Risk factors for carriage of antimicrobial-resistant bacteria in community dwelling-children in the Asia-Pacific region: a systematic review and meta-analysis

Yi Qi Chan¹†, Kailin Chen¹-²†, Gilbert T. Chua³, Peng Wu²,4, Keith T. S. Tung³, Hing Wai Tsang³, David Lung⁵, Patrick Ip³ and Celine S. L. Chui²,4,6*

¹Centre for Safe Medication Practice and Research, Department of Pharmacology and Pharmacy, Li Ka Shing Faculty of Medicine, The University of Hong Kong, Hong Kong, China; ²Laboratory of Data Discovery for Health (D²4H), Hong Kong Science and Technology Park, Sha Tin, Hong Kong, China; ³Department of Paediatrics and Adolescent Medicine, School of Clinical Medicine, Li Ka Shing Faculty of Medicine, The University of Hong Kong, Hong Kong, China; ⁴School of Public Health, Li Ka Shing Faculty of Medicine, The University of Hong Kong, Hong Kong, China; ⁵School of Pathology, Hong Kong Children's Hospital, Hong Kong, China; ⁶School of Nursing, Li Ka Shing Faculty of Medicine, The University of Hong Kong, Hong Kong, China

*Corresponding author. E-mail: cceline@connect.hku.hk
†Co-first author. Y.Q.C. and K.C. contributed equally to this article.
@ChuiCeline, @hku_son, @hku_sph, @HKUMed

Received 15 November 2021; accepted 13 March 2022

Background: Antimicrobial resistance is an increasingly important issue in public health as antibiotics are over-used. Resistance to antimicrobial agents can pose significant challenges to infection treatment.

Objectives: To evaluate risk factors associated with carriage of antimicrobial-resistant (AMR) bacteria in children in the Asia-Pacific region to consolidate evidence for future implementation of antibiotic prescribing practice.

Methods: Three electronic databases—PubMed, EMBASE and Cochrane Library—were searched. Observational studies that investigated the risk factors for carriage of MRSA, penicillin-resistant Streptococcus pneumoniae, ESBL-producing Escherichia coli and Klebsiella pneumoniae among the paediatric population in community settings in the Asia-Pacific region were considered eligible. Summary statistics from the identified studies were pooled using meta-analyses.

Results: From the 4145 search results, 25 papers were included in this review. Sixteen papers were included in the meta-analysis based on reported risk factors. Young age of 2–6 months compared with children aged 7–60 months (OR 2.74, 95% CI: 1.75–4.29), antibiotic use within the past 3 months (OR 2.65, 95% CI: 1.70–4.12), daycare attendance (OR 1.49, 95% CI: 1.17–1.91) and hospital admission within the past 3 months (OR 3.43, 95% CI: 2.13–5.51) were found to be significant risk factors for AMR bacterial carriage, whilst breastfeeding (OR 0.69, 95% CI: 0.60–0.81) and concurrent colonization of S. pneumoniae (OR 0.59, 95% CI: 0.38–0.91) are protective factors.

Conclusions: The findings support that there are a number of significant risk factors associated with carriage of AMR bacteria in the Asia-Pacific paediatric population. To combat antimicrobial resistance in the future, these risk factors should be considered, and measures taken to mitigate associated carriage.

Introduction

The emergence of antimicrobial resistance in bacteria is an increasing threat to both public health and effective clinical management. Strains of carbapenem-resistant ESBL-producing Enterobacteriaceae, MRSA, vancomycin-resistant Staphylococcus aureus and penicillin non-susceptible Streptococcus pneumoniae are ranked among the 12 drug-resistant priority pathogens identified by WHO.¹ A previous study has shown that patients with antimicrobial-resistant (AMR) bacterial infection may experience higher morbidity and mortality than do patients with antimicrobial-susceptible bacterial infections, resulting in a lengthened duration and increased cost of hospitalization by US $6000–30000.²
The paediatric population are particularly vulnerable subjects as they have immature immune systems compared with healthy adults.\textsuperscript{3} Since children generally have poor hygiene practice and are unaware of potential pathogenic sources,\textsuperscript{3} they are frequently exposed to AMR pathogens that are associated with significant mortality and morbidity. Colonized resistant bacteria may be shed to the environment or transmitted unintentionally from carriers to other individuals, leading to possible infections. Antimicrobial resistance patterns differ by population, age and geographical location of investigation. There has been a previous study that systematically reviewed antimicrobial resistance patterns in children in Africa, however, reviews on the community prevalence and resistance pattern of the abovementioned top priority pathogens among the paediatric population in Asia-Pacific region are limited.\textsuperscript{4} The prevalence and antimicrobial resistance pattern among children in Asia-Pacific region might also be different from American continents and other parts of the world due to different living environments and living habits. Therefore, it is important to understand the risk factors of AMR bacteria carriers in the Asia-Pacific region to identify the potential high-risk groups and to inform possible interventions. As carriage of AMR \textit{S. aureus}, \textit{S. pneumoniae}, \textit{Escherichia coli} and \textit{Klebsiella pneumoniae} are associated with significant morbidity and mortality in infected individuals, including children\textsuperscript{5}, this study aimed to systematically review the current literature on the risk factors associated with carriage of these four of the most commonly carried bacteria in the community paediatric population in Asia-Pacific regions.

