Antimicrobial susceptibility of bacterial isolates from clinical specimens in four Pacific Island countries, 2017–2021

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Summary

Background There are limited antimicrobial resistance (AMR) surveillance data from low- and middle-income countries, especially from the Pacific Islands region. AMR surveillance data is essential to inform strategies for AMR pathogen control.

Methods We performed a retrospective analysis of antimicrobial susceptibility results from the national microbiology laboratories of four Pacific Island countries – the Cook Islands, Kiribati, Samoa and Tonga – between 2017 and 2021. We focused on four bacteria that have been identified as 'Priority Pathogens' by the World Health Organization: *Staphylococcus aureus*, *Escherichia coli*, *Klebsiella pneumoniae* and *Pseudomonas aeruginosa*.

Findings Following deduplication, a total of 20,902 bacterial isolates was included in the analysis. The most common organism was *E. coli* (n = 8455) followed by *S. aureus* (n = 7830), *K. pneumoniae* (n = 2689) and *P. aeruginosa* (n = 1928). The prevalence of methicillin resistance among *S. aureus* isolates varied between countries, ranging from 8% to 26% in the Cook Islands and Kiribati, to 43% in both Samoa and Tonga. Ceftriaxone susceptibility remained high to moderate among *E. coli* (87%–94%) and *K. pneumoniae* (72%–90%), whereas amoxicillin + clavulanate susceptibility was low against these two organisms (50%–54% and 43%–61%, respectively). High susceptibility was observed for all anti-pseudomonal agents (83%–99%).

Interpretation Despite challenges, these Pacific Island laboratories were able to conduct AMR surveillance. These data provide valuable contemporary estimates of AMR prevalence, which will inform local antibiotic formularies, treatment guidelines, and national priorities for AMR policy.

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Keywords: Antibiotic resistance; Antimicrobial; Public health surveillance; Pacific islands; Bacteriology; Epidemiology

Introduction

Antimicrobial resistance (AMR) is a global health threat that can lead to increased mortality, prolonged length of hospital stay and higher healthcare costs.[1] AMR has a disproportionate impact on low- and middle-income countries, due to their higher overall prevalence of

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Research in context

Evidence before this study

Antimicrobial resistance (AMR) is an increasing threat to health worldwide, with surveillance identified as a key component of global strategies to contain AMR. Surveillance data can guide clinicians' choice of antibiotics for their patients, inform policymakers as they determine national AMR priorities, and permit monitoring of trends over time to evaluate the success (or failure) of interventions. There have been few published AMR surveillance data from the Pacific Islands.

Added value of this study

We present AMR surveillance data from four Pacific Island countries over five years, focusing on four bacterial pathogens. There was large variation in the proportion of methicillin-resistant *Staphylococcus aureus*, ranging from 8% in the Cook Islands to 43% in Samoa and Tonga. Among *Escherichia coli* and *Klebsiella pneumoniae*, susceptibility was high to ceftriaxone however this was much lower for oral agents such as amoxicillin + clavulanate and sulfamethoxazole + trimethoprim.

Implications of all the available evidence

Our study demonstrates the feasibility of Pacific Island countries conducting high-quality AMR surveillance, despite facing numerous challenges. These data provide detailed, contemporary estimates of AMR, which can inform local treatment guidelines and national AMR policies. Further research is required to better characterise and understand the variation in AMR within and between Pacific Island countries and territories.

infectious diseases, reduced capacity for AMR detection and surveillance, more limited access to second-line antimicrobials, and having fewer regulations for the use of antimicrobials among both humans and animals.[2]

Surveillance has been recognised by the World Health Organization (WHO) as a key strategic objective to address AMR.[3] Surveillance provides an initial measurement of the problem, allows responses to be tailored to the local context, and facilitates evaluation of strategies to combat AMR. It can be difficult to obtain high-quality AMR surveillance data in low- and middle-income countries. Challenges may include limited laboratory infrastructure, low numbers of trained staff, absence of health information systems and interrupted availability of consumables and reagents.[4] Availability of supplies is particularly relevant to Pacific Island laboratories, given their relative isolation and lengthy supply chains.

The Pacific Island countries and territories (PICTs) are made up of 22 members of the Secretariat of the Pacific Community. Their population of 12 million residents is spread over hundreds of different islands, spanning a region that covers more than 15% of the earth's surface. Almost every PICT is defined by the World Bank as low- or middle-income.[5]

To date there are limited AMR surveillance data from PICTs. The WHO's flagship AMR surveillance system, the Global Antimicrobial Resistance and Use Surveillance System (GLASS), has not yet received any data from PICTs.[6] A recent international collaboration to calculate the global burden of AMR contained very few data from PICTs, and just one dataset containing linked microbiology and outcome data.[7] Recently, efforts have been made to improve knowledge of AMR in PICTs. A 2019 scoping review analysed publications from the previous 70 years and demonstrated that many papers were old and focused primarily on resistance among Gram positive cocci.[8] In 2020, an antibiogram from Vanuatu was published, providing insights into AMR in that country.[9] High-quality AMR surveillance data from PICTs can assist those countries to design rational testing protocols for microbiology laboratories, develop effective antimicrobial prescribing guidelines for clinicians, and make informed decisions on which antimicrobials should be included in national formularies.

The aim of this study was to report the prevalence of AMR for key bacterial pathogens from clinical specimens in four Pacific Island countries between 2017 and 2021. In order to improve the quality and comparability of data, we have followed the recently published Microbiology Investigation Criteria for Reporting Objectively (MICRO) framework for reporting and interpreting clinical microbiology data.[10]

Methods

Study design

We performed a descriptive study of the antimicrobial susceptibility results from four national referral laboratories between 1 January 2017 and 31 December 2021. Four bacteria were assessed: *S. aureus, E. coli, K. pneumoniae* and *Pseudomonas aeruginosa*. These bacteria were chosen because they are some of the most commonly encountered pathogens cultured in Pacific Islands microbiology laboratories, susceptibility testing and reagents (Mueller-Hinton media) are readily available in PICT laboratories, and drug-resistant isolates of all four are classified as Critical or High priority pathogens by the WHO.[11]

All diagnostic clinical samples during the specified time period were included in the study. The samples had been collected as per clinician discretion for the purposes of patient care. Both sterile (e.g. blood or

cerebrospinal fluid) and non-sterile (e.g. urine or pus/wound swab) samples were included, however we have not analysed data by sample type as this information was not available for all countries.

Setting

The four Pacific Island countries included in this study – the Cook Islands, Kiribati, Samoa, and Tonga – are shown in Fig. 1.

The Cook Islands

The Cook Islands is comprised of 15 islands, 13 of which are inhabited. It has a population of approximately 15,000, three-quarters of whom live on the main island of Rarotonga.[12] Data for this study came from the national referral laboratory at Rarotonga Hospital, the country's main hospital with 80 beds. It is the only microbiology laboratory in the Cook Islands, servicing the entire population including samples sent from the outer islands.

The laboratory maintains an Excel (Microsoft Corporation) spreadsheet of all microbiology results including organism identification, susceptibility results, and patient data such as name, sex, age, sample type and patient location.

