% CI
Study year	−0.002	−0.011, 0.007	0.007	−0.017, 0.031
Age group[a]				
Children (0–17 years)	Referent		Referent	
Adults (18–64 years)	−0.022	−0.010, 0.056	−0.117	−0.313, 0.079
Older adults (≥65 years)	0.097	0.002, 0.192	0.148	−0.111, 0.407
All ages/not reported	0.019	−0.073, 0.110	−0.240	−0.527, 0.046
GNI per capita[b]	0.021	0.003, 0.039	0.014	−0.044, 0.072
Population group				
Inpatients	Referent		Referent	
Outpatients	−0.112	−0.201, −0.022	−0.151	−0.403, 0.101
Mixed	−0.103	−0.306, 0.099	0.036	−0.465, 0.536
Healthy participants	−0.097	−0.163, −0.030	−0.225	−0.423, −0.027
Model characteristics	$k = 80$, $I^2 = 98.06\%$, $R^2 = 24.71\%$		$k = 51$, $I^2 = 97.44\%$, $R^2 = 14.74\%$	

CI, confidence interval; GNI, gross national income.
[a] Median or average of participants included in the study.
[b] World Bank data for country GNI per capita in 2016 [29].

Table 4
Variables potentially associated with the prevalence and resistance proportion of methicillin-resistant *Staphylococcus aureus* (MRSA) infections identified in the meta-regression analysis.

	Prevalence		Resistance proportion	
	β	95% CI	β	95% CI
Study year	0.008	−0.001, 0.017	0.001	−0.007, 0.009
Age group[a]				
Children (0–17 years)	Referent		Referent	
Adults (18–64 years)	0.090	−0.018, 0.199	0.038	−0.084, 0.160
Older adults (≥65 years)	0.044	−0.123, 0.211	0.046	−0.132, 0.224
All ages/not reported	0.108	−0.004, 0.220	0.026	−0.100, 0.152
GNI per capita[b]	0.022	0.005, 0.039	−0.024	−0.041, −0.007
Source of infection				
Hospital-associated	Referent		Referent	
Community-associated	−0.011	−0.112, 0.091	−0.315	−0.413, −0.217
Hospital- or community-associated	0.058	−0.032, 0.148	−0.100	−0.183, −0.017
Livestock/animal-associated	−0.128	−0.341, 0.086	−0.417	−0.716, −0.119
Model characteristics	$k = 136$, $I^2 = 99.84\%$, $R^2 = 10.86\%$		$k = 242$, $I^2 = 99.47\%$, $R^2 = 21.47\%$	

CI, confidence interval; GNI, gross national income.
[a] Median or average of participants included in the study.
[b] World Bank data for country GNI per capita in 2016 [29].

includes clinical samples that test negative for *S. aureus*. Whilst prevalence and resistance proportions for MRSA infections measured by sample-based and isolate-based strategies are useful for surveillance purposes as they indicate the proportion of MRSA isolates detected in a specific population and in *S. aureus* isolates, respectively, this review indicates that these measures may be particularly vulnerable to differences in the demographic and health status of populations studied. The interpretability of either sample-based or isolate-based data is largely limited by the lack of relevance to patients and their clinical conditions.

Of the 229 studies included in this review, substantial disparities in the demographic and health status of the populations studied, screening and sampling policies, and study periods were observed, similar to what Dulon et al. reported in an earlier review on MRSA prevalence in European healthcare settings [35]. These factors, along with differences in study settings, AST methods and sampling sites, were often suggested as potential sources of heterogeneity in MRSA detection [35–37]. This is consistent with findings from the current meta-analysis where study heterogeneity was found to account for >99% of the variance between study estimates of MRSA prevalence and resistance proportions.

Of all potential contributors to variability in MRSA carriage estimates at the population level, relatively better-documented ones include age group [38,39] and sample population groups based on health and admission status (i.e. inpatient, outpatient and healthy people) [40]. In the current study, a higher MRSA carriage prevalence was found in adults aged ≥65 years compared with children aged <18 years. Whilst existing literature on differences in MRSA carriage among different age groups is inconsistent [41], the higher MRSA carriage prevalence in older adults reported in the current study might be the result of the fact that most of the studies were conducted in long-term care facilities or nursing homes in the region [42–45]. This is in contrast to MRSA carriage studies in children or adults that were often conducted in community settings among healthy participants [46–71]. MRSA carriage was also found to be lower in outpatients and healthy participants compared with inpatients, which is congruent with the increased likelihood of exposure to resistant organisms in the hospital setting among inpatients [40].