### Methods

In December 2020, a systematic search of the literature was performed in PubMed, EMBASE and Cochrane Library using the search strategies described in Table S1 (available as Supplementary data at JAC-AMR Online). The search strategy included keywords in MeSH terms and Emtree thesaurus that are relevant to the prevalence of carriage of AMR \textit{S. aureus}, \textit{S. pneumoniae}, \textit{E. coli} and \textit{K. pneumoniae} in community paediatric populations of Asia-Pacific regions and associated risk factors for such colonization. We conducted the study in accordance with the preferred reporting items for studies in reviews and meta-analyses (PRISMA) to ensure consistency and clarity of reporting.

### Eligibility criteria

Observational studies that investigated the prevalence and risk factors for carriage of AMR bacteria of interest in the community paediatric populations of Asia-Pacific regions according to World Bank classification were included. Paediatric population refers to a group of child participants aged 0–18 years that were recruited at the respective study sites. Community studies are defined as where participants were not hospitalized at the time of recruitment. They were often referred to as healthy children recruited from school or the community (non-clinical setting). Those who visited healthcare facilities, which are defined as hospitals, clinics, outpatient clinics and healthcare centres that provide healthcare services for regular health maintenance or vaccination, were considered as community participants as long as they were stated as healthy children or did not have any infections. Sub-healthy children are currently infected children and have different bacterial flora from healthy children. Their AMR bacterial pattern is different from that of healthy children, so studies that recruited sub-healthy children were excluded. Those hospitalized patients were not included because they had close contact with healthcare professionals and stayed in close proximity with other patients, which potentially increased their exposure to AMR bacteria and chances of nosocomial infections. Only studies that screened for AMR bacterial carriage were included. Any bacterial strains isolated from samples collected from the nose, nasopharyngeal space, throat, oropharyngeal space, rectum or stool without suspected/confirmed infection were considered as bacterial carriage. Only studies that examined the risk factors in a multivariate analysis were included.

### Data extraction

Two investigators (Y.Q.C. and K.C.) independently extracted data from the full text of the eligible studies and decided which studies to include. Study characteristics such as study design, study year, study period, study participants, the prevalence of AMR bacterial carriage and laboratory methods used for detection of antimicrobial resistance were extracted from the included studies. Significant risk factors for AMR bacterial carriage were also extracted from multivariate analyses. If a study reported data from both community and non-community settings such as the inpatient and outpatient settings in the hospitals, only the data collected from community participants were considered in this review. Any discrepancies were addressed by consulting a third investigator (C.S.L.C.) until consensus has been reached.

### Study quality assessment

The Newcastle-Ottawa scale (NOS) was used to assess the quality for non-randomized observational studies as recommended by the Cochrane Collaboration.\textsuperscript{6} The scale (Table S2) used in this study was modified based on Forster et al.,\textsuperscript{7} which is applicable to cross-sectional or prospective observational studies. Three components were assessed for all included studies: representativeness of the exposed cohort, ascertainment of the exposure (risk factors) and assessment of the outcome (AMR bacterial carriage). If the study fulfilled all three components, we considered the quality as high. It was classified as moderate or low if it fulfilled two or one or less components, respectively. The scoring was conducted by two investigators (Y.Q.C. and K.C.) independently and discrepancies were reconciled by joint evaluation of the original article. Studies classified as moderate quality or above were included in the meta-analysis.