Kiribati

The Republic of Kiribati is comprised of 33 islands, 21 of which are inhabited. It has a total population of approximately 120,000, half of whom live on the main island of Tarawa.[12] Data for this study came from the national referral laboratory at Tungaru Central Hospital (TCH), the country's largest hospital with 125 beds. This laboratory services the population of Tarawa as well as any samples from the smaller Southern Kiribati Hospital (20 beds) on the island of Tabiteuea. The TCH laboratory services around two-thirds of the Kiribati population.

The laboratory maintains paper records of all microbiology results and patient data as described above for the Cook Islands. These paper records were reviewed for this study to produce aggregated, annual antibiogram results (without any patient-level data) for the four bacteria of interest.

Samoa

The Independent State of Samoa is comprised of two main islands (Savai'i and Upolu) and four smaller islands. It has a total population of approximately 200,000.[12] Data for this study came from the national

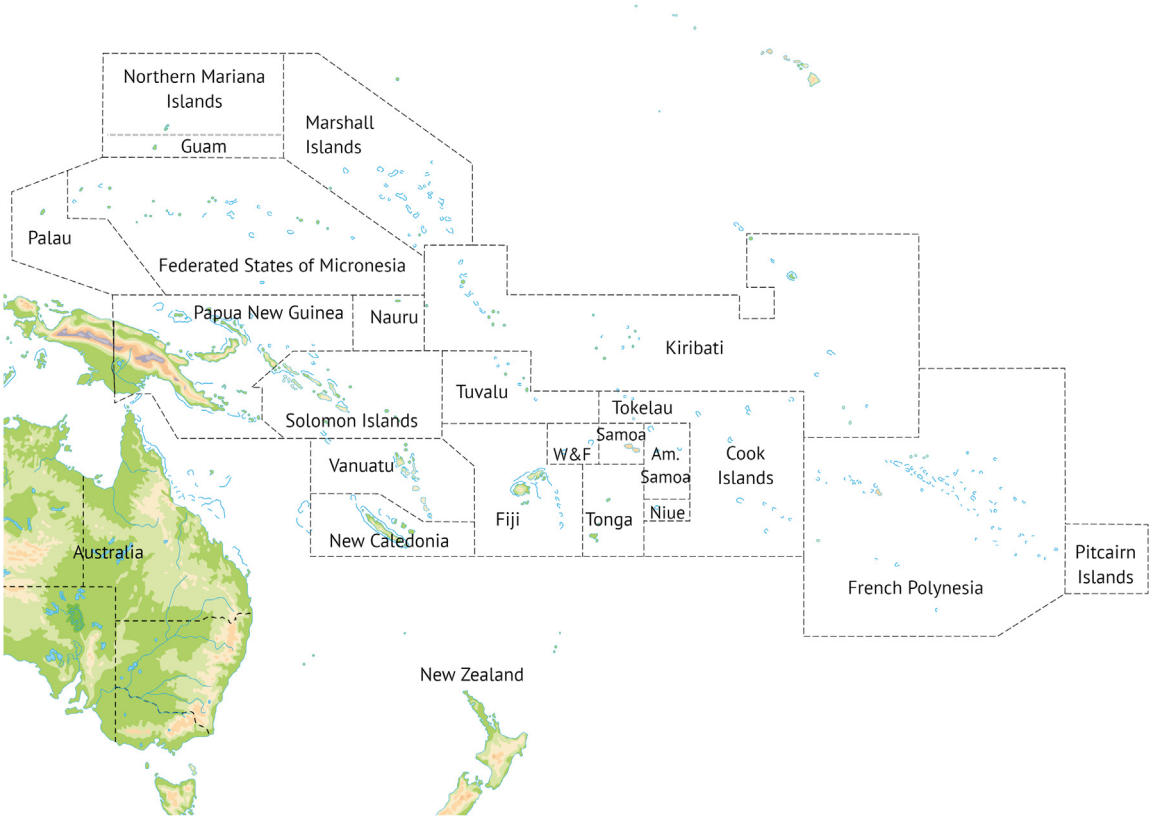

***Fig. 1:* Map of Pacific Island countries and territories, Australia and New Zealand**. Source: Shutterstock/frees. Reproduced with permission of Shutterstock. W&F = Wallis and Futuna.

referral laboratory at the Tupua Tamasese Mea'ole Hospital (TTMH) located in the capital, Apia. TTMH is Samoa's largest hospital with 250 beds. The TTMH laboratory services the entire island of Upolu (population 155,000), representing three-quarters of the national population.

The laboratory maintains a Microsoft Excel spreadsheet of all microbiology results and patient data as described above for the Cook Islands. No results were available for non-blood, non-urine samples between January and May 2017.

Tonga

The Kingdom of Tonga is comprised of around 170 islands, 36 of which are inhabited. It has a total population of approximately 100,000, three-quarters of whom live on the main island of Tongatapu.[12] Data for this study came from the national referral laboratory at the Vaiola Hospital located in the capital, Nuku'alofa. Vaiola Hospital is Tonga's largest hospital with 200 beds, and contains the only microbiology laboratory in Tonga. It is uncommon for samples to be sent from the outer islands for testing.

Since 2015, the Vaiola Hospital laboratory has been collating antimicrobial resistance data using WHONET, software developed by the WHO for entry, storage and analysis of antimicrobial susceptibility testing results. Antibiogram data for this study were extracted from historical aggregated WHONET reports, which did not contain any patient-level data.

Microbiological testing

A detailed description of the microbiological testing processes within each country's laboratory is provided in the Supplementary Methods.

In brief, all countries used basic phenotypic and biochemical testing (include coagulase and catalase) to identify *S. aureus* isolates. The three Gram negative organisms were identified with the use of commercial biochemical testing systems.

For antimicrobial susceptibility testing, all laboratories used disk-diffusion with the exception of Samoa, where disk diffusion was replaced by an automated broth microdilution system from January 2020 onwards. Clinical and Laboratory Standards Institute (CLSI) breakpoints were used in Kiribati and Tonga, whereas European Committee on Antimicrobial Susceptibility Testing (EUCAST) breakpoints were used in the Cook Islands and Samoa. For the purpose of analysis in this paper, isolates classified as 'Intermediate' or 'Susceptible Increased Exposure' by EUCAST were considered 'Susceptible', whereas isolates classified as 'Intermediate' by CLSI were considered 'Resistant.'[13]

All laboratories used resistance to cefoxitin as a surrogate marker for the detection of methicillin-resistant *S. aureus* (MRSA).[14] Testing for extended-spectrum beta-lactamase (ESBL) production among Enterobacterales was performed using either the double-disk synergy test or the combination disk method,[15] however for most laboratories this was only conducted on a subset of isolates. ESBL results were unavailable in datasets provided by three of the four countries, so were not included in our study.

Of note, across all countries, antimicrobial susceptibility testing was not routinely performed on *P. aeruginosa* grown from wound swabs unless specifically requested by clinicians. This would have reduced the number of isolates included in the study, but included isolates were more likely to be clinically relevant.

Duplicate results

In managing duplicate results, where possible, we followed the recommendations of the WHO GLASS guide to preparing aggregated AMR data.[16]

The microbiology datasets from the Cook Islands and Samoa contained unique patient identifiers. For each calendar year, only one result was included for each patient per pathogen and specimen type (blood, urine or other). For Kiribati and Tonga, duplicate results had been excluded during the local data aggregation process.

Patient location

The Cook Islands and Samoa datasets also contained data on patient location at the time of specimen collection. We performed further analyses in these two countries to assess for differences in prevalence of AMR based on location.