For MRSA infections, no statistically significant differences in prevalence or resistance proportions across age groups were found. Previous studies also suggested an inconsistent pattern in MRSA infections among different age groups [72], with some

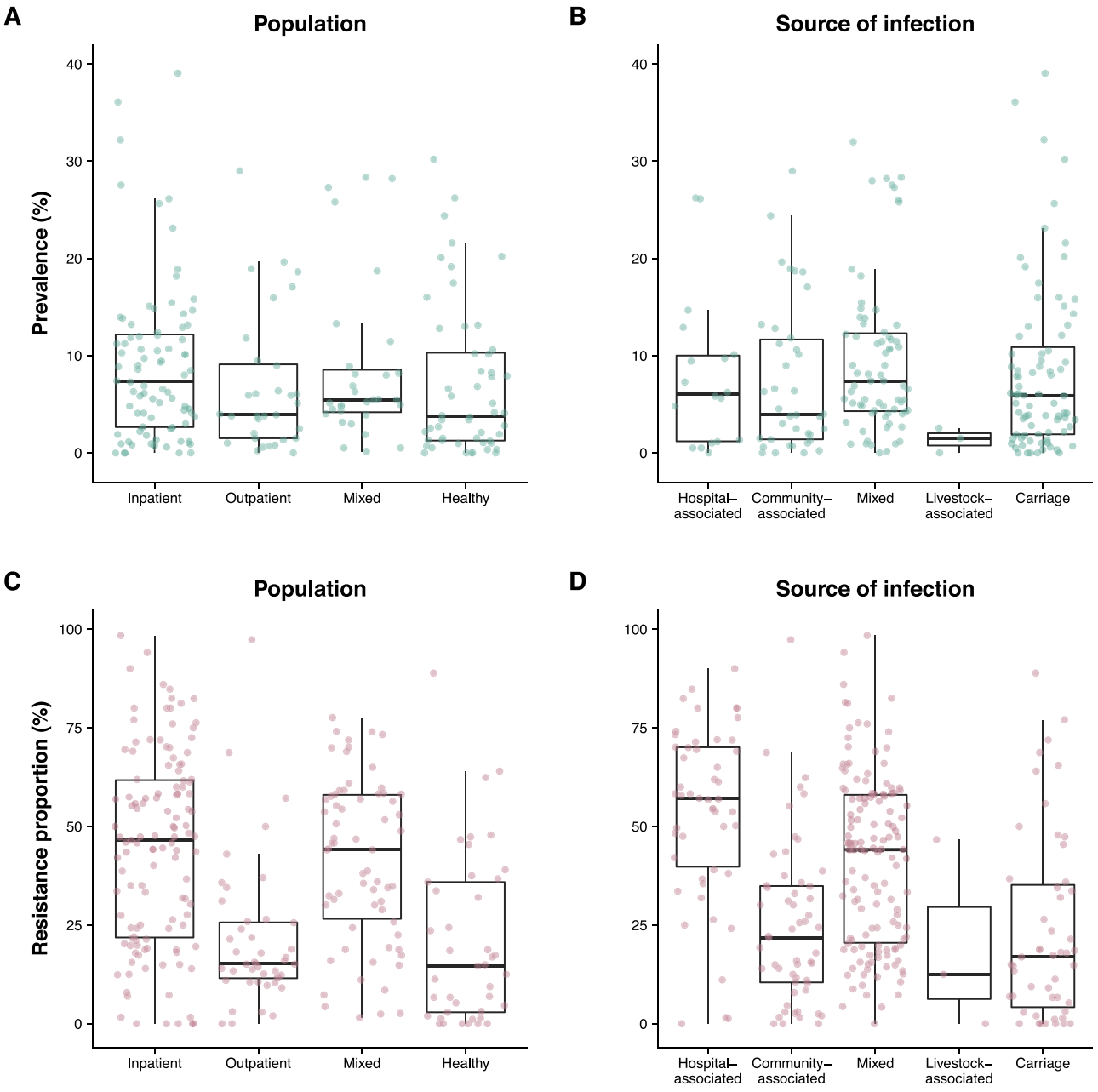

Fig. 4. Methicillin-resistant *Staphylococcus aureus* (MRSA) prevalence and resistance proportions by source of infection and population segment. (A) MRSA prevalence reported in selected countries by source of patients or persons sampled. (B) MRSA prevalence reported in selected countries by source of infection. (C) MRSA resistance proportion reported in selected countries by source of patients or persons sampled. (D) MRSA resistance proportion reported in selected countries by source of infection. MRSA prevalences and resistance proportions for studies with unknown source of infection or population groups are not included.

studies reporting a higher prevalence of MRSA infections in older adults [73] and others showing the prevalence of MRSA infections to be higher in children and young adults [74,75]. Nevertheless, the current study suggested that resistance proportions of MRSA infections varied by source of infection. Consistent with previous studies, resistance proportions for CA-MRSA appear to be lower than HA-MRSA infections [6], reflecting the higher proportion of MRSA among *S. aureus* found in healthcare settings compared with community settings.