### Meta-analysis

Risk factors indicated by multivariate analysis from two or more studies were quantitatively synthesized using RevMan 5 software. The OR and the 95% CI for that particular risk factor were included into a forest plot and used for estimation of the pooled OR. Risk factors that were only discussed by one article or discussed by two or more articles that were too heterogeneous for meta-analysis were described in the narrative review. Pooled estimates of risk factors were estimated based on the random effects model. Different kinds of risk estimates such as OR or relative risk (RR) were meta-analysed separately. \textsuperscript{1} was used to measure heterogeneity of study results due to true variation rather than chance. Generally, 25%, 50% and 75% are used as a cut-off for low, moderate and high heterogeneity levels.\textsuperscript{8} Sensitivity analyses were conducted to test whether the heterogeneity can be reduced by removing the studies that are likely to be concern. For example, a study that investigated a different bacterial species compared with other studies might be removed.

### Results

A total of 4145 citations were identified. The process of article screening is illustrated in Figure S1. A total of 25 studies were included in the qualitative synthesis. Among them, 17 studies were conducted in the healthcare facility setting and 8 in the community setting. Most studies focused on MRSA (n = 15) and penicillin-resistant \\textit{S. pneumoniae} (n = 7), fewer on ESBL-producing \textit{E. coli}}
(n = 3) and K. pneumoniae (n = 1). Throat swabs (n = 1), nasal swabs (n = 16), nasopharyngeal swabs (n = 8) and stool samples (n = 3) were collected for bacterial isolation and susceptibility testing in the studies. The MRSA prevalence ranges from 0.6% to 13.2% for nasal and nasopharyngeal samples. The ESBL producing E. coli prevalence ranges from 9% to 60% for stool samples. The penicillin-resistant S. pneumoniae prevalence ranges from 0.40% to 14.6% for nasopharyngeal samples. They were all classified as moderate or high quality. Table S3 summarizes the characteristics and results of quality assessment of the 25 studies, of which 16 were included in the meta-analysis. The studies included in the meta-analysis had various designs including cross-sectional (n = 8) and prospective observational study (n = 8). The studies were conducted in Asia-Pacific countries or regions including East Asia (n = 10), South Asia (n = 2), Middle East (n = 3) and a combination of Asian countries (n = 1). The studies recruited participants from local clinics/healthcare centres/outpatient clinics/hospitals (n = 9), some were from the community (n = 2), and some were from preschool/kindergarten/daycare centres/schools (n = 5).

Narrative review
A total of nine studies that were not included in the meta-analysis had various study designs including cross-sectional (n = 5) and prospective observational (n = 4). Adler et al.9 met the eligibility criteria for meta-analysis but this study was excluded from the meta-analysis since it reported RR instead of OR. The studies were conducted in Asia-Pacific countries or regions including the Middle East (n = 2), East Asia (n = 3), Central Asia (n = 2) and South Asia (n = 2). The majority of the studies recruited participants from local clinics/healthcare centres/hospitals (n = 5), preschool/kindergarten/daycare centres/schools (n = 2), or mixed settings including healthcare visits, hospitals or kindergarten/schools (n = 2). Four studies10–13 reported that geographical location of residency is a significant risk factor for AMR bacterial carriage. As these studies categorized the geographical location of residency differently (Northern Taiwan and Southern Taiwan, urban residency and non-urban residency, etc.), directly pooling the estimates from these studies would not be valid due to the high heterogeneity. Directly pooling the estimates of three studies11,14,15 that reported that larger family size is a significant risk factor for AMR bacterial carriage is also invalid since they investigated different family size ranges. Two studies16,17 also reported that family member or household contact being a healthcare worker is a significant risk factor for AMR bacterial carriage.

Meta-analysis
Of the 16 studies eligible for meta-analysis, risk factors such as daycare attendance, children aged 2–6 months, history of hospital admission and antibiotic use within the past 3 months have been associated with increased carriage of AMR bacteria of interest while sex was not associated with increased AMR bacterial carriage. The ORs of risk factors associated with antimicrobial resistance were meta-analysed, generating forest plots (Figure S2). These seven risk factors can be grouped into demographic (age and sex), medical history (history of hospital admission within the past 3 months, antibiotic use within the past 3 months and colonization by S. pneumoniae) and lifestyle (daycare attendance and breastfeeding status).