For the Cook Islands, patient locations were classified as either 'inpatient' (all samples from the wards of Rarotonga Hospital, excluding the Emergency Department [ED]), 'outpatient' (all other samples from the island of Rarotonga, including ED patients at Rarotonga Hospital), 'outer islands' (all samples from islands other than Rarotonga) and 'unknown' (if location not specified).

For Samoa, whose contributing laboratory only serviced the main island of Upolu, patient locations were classified as either 'inpatient' (all samples from wards of TTMH, excluding the ED), 'outpatient' (all other samples, including ED patients at TTMH) or 'unknown' (if location not specified, or if sample labelled as coming from a clinic that managed both inpatients *and* outpatients).

Statistical analysis

This was primarily a descriptive study with antimicrobial susceptibility results reported as proportions, using the total number of isolates that were tested against that antimicrobial as the denominator.

Comparisons of antimicrobial susceptibility between groups (i.e., patient location or country) were made using the Chi-squared test. No adjustments were made for

multiple comparison but exact p-values are provided in the Supplementary Appendix so that a Bonferroni correction can be calculated, if desired.

To assess change in antimicrobial susceptibility over time for each country, we used linear regression to calculate the slope (i.e., rate of change).

Analyses were performed using both the R statistical software platform version 3.6.1 (RStudio version 1.2.1335) and Stata version 17.0 (StataCorp, TX, USA).

Quality assurance

All four countries participate in an external quality assurance program facilitated by the Pacific Pathology Training Centre (PPTC) in New Zealand. Over the preceding 10 years, all four laboratories scored >80% for all assessments involving each of the four organisms included in this study (Supplementary Appendix Table S10).

Ethics

Ethics and research approval was provided by the Alfred Hospital Ethics Committee (779/19), the Cook Islands Foundation for National Research (05–21), the Kiribati Ministry of Health and Medical Services Ethics Committee, the Samoan Health Research Committee, and the Tonga National Health Ethics and Research Committee (MH53:02).

Role of the funding source

The funder had no role in the study design, results analysis, or manuscript preparation.

Results

Overall, the four laboratory datasets contained 20,902 relevant bacterial isolates collected between January 2017 and December 2021. The largest contributor was Samoa (n = 9007), followed by Kiribati (n = 4518), the Cook Islands (n = 4109) and Tonga (n = 3268). The most common organism included was *E. coli* (n = 8455), followed by *S. aureus* (n = 7830), *K. pneumoniae* (n = 2689) and *P. aeruginosa* (n = 1928).

The Cook Islands

There were 4109 bacterial isolates included from the Cook Islands. The most common organism was *S. aureus* (n = 2049), followed by *E. coli* (n = 1213), *K. pneumoniae* (n = 495) and *P. aeruginosa* (n = 352). Over half of samples were from females (n = 2325), and the most frequent sample type was pus/wound swab (n = 2,729, 66.4%), followed by urine (n = 1202, 29.3%) and sputum (n = 93, 2.3%). There were 20 positive blood cultures included over the study period. Pus/wound swabs accounted for most isolates among *S. aureus* (1956/2049, 95.5%), *P. aeruginosa* (328/352, 93.2%), and *K. pneumoniae* (301/495, 60.8%), but *E. coli* was most frequently isolated from urine (1044/1213, 86.1%).

Antimicrobial susceptibility

The percentage of organisms susceptible to antimicrobials in the Cook Islands over the study period is presented in Fig. 2 (see also Supplementary Table S1).

Among *S. aureus* isolates, susceptibility was high (>85%) against all first-line antimicrobials across all years of the project. The proportion of *S. aureus* isolates with methicillin-resistance (MRSA) was stable, ranging between 5.9% in 2018 and 11.8% in 2020.

Among *E. coli* isolates, susceptibility to ceftriaxone remained over 90% but fell at a rate of 1.77 percentage points per year (95% CI 0.86 to 2.65, p = 0.01). Ceftriaxone susceptibility among *K. pneumoniae* isolates fell at a similar rate of 2.10 percentage points per year; however, this trend was not statistically significant. For both organisms, susceptibility to amoxicillin + clavulanate was frequently below 50%, yet other antimicrobials retained susceptibility rates above 80–85%. Meropenem was tested against a subset of eight isolates (six *E. coli*, two *K. pneumoniae*) over the study period: 100% were susceptible. Of note, there was a marked rise in nitrofurantoin susceptibility among *E. coli* isolates from 2020 onwards – on review of laboratory protocols there was no modification to testing processes to explain this change.

Among *P. aeruginosa* isolates, susceptibility was very high (≥95%) to all tested antimicrobials throughout the study period. Only one-third (117/352, 33%) of isolates were tested against meropenem; despite this selective testing strategy, susceptibility remained 100% for all years except 2017.

Patient location

A total of 338 samples were from inpatients at Rarotonga Hospital, 3169 samples were from outpatients on the island of Rarotonga, 581 samples were from outer islands and 21 samples were from patients with an unknown location. The antimicrobial susceptibility of isolates according to patient location, after excluding cases with unknown location, is presented in Fig. 3 (see also Supplementary Table S6).

Antimicrobial susceptibility was lower among inpatients than outpatients for nearly all drug–bug combinations, with the exception of *P. aeruginosa*, which had very high (>97%) susceptibility to all antimicrobials regardless of location. Isolates sent from the outer islands generally had susceptibility that was comparable to, or higher than, Rarotonga outpatient isolates.

The largest absolute differences in susceptibility between locations were seen among *E. coli* and *K. pneumoniae*, but just one combination (sulfamethoxazole + trimethoprim against *E. coli*) reached statistical significance. Among *S. aureus*, with a greater number of isolates tested, there were modest absolute differences in susceptibility between groups but more of these reached statistical significance.