As *S. aureus* most commonly causes skin and soft tissue, respiratory tract and bloodstream infections [76], most studies included in this review reported prevalences and resistance proportions of MRSA infections in isolates sampled from one or more of these sites. No statistically significant differences in prevalences or resistance proportions of MRSA infections in blood, respiratory tract, or skin and wound samples were found. An important caveat to this finding is that we did not record and consider the type of infection associated with the collection of samples for testing (e.g. blood samples collected from patients with respiratory infections are not differentiated from those collected from patients with bacteraemia).

Given the highly circumstantial nature of prevalence and resistance proportions measured by isolate-based and sample-based approaches, it may be useful to consider moving towards surveillance approaches (such as case-based surveillance) in which pathogens and resistance patterns identified through laboratory testing can be explicitly related to patients' clinical conditions or diseases, which may provide data of clinical relevance to guide medical practice and at the same time reduce data variability within the sample population. The levels of AMR measured by

isolate-based and sample-based strategies typically contain little information about the proportion of MRSA infections within a specific group of infections, such as skin infections or lower respiratory tract infections such as pneumonia. Studies using isolate-based measurement strategies tend to collect subsequent clinical samples for testing within a selected period, whilst sample-based strategies tend to collect samples from groups defined by their health or hospitalisation status.

In contrast to a recent study by Alvarez-Uria et al. that found a negative association between GNI per capita and methicillin resistance in *S. aureus* isolates [77], the prevalence of MRSA infections and carriage significantly increased with GNI per capita in the current study. However, a significant negative association was found between GNI per capita and resistance proportions of MRSA infections. As Alvarez-Uria et al. included mostly data from European countries and only two countries from Asia-Pacific (Thailand and Australia) [77], this may suggest that the differences in proportions of MRSA infections and carriage by country income status in Asia-Pacific may be different than Europe, in that better-resourced countries in Asia may have higher methicillin resistance among *S. aureus* isolates compared with countries with less resources. However, unlike Europe where countries with higher GNI per capita tend to have a lower rate of antibiotic consumption and better AMR surveillance and stewardship, this correlation is still unclear in Asia-Pacific countries. Generally, better-resourced countries in Asia-Pacific have more AMR surveillance and stewardship programmes in place [16], but differences in antibiotic consumption between better and less well-resourced countries may be less apparent in the region compared with European countries [78]. For instance, in a systematic review by Morgan et al., better-resourced countries in Europe reported less non-prescription use of antimicrobials in the general population than less well-resourced countries [78]. This is in contrast to countries in Asia where non-prescription use of antimicrobials in China was reported to be 36% compared with Indonesia (17%), India (18%), Vietnam (62%) and Bangladesh (86%) [78].

This review has several limitations. First, as the review was limited to data published in international bibliographic databases, the findings derived from the review may lack the insights of unpublished data from health authorities in the Asia-Pacific region. However, the reported resistance proportions and prevalence of MRSA in the countries included in the study are generally comparable with data reported to the Global Antimicrobial Resistance Surveillance System (GLASS) [79]. Second, the inclusion of only published literature written in English also excluded data that were presented in other languages. Although a formal quality assessment was not conducted on included studies, several quality-related exclusion criteria were incorporated to exclude studies that are likely to be of lower quality, including lack of information on laboratory methods and clearly defined study periods.

In conclusion, the resistance proportions and prevalence of MRSA infections in the Asia-Pacific region are comparable with those reported in other regions. Although there appears to be no significant secular changes in prevalence or resistance proportions of MRSA infections and carriage in Asia-Pacific, these results highlight the greater influence of country income status and the characteristics of the sample population on these measures compared with methodological differences in AST as well as the need to compare and consider MRSA prevalence and resistance proportions separately as these are two distinct metrics.

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Competing interests

BJC has received research funding from Sanofi Pasteur for a study of influenza vaccine effectiveness. All other authors declare no competing interests.

Ethical approval

Not required.

Appendix A. Supplementary data

Supplementary data associated with this article can be found, in the online version, at https://doi.org/10.1016/j.jgar.2018.08.014.

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