Demographics
Nine studies10,15,18–24 reported sex can be a risk factor for AMR bacterial carriage while two studies10,23 reported male sex is a risk factor and six studies10,15,19,21,22,24 reported the opposite findings. The pooled OR for male sex is 0.96 (95% CI, 0.74–1.24). The heterogeneity of the meta-analysis was moderate (I² = 68%). We conducted two sensitivity analyses by considering studies with the same bacteria of interest only. Six studies15,19–23 investigated MRSA whilst two studies10,18 investigated penicillin non-susceptible S. pneumoniae. In the sensitivity analyses, the overall pooled estimate for MRSA only increased to 1.2 (95% CI 0.76–1.88) with I² = 77% whilst it decreased to 0.89 (95% CI 0.71–1.11) with I² = 0% for S. pneumoniae only. None of them resulted in a statistically significant outcome. Studies investigating age as a risk factor often examined different age ranges. Directly pooling the estimates from different studies would not be valid due to the high heterogeneity. We therefore only synthesized findings from studies11,25 investigating the same age range. Two of the studies11,25 reported that the risk for MRSA carriage among 2- to 6-month-old children was significantly higher when compared with children aged 7 to 60 months with OR 2.74 (95% CI 1.75–4.29), I² = 72%.

Lifestyle
The pooled results in our meta-analysis of the six studies10,11,22,25–27 support an association between daycare attendance and risk for AMR bacterial carriage [OR 1.49 (95% CI 1.17–1.91, I² = 57%)]. Three studies10,22,25 reported breastfeeding status is protective against MRSA carriage among 2- to 6-month-old children [OR 0.69 (95% CI 0.60–0.81, I² = 0%)].

Medical history
Two studies11,22 reported that concurrent colonization of S. pneumoniae is a significant protective risk factor for MRSA carriage in healthy children with moderate heterogeneity [OR 0.59 (95% CI 0.38–0.91, I² = 53%)]. Two studies23,26 reported that history of hospital admission within the past 3 months is a significant risk factor for AMR bacterial carriage with low heterogeneity [OR 3.43 (95% CI 2.13–5.51, I² = 0%)]. The pooled results in our meta-analysis of five studies18,20,23,29,30 reported that antibiotic use within the past 3 months among young children is a risk factor for carriage of AMR bacteria (penicillin non-susceptible S. pneumoniae, MRSA and ESBL-producing Enterobacteriaceae). The pooled estimate [OR 2.65 (95% CI 1.70–4.12)] shows that the results are significant. The heterogeneity was moderate (I² = 31%). A sensitivity analysis was conducted for two studies20,23 that both investigated MRSA. The I² reduced from 31% to 0% and the overall pooled OR increased to 6.19 (95% CI 2.64–14.53). The similar and significant results supported that antibiotic use within the past 3 months is associated with MRSA carriage.

Discussion
To our knowledge, this is the first review in the Asia-Pacific region to summarize and pool significant risk factors for carriage of MRSA penicillin non-susceptible S. pneumoniae, ESBL-producing
E. coli and K. pneumoniae in the community paediatric environment.

In the results, the prevalence range of colonization with bacteria of our interest in the studies is wide even though some of the studies were conducted in the same region. This is possibly due to a number of reasons. Firstly, the difference in the locations and their distribution of study setting is one of the contributors to the variance. For example, one study collected samples from children from primary schools situated in areas of older public housing and in new towns in Hong Kong while the other study collected samples from children in 18 school districts distributed over the whole of Hong Kong. Another possible reason could be the difference in laboratory guidelines used in the studies. For example, three studies were all conducted in Hong Kong but one study used CLSI while the other two studies used NCCLS to identify penicillin non-susceptible S. pneumoniae. The third reason could be the difference in study periods. Two studies were performed before 2001 while another study was performed from 2013 to 2014. It is possible that the epidemiology of AMR bacterial carriage has changed after more than a decade. Furthermore, it might be due to the differences in the characteristics of the study participants. There is large variance in the prevalence in two studies that both investigated MRSA and were conducted in the same geographical location. The first of these studies found the OR of MRSA carriage in children attending preschool was four times higher compared with children attending no school. The second study was conducted among preschool children while the first study was conducted among no school, preschool and school children, so the prevalence of MRSA in the second study (10.2%) is expected to be higher than that in the first study (1.02%).