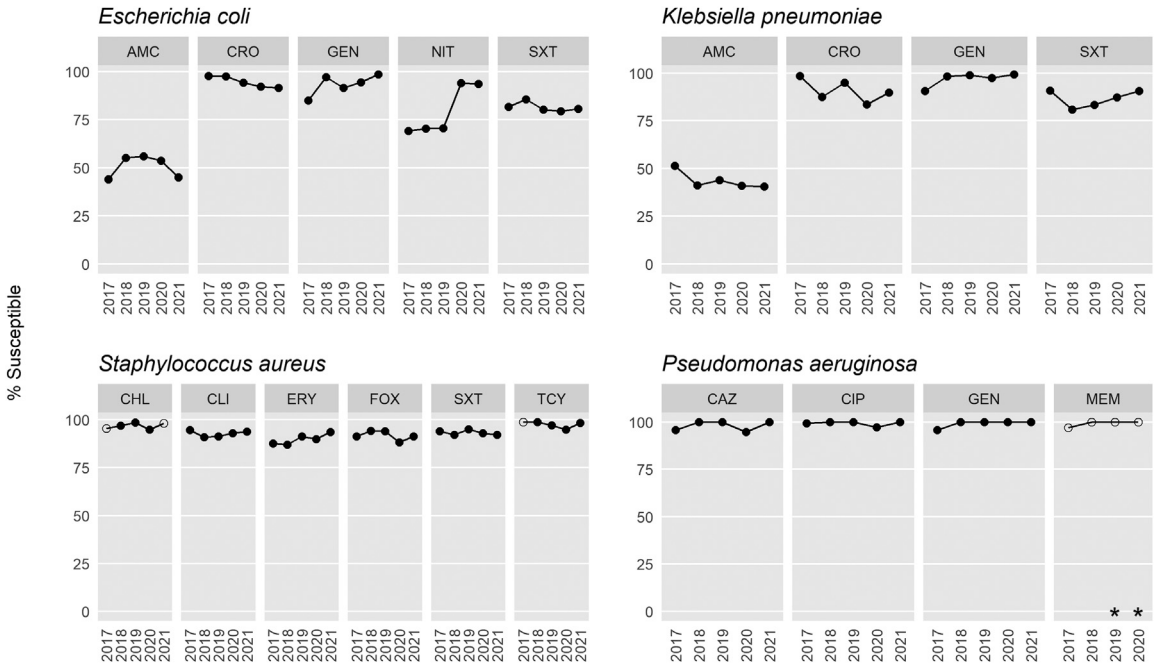

***Fig. 2:* Antimicrobial susceptibility in the Cook Islands by calendar year**. AMC = amoxicillin + clavulanate. CAZ = ceftazidime. CIP = ciprofloxacin. CHL = chloramphenicol. CLI = clindamycin. CRO = ceftriaxone. ERY = erythromycin. FOX = cefoxitin. GEN = gentamicin. MEM = meropenem. NIT = nitrofurantoin. SXT = sulfamethoxazole + trimethoprim. TCY = tetracycline. Open circles indicate any years when <70% of isolates were tested against that antimicrobial, otherwise closed circles are used. Asterisks indicate years when n < 30 isolates were tested against that antimicrobial. FOX is used to determine MRSA status. NIT only tested against urinary *E. coli* isolates.

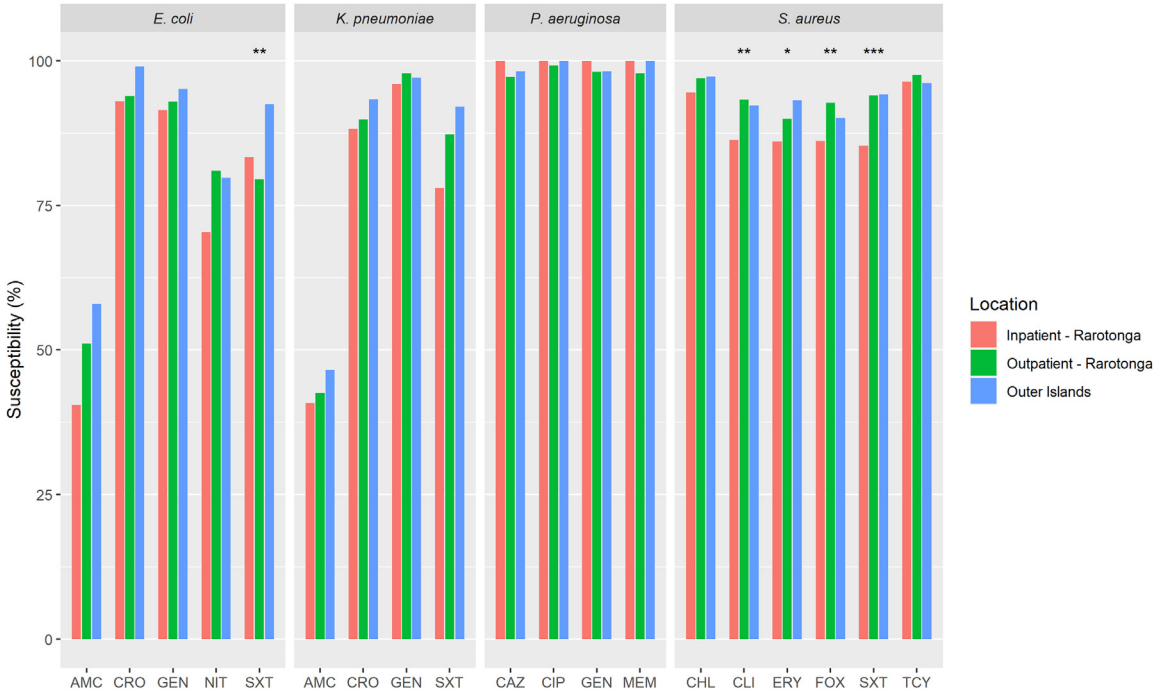

***Fig. 3:* Antimicrobial susceptibility in the Cook Islands by patient location**.*p < 0.05. **p < 0.01. ***p < 0.001. AMC = amoxicillin + clavulanate. CAZ = ceftazidime. CIP = ciprofloxacin. CHL = chloramphenicol. CLI = clindamycin. CRO = ceftriaxone. ERY = erythromycin. FOX = cefoxitin. GEN = gentamicin. MEM = meropenem. NIT = nitrofurantoin. SXT = sulfamethoxazole + trimethoprim. TCY = tetracycline.

Impact of deduplication

Employing alternative deduplication methods – including not performing any deduplication at all – had minimal impact on the reported susceptibility results from the Cook Islands (Supplementary Table S8). Compared to the main analysis, the median change in susceptibility for each alternative method was less than 1 percentage point.

Kiribati

There were 4518 bacterial isolates included from Kiribati, with the most common organism being *E. coli* (n = 2189), followed by *S. aureus* (n = 1073), *K. pneumoniae* (n = 685) and *P. aeruginosa* (n = 571). A breakdown by sample type or patient location was not possible, due to the aggregated nature of the Kiribati dataset.

Antimicrobial susceptibility

The percentage of organisms susceptible to antimicrobials in Kiribati over the study period is presented in Fig. 4 and Supplementary Table S2.

Among *S. aureus* isolates, the proportion that were MRSA remained between 15 and 20% for the first four years of the study but rose to 42.2% in 2021. Tetracycline susceptibility fell at a high rate of 4.55 percentage points per year, but this failed to reach statistical significance. There was year-on-year variability in susceptibility to other first-line agents, but in 2021, only two antimicrobials (chloramphenicol and sulfamethoxazole + trimethoprim) retained susceptibility >80%.

Among *E. coli* and *K. pneumoniae* isolates, annual susceptibility to ceftriaxone ranged between 64% and 97%, with the highest susceptibility results in the final two years of the study. Susceptibility was low against the oral agents amoxicillin + clavulanate and sulfamethoxazole + trimethoprim, consistently below 70% and dipping below 50% at times. Meropenem was tested against a subset of 156 isolates over the study period: 85.5% (100/117) of *E. coli* and 82.1% (32/39) of *K. pneumoniae* were susceptible. Retrospective testing to confirm meropenem non-susceptibility was not possible, as bacterial isolates in Kiribati are not routinely stored or sent to a tertiary laboratory.

Among *P. aeruginosa* isolates, susceptibility remained >80% for all antimicrobials for all years of the project except for ceftazidime in 2017 (76.7%) and gentamicin in 2021 (58.9%)

Samoa

There were 9007 bacterial isolates included from Samoa. The most common organism was *E. coli* (n = 3780), followed by *S. aureus* (n = 3211), *K. pneumoniae* (n = 1175) and *P. aeruginosa* (n = 841).

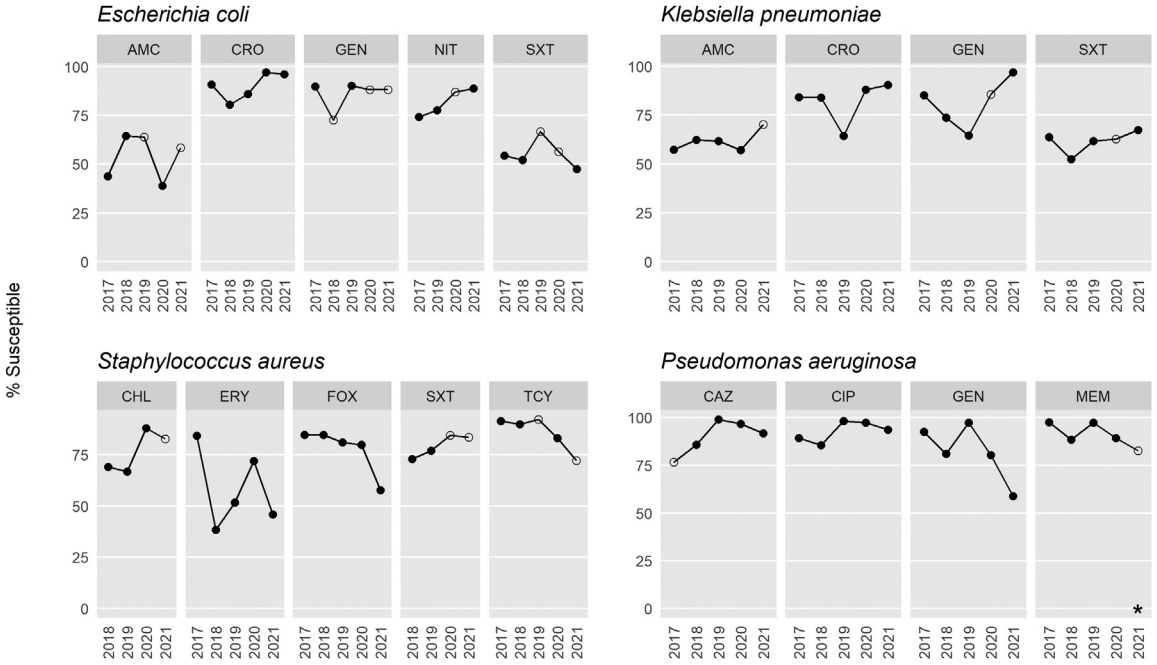

***Fig. 4:* Antimicrobial susceptibility in Kiribati by calendar year**. AMC = amoxicillin + clavulanate. CAZ = ceftazidime. CIP = ciprofloxacin. CHL = chloramphenicol. CLI = clindamycin. CRO = ceftriaxone. ERY = erythromycin. FOX = cefoxitin. GEN = gentamicin. MEM = meropenem. NIT = nitrofurantoin. SXT = sulfamethoxazole + trimethoprim. TCY = tetracycline. Open circles indicate any years when <70% of isolates were tested against that antimicrobial, otherwise closed circles are used. Asterisks indicate years when n < 30 isolates were tested against that antimicrobial. FOX is used to determine MRSA status. NIT only tested against urinary *E. coli* isolates.

More than half of the samples (n = 5598) were from females, and the most frequent sample type was urine (n = 3555), followed by pus/wound swab (n = 2778), blood (n = 1970) and sputum (n = 265). Pus/wound swabs accounted for the most isolates among *P. aeruginosa* (534/841, 63.5%) and *S. aureus* (1859/3211, 57.9%), while urine was the most common sample type for *E. coli* (2719/3780, 71.9%) and *K. pneumoniae* (579/1175, 49.3%).

Antimicrobial susceptibility

The percentage of organisms susceptible to antimicrobials in Samoa over the study period is presented in Fig. 5 (see also Supplementary Table S3).

Among *S. aureus* isolates, the proportion that were MRSA was initially very high at 48.8% in 2017, but reduced across the study period at a rate of 3.24 percentage points per year (95% CI 1.84 to 4.65, $p < 0.01$). High susceptibility was retained against most other oral agents, and by 2021, >95% of isolates were susceptible to chloramphenicol, sulfamethoxazole + trimethoprim and tetracycline. Focusing solely on blood culture isolates, the proportion of MRSA across the entire study period was 38.2% (378/990).

Among *E. coli* and *K. pneumoniae* isolates, annual susceptibility to ceftriaxone was mostly stable at around 86–88% and 70–75%, respectively. Of concern, in 2021 susceptibility among *E. coli* to the oral agents amoxicillin + clavulanate and sulfamethoxazole + trimethoprim had fallen below 50%. Meropenem was tested against a subset of 892 isolates over the study period: 99.4% (508/511) of *E. coli* and 97.4% (371/381) of *K. pneumoniae* were susceptible. Focusing solely on blood culture isolates, the proportion of *E. coli* susceptible to ceftriaxone across the entire study period was 86.3% (543/629).

Among *P. aeruginosa* isolates, susceptibility to all tested agents remained >85% each year with the exception of 2017 (when some data were missing), and also ceftazidime in 2020 (81.2%).

Patient location

2766 samples were from inpatients, 4935 samples were from outpatients, and for 1306 samples the patient location category was unknown. The proportion of isolates susceptible to various antimicrobials, comparing inpatients to outpatients, is presented in Fig. 6 (see also Supplementary Table S7). Inclusion of the isolates with unknown location category did not significantly alter the results (Supplementary Fig. S1).

Antimicrobial susceptibility was lower among inpatients than outpatients for nearly all organism/antimicrobial combinations. This difference was most pronounced among *K. pneumoniae*, where