Attendance of daycare centres was shown to be an important environmental factor leading to carriage of AMR bacteria in our meta-analysis, which is the same as our hypothesis. Daycare centres are set up for children whose parents need to work and cannot take care of their kids during daytime. Those children are often taken care of by a group. The potential for carriage of AMR bacteria is increased in crowded spaces. For instance, studies have shown that daycare attendance increased the risk of acute otitis media infection 2- to 3-fold. In addition, children have lower hygiene awareness and have poor control over toileting behavior. Resistant bacteria can easily be spread by physical contact of contaminated excrement or shared items. Moreover, higher risk procedures like diaper changing or food handling are usually performed by the same daycare centre worker for convenience, which may facilitate transmission of resistant enteric pathogens.

Overall, attendance of daycare centres as a risk factor for AMR bacterial carriage is consistent with our study findings.

A protective effect of breastfeeding against carriage of AMR bacteria in healthy children was shown in the meta-analysed studies. Previous studies have shown that breast milk contains secretory IgA antibodies, which serve as the first line of defence in the intestinal epithelium to bind with invading enteric pathogens. Glycoconjugates in breast milk such as glycoprotein, glycolipid and free oligosaccharides can adhere to pathogens by their sugar epitopes. Besides the bactericidal capability of these nutrients, they serve the purpose of probiotics to develop beneficial microorganisms namely Bifidobacterium and Lactobacillus in the infant to minimize colonization by AMR bacteria. A research study published in Nature Communications has discovered that babies breastfed for at least 6 months had reduced carriage of enteric AMR bacteria compared with those breastfed for a shorter period or not at all. Breastfeeding may also support the important organ development of the infant’s immune system. In our meta-analysis, age of 2–6 months was also found to be a risk factor for AMR bacterial carriage. Infants’ immune systems are not yet fully developed. Innate immunity components such as monocytes, phagocytes and neutrophils are incapable both in number and function. Immunity before the age of 6 months relies on the antibody IgG passively transferred from the maternal placenta during the third trimester. However, this adaptive immunity is short-lived and gradually dies down. Therefore, infants aged 2–6 months are more susceptible to bacterial invasion or colonization and are therefore more susceptible to AMR infection. This is consistent with our findings that age of 2–6 months is a significant risk factor for antimicrobial resistance. In addition, parental carriage status can also be a risk factor for carriage at young age. One study in the meta-analysis reported that having an MRSA-carrier parent is a significant risk factor for MRSA carriage in children. Another study also showed that parental S. aureus carriage is associated with S. aureus carriage in young children, possibly due to transmission from parents to their children. The transmission can be either due to their close contact with their infants during infancy, or vertical transmission during labour.

In our meta-analysis of two studies that investigated the risk factor for young age, the results were highly heterogeneous. The first of these studies was conducted in both northern and southern areas of Taiwan while the second study was conducted in southern Taiwan. Previous studies reported that the nasal carriage rate of MRSA in southern Taiwan was lower than in northern Taiwan. The difference between the locations of studies may potentially cause the high heterogeneity observed in our results.

Our analysis showed concurrent colonization of S. pneumoniae is protective for carriage of MRSA, which may be explained by the mutual exclusiveness and antagonism between the two species. It is known that, just like any other organism, bacteria compete with each other for survival. To colonize in the host in order to absorb the nutrients, the usual way for bacteria is to attach and grow on the nutrient-limited epithelium or mucosa, then evade the host immunity and finally infect the host. Commensal S. pneumoniae was suggested to be bactericidal towards S. aureus through a hydrogen peroxide-mediated pathway. More evidence suggested that nasopharyngeal carriage of S. aureus was inversely related to S. pneumoniae as the introduction of S. pneumoniae vaccines reduced S. aureus infection in Africa. To conclude, it supports our study findings in the meta-analysis.

Antibiotic use is suggested to be the dominant reason for antimicrobial resistance development. Resistance genes are found naturally, but the selection pressure of antibiotics eliminates those susceptible bacteria and the remaining resistant ones can thrive. In hospital settings, it has also been revealed that clinical areas such as the ICU or burn unit where frequent antibiotic use occur had higher prevalence of AMR bacteria, making nosocomial infection more difficult to treat. This is consistent with the findings in our meta-analysis: prior antibiotic use is a
risk factor for AMR bacterial carriage. The analysis was with moderate heterogeneity potentially due to the studies included having different pathogens. The results were consistent after we conducted sensitivity analysis to include only studies investigating MRSA with low heterogeneity. However, our study was not able to study the correlation between time of antibiotic use and the development of antimicrobial resistance. Future studies may investigate the relationship between AMR development and time.