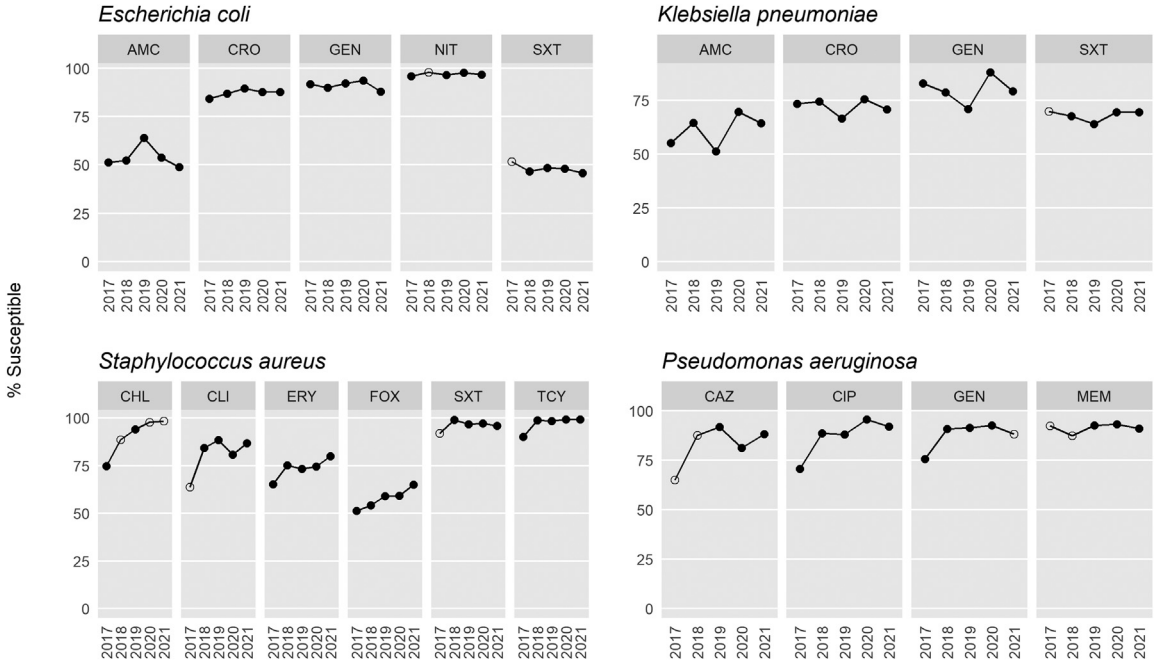

***Fig. 5:* Antimicrobial susceptibility in Samoa by calendar year.** AMC = amoxicillin + clavulanate. CAZ = ceftazidime. CIP = ciprofloxacin. CHL = chloramphenicol. CLI = clindamycin. CRO = ceftriaxone. ERY = erythromycin. FOX = cefoxitin. GEN = gentamicin. MEM = meropenem. NIT = nitrofurantoin. SXT = sulfamethoxazole + trimethoprim. TCY = tetracycline. Open circles indicate any years when <70% of isolates were tested against that antimicrobial, otherwise closed circles are used. FOX is used to determine MRSA status. NIT only tested against urinary *E. coli* isolates.

susceptibility was at least 20 percentage points lower for all four antimicrobials tested. The largest difference was seen with ceftriaxone: 83% among outpatients vs 53% among inpatients ($p < 0.001$). Just three organism/antimicrobial combinations had lower susceptibility among outpatients, and two of these involved *S. aureus* where the difference was under one percentage point.

Impact of deduplication

Employing alternative deduplication methods – including not performing any deduplication at all – had minimal impact on the reported susceptibility results from Samoa (Supplementary Table S9). Compared to the main analysis, the median change in susceptibility for each alternative method was 1 percentage point or less.

Tonga

There were 3268 bacterial isolates included from Tonga. The most common organism was *S. aureus* (n = 1497), followed by *E. coli* (n = 1273), *K. pneumoniae* (n = 334) and *P. aeruginosa* (n = 164). Breakdown by sample type or patient location was not possible, due the aggregated nature of the existing dataset in Tonga.

Antimicrobial susceptibility

The percentage of organisms susceptible to antimicrobials in Tonga over the study period is presented in Fig. 7 (see also Supplementary Table S4).

Among *S. aureus* isolates, a consistently elevated proportion were MRSA with a peak of 52% in 2019. However, susceptibility to other first-line antimicrobials remained very high, frequently above 95% for many agents.

Among *E. coli* and *K. pneumoniae* isolates, susceptibility to ceftriaxone fluctuated between 65% and 92%, with susceptibility consistently lower among *K. pneumoniae*. Of concern, in 2021, no first-line antimicrobial had susceptibility >80% against *K. pneumoniae* despite a relatively high number of isolates tested that year (n = 95). Meropenem was tested against a subset of 20 isolates (19 *E. coli*, 1 *K. pneumoniae*) over the study period: 100% were susceptible.

In Tonga only two agents (ciprofloxacin and gentamicin) are routinely tested against *P. aeruginosa*. Both retained very high (>90%, and frequently 100%) susceptibility throughout the study period.

Overall

The proportion of bacteria susceptible to each antimicrobial in each country across the entire study period is shown in Fig. 8 (see also Supplementary Appendix Table S5). Although some differences were quite large, examination of the variation in susceptibility indicated that not all differences were clinically significant – for instance, *E. coli* against amoxicillin + clavulanate, where susceptibility results all fell within 5 percentage points of each other.

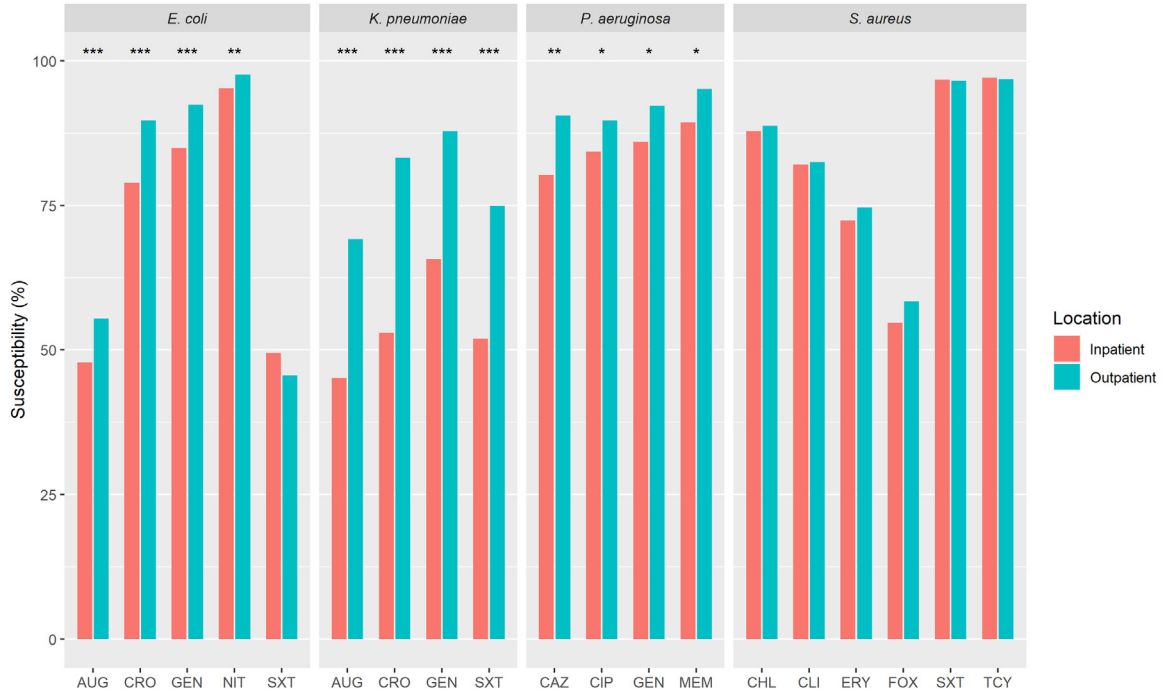

***Fig. 6:* Antimicrobial susceptibility in Samoa by patient location**. *p < 0.05. **p < 0.01. ***p < 0.001. AMC = amoxicillin + clavulanate. CAZ = ceftazidime. CIP = ciprofloxacin. CHL = chloramphenicol. CLI = clindamycin. CRO = ceftriaxone. ERY = erythromycin. FOX = cefoxitin. GEN = gentamicin. MEM = meropenem. NIT = nitrofurantoin. SXT = sulfamethoxazole + trimethoprim. TCY = tetracycline.

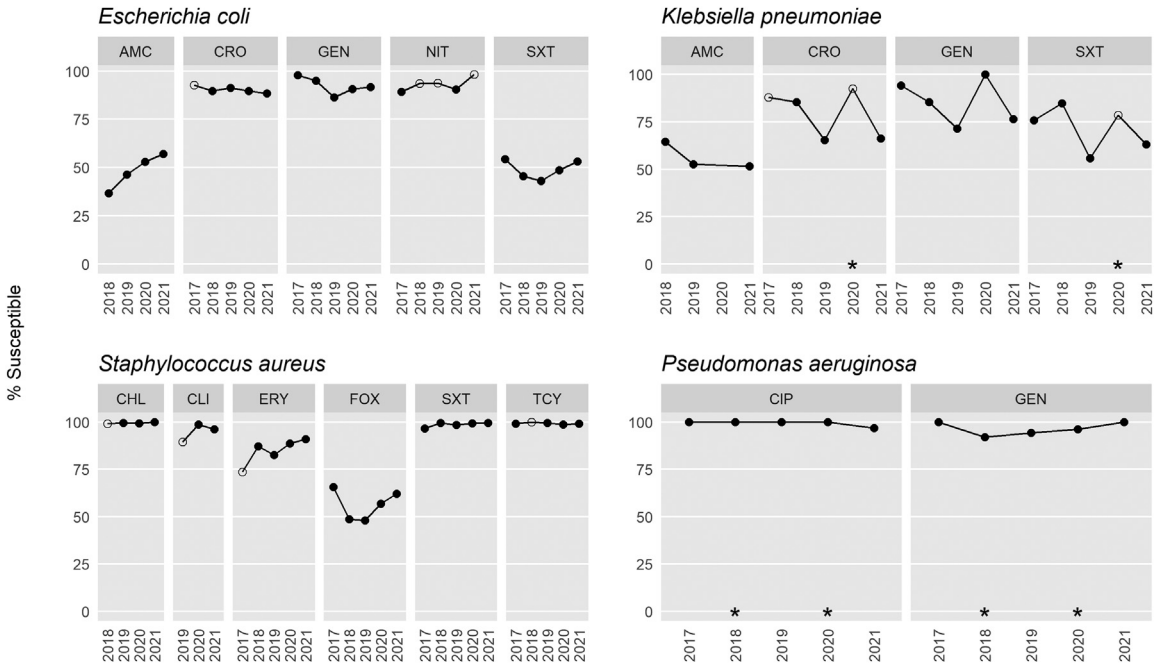

Fig. 7: **Antimicrobial susceptibility in Tonga by calendar year**. AMC = amoxicillin + clavulanate. CAZ = ceftazidime. CIP = ciprofloxacin. CHL = chloramphenicol. CLI = clindamycin. CRO = ceftriaxone. ERY = erythromycin. FOX = cefoxitin. GEN = gentamicin. MEM = meropenem. NIT = nitrofurantoin. SXT = sulfamethoxazole + trimethoprim. TCY = tetracycline. Open circles indicate any years when <70% of isolates were tested against that antimicrobial, otherwise closed circles are used. Asterisks indicate years when n < 30 isolates were tested against that antimicrobial. FOX is used to determine MRSA status. NIT only tested against urinary *E. coli* isolates.

Susceptibility results between countries were most similar for both *E. coli* and *P. aeruginosa*, almost all antimicrobials had results that clustered within ranges of between 5 and 13 percentage points, and those with larger ranges were often driven by solitary outliers (e.g. *E. coli* against sulfamethoxazole + trimethoprim in the Cook Islands). There was increased variation in countries' susceptibility results for *K. pneumoniae*, all antimicrobials had results with ranges of between 18 and 25 percentage points. The greatest variation was seen among *S. aureus*, with three antimicrobials (chloramphenicol, cefoxitin and erythromycin) having results with a range greater than 20 percentage points. The largest range observed in the study was 35 percentage points, for cefoxitin, between Cook Islands (92% susceptible) and Samoa and Tonga (both 67% susceptible).

Discussion

Our research contributes to a greater understanding of AMR in the Pacific Islands, by providing comprehensive data on the prevalence of AMR among four major bacterial pathogens in four countries over five years. All laboratories followed internationally recognised standards and actively participated in a quality assurance program. We found the prevalence of AMR in these Pacific Island countries was low to moderate by global standards, except for the high proportion of MRSA in Samoa and Tonga, as well as the high levels of resistance to key oral agents against *E. coli* and *K. pneumoniae*.

A striking finding of our analysis was the difference in overall MRSA prevalence between the four countries, ranging between 8% in the Cook Islands, 26% in Kiribati and 43% in both Samoa and Tonga. Other PICTs have mostly reported low MRSA prevalence, such as 3% in Vanuatu[9] and 7%–8% in Fiji.[17,18] Fifteen years ago, a Samoan outpatient study of 196 isolates reported MRSA prevalence of just 17%, suggesting resistance may have increased there in the decade prior to our project.[19] The only PICT with MRSA prevalence comparable to our Samoa and Tonga results is Papua New Guinea, where 48% of *S. aureus* isolates at the country's main hospital were MRSA.[20] Among neighbouring high-income countries, MRSA prevalence is moderate in Australia at 17–19%[21,22] and low in New Zealand at 9%.[23] Unfortunately, there is little published data on the molecular epidemiology of MRSA within PICTs. A Samoan study of 34 MRSA isolates demonstrated a diversity of sequence types (STs) – no single ST was responsible for more than 30% of isolates, and the 'South West Pacific' clone ST30-IV was relatively uncommon (12%).[19] Aside from molecular factors, higher rates of MRSA could also be driven by social factors such as overcrowding, or

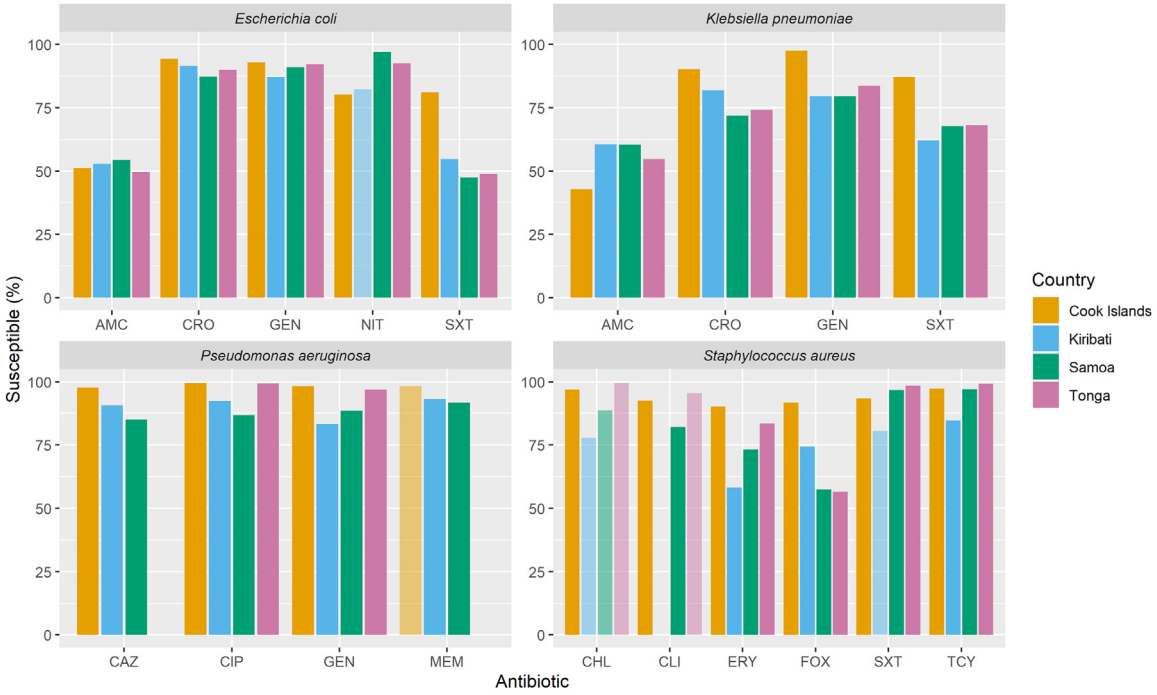

***Fig. 8:* Overall antimicrobial susceptibility by country, 2017–2021**. AMC = amoxicillin + clavulanate. CAZ = ceftazidime. CIP = ciprofloxacin. CHL = chloramphenicol. CLI = clindamycin. CRO = ceftriaxone. ERY = erythromycin. FOX = cefoxitin. GEN = gentamicin. MEM = meropenem. NIT = nitrofurantoin. SXT = sulfamethoxazole + trimethoprim. TCY = tetracycline. Bars with lighter shading indicate when <70% of isolates were tested against that antimicrobial.

health factors such as rates of underlying skin diseases like scabies or impetigo.[24] However, the reported differences in these factors across the PICTs in our study do not correlate with the observed variation in MRSA.[25,26] A final potential driver of elevated MRSA is antibiotic consumption, which can increase selective pressure for resistant strains. While equivalent data from other PICTs are lacking, it is notable that Samoa – a country with a high rate of MRSA – also has published evidence of very high beta-lactam antibiotic consumption by global standards.[27]

Overall, across the four countries studied, susceptibility to ceftriaxone among *E. coli* and *K. pneumoniae* ranged between 87-94% and 72–90%, respectively. These are comparable to results among bloodstream isolates in Australia (87% among *E. coli*, and 91% among *K. pneumoniae*)[22] and hospitalised patients in the United States (87% among all Enterobacterales),[28] however much higher than the 60% susceptibility recently reported among 162 consecutive Enterobacterales bloodstream isolates in Fiji.[29] Ceftriaxone resistance among Enterobacterales is often mediated by ESBL production, and such organisms have been labelled a 'Critical' Priority Pathogen for AMR research by the WHO.[11] Unfortunately, our understanding of the primary mechanisms of ceftriaxone resistance in PICTs is limited by a paucity of sequencing data. One recent study from Fiji reported that CTX-M-15 and OXA-1 were the most frequently identified resistance genes among *E. coli* and *K. pneumoniae*, however this was based on a subset of 61 isolates.[29] We note with concern that for many PICTs, susceptibility to the oral agents amoxicillin + clavulanate and sulfamethoxazole + trimethoprim was close to 50%, with implications for local antibiotic guidelines especially for management of abdominal and urinary infections in the community. Finally, meropenem-resistance among *E. coli* and *K. pneumoniae* appeared to be very infrequent: despite a selective testing strategy (that can inflate the reported proportion of resistance), most PICTs had susceptibility at or close to 100%.

Our study demonstrates the feasibility of performing AMR surveillance in low- and middle-income countries, and specifically PICTs, despite multiple challenges faced by local laboratories. These include staffing numbers, lengthy supply chains, intermittent stock-outs, managing equipment and reagents in a warm and humid climate, and in some settings the use of paper-based records.[4] Obtaining and analysing microbiology results was far easier in countries that had existing electronic databases with line-level data (i.e., providing information on every single isolate), rather than aggregated data. With line-level data, susceptibility rates could be stratified not only by patient location, as in this study, but also

by age or specific wards to provide a more nuanced understanding of local AMR patterns. In turn, this knowledge can guide specific antimicrobial recommendations, or identify sites of high AMR prevalence. The introduction of electronic laboratory systems should be prioritised in PICTs to improve the accessibility and standardisation of antimicrobial susceptibility data.

Accurate and reliable national AMR surveillance data can have numerous benefits for countries and their citizens. First, they can form the basis of antibiotic guidelines to help ensure patients receive locally appropriate antibiotic therapy. Based on our results, Samoa and Tonga should prioritise non-beta-lactam antibiotics for empiric treatment of skin infections where *S. aureus* is suspected, whereas empiric beta-lactams would be appropriate in the Cook Islands. Second, AMR surveillance data can inform national antimicrobial formularies, ensuring that appropriate alternatives are readily available if susceptibility to first-line agents is low. Third, AMR surveillance can identify sudden changes in resistance. This has implications for infection prevention and control, especially in the hospital setting – a rapid change in an organism's susceptibility profile could represent an outbreak of a resistant strain. It is encouraging that for all four PICTs conducting surveillance in this study – three of which also had recently introduced local antibiotic guidelines – the prevalence of AMR remained largely stable over time, and indeed had statistically significant falls for some key pathogens (such as MRSA in Samoa). Finally, AMR surveillance data can help policymakers identify the most appropriate pathogens (e.g. *S. aureus*) or syndromes (e.g. skin infections) to focus on when prioritising strategies to contain AMR.

There are some potential limitations of this study. First, hospitalised patients and patients failing antimicrobial therapy may be overrepresented in the data, as these groups are more likely to have samples collected for culture. These patients are also more likely to have resistant pathogens. Second, the PICTs in this study followed different laboratory standards, including different breakpoints for susceptibility testing, so a small number of equivalent isolates with identical disk zone sizes would have been categorised differently between countries. Third, we were unable to classify infections as either healthcare-associated or community-acquired – even for countries with more detailed datasets – as no data were available on the timing of patient admission. AMR was higher among inpatient samples, suggesting that healthcare-associated infections may be more resistant, however this hypothesis requires further study. Fourth, the final two years of data were collected during the COVID-19 pandemic so may be less representative. Although none of the PICTs in this study had community transmission of COVID-19 until 2022, all had strict border travel restrictions from March 2020 until the end of data collection in December 2021. Finally, we observed intermittent low testing of particular antimicrobials for reasons that are hard to retrospectively assess. One likely reason was supply shortages of antimicrobial disks; this could inflate the apparent rate of AMR if selective testing was then employed, alternatively this could have no impact if testing was ceased entirely when stock was low.

Conclusion

We have presented comprehensive antimicrobial susceptibility data from the national microbiology laboratories of four Pacific Island countries. Overall rates of AMR were low to moderate, and mostly stable across the five-year period. There was a notable difference in the prevalence of MRSA between countries. These data can inform local prescribing guidelines and formularies, identify which organisms should be prioritised by each country, and provide a contemporary reference against which future surveillance can be compared. In order to better understand the drivers and transmission of AMR in the Pacific Islands region, research priorities include comparing the frequency of AMR in healthcare-associated infections and community infection, describing the molecular epidemiology of priority pathogens (such as MRSA in Samoa and Tonga), and quantifying antimicrobial consumption across PICTs.

Contributors

MJL and RJE conceived, designed and initiated the study. PE, TF, EI, LI, HL, MM, RT, DT and GW collected antimicrobial susceptibility data, and curated their respective datasets. MJL cleaned and analysed data. MJL and SJL performed statistical analyses. MJL prepared figures and tables. MJL, RJE and AYP wrote the first draft. All authors contributed to subsequent drafts and have all read and agreed to the published version of the manuscript.

Data sharing statement

Most of the data supporting the findings of this study are available in the Supplementary Appendix. Additional aggregated data are available from the corresponding author, RJE, upon reasonable request.

Declaration of interests

The authors have no relevant conflicts of interest to declare.

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Appendix A. Supplementary data

Supplementary data related to this article can be found at https://doi.org/10.1016/j.lanwpc.2022.100677.

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