Our meta-analysis revealed that hospital admission within the past 3 months increases the carriage of AMR bacteria. Hospitals are an ideal environment for antimicrobial resistance development due to the high volume of antibiotics used for treatment of infections. It has been shown that more than half of the inpatient cases in acute hospitals received prophylactic or therapeutic antibiotics. Resistant strains are cultivated in patients during antibiotic therapy that may be transferred to healthcare workers or other sick patients in the confined ward areas during hospital stay. Cross transmission of AMR bacteria is achieved by physical contact during treatment or the consultation process or by the use of invasive devices. Therefore, this agrees with the results of our meta-analysis that hospital admission is associated with MRSA carriage.

Previous studies have also shown that male patients were more susceptible to MRSA acquisition. The two sexes also demonstrated differences in innate immune response towards infectious pathogens. Males generate less protective humoral and cell-mediated immune responses compared with females, thus they are more susceptible to microbial infection. However, our meta-analysis did not support any association with either sex. Further investigation on the sex difference in AMR bacterial carriage is warranted.

Some included studies described in the narrative review also reported significant risk factors. Since S. aureus is a commensal bacterium in humans, it can be transmitted among household contacts by a contaminated environment that can then act as an intermediate source. Therefore, crowding and large family size are a risk factor for S. aureus carriage, which is consistent with the findings that greater family size is a significant risk factor for bacterial carriage from three studies. Healthcare workers are also a known important reservoir for MRSA carriage. It is plausible that having a family member or household contact who is a healthcare worker is a significant risk factor for MRSA carriage, which has been reported in studies. However, the study settings were too heterogeneous to be included in the meta-analysis to draw a meaningful conclusion. Further investigation of these risk factors reported in a comparable manner is warranted.

A systematic review reported the global evidence of the prevalence of bacterial resistance in children’s urinary tract infection (UTI) and associations with the use of common antibiotics in primary care; they found significant pooled ORs for antibiotic exposure time between 0–1 month, 0–3 months and 0–6 months, while we have similar findings that there is a significant association between any AMR bacteria or MRSA carriage and antibiotic use within the previous 3 months. What this study adds is that not only is bacterial resistance in UTI among children high, MRSA or other AMR bacterial carriage caused by antibiotic use among children is also substantial. Another systematic review reported the high prevalence of bacterial resistance among children with symptomatic UTI against different classes of antibiotics in Asia-Pacific region while we also found ESBL-producing E. coli and K. pneumoniae carriage among asymptomatic children is prevalent.

In addition to the risk factors discussed above, it is important to consider the role of integrated ecosystem when addressing antimicrobial resistance issues. The current One Health approach’s primary focus is on limiting the use of antibiotics in food animals. Recent systematic reviews and meta-analyses found a reduction in antibiotic use in food animals caused a decrease in AMR bacterial carriage in animals and there is limited evidence it could cause some reduction in humans. Studies have also found wildlife ecosystems might be an essential reservoir of resistant organisms and resistance genes. Resistance genes can also be found in aquatic systems and there is some evidence to suggest horizontal gene transfer from aquatic bacteria to human pathogens. Furthermore, environmental contamination with resistance genes, resistant organisms and antibiotic residues plays an important role in antimicrobial resistance, which is related to antibiotic administration in both humans and in food production (livestock, aquaculture and cropland) through run-off. Therefore, using a comprehensive and holistic One Health approach that incorporates human, animal, environmental, ecosystem and wildlife perspectives is strongly encouraged in future antimicrobial resistance studies.

**Strengths and limitations**

We undertook a rigorous systematic review and meta-analysis including all relevant literature to date. Reviewer selection bias was minimized by using a predefined search strategy for selection and data extraction was conducted by two independent authors. Differences in locations of studies, study population and pathogen of interest studied will not allow us to draw a meaningful pooled estimate. However, the findings from this review were consistent with the published literature, which support that age, antibiotic use within the past 3 months, daycare attendance and hospital admission within the past 3 months are significant risk factors for AMR bacterial carriage whilst breastfeeding and concurrent colonization of S. pneumoniae are protective factors. The consistent results from sensitivity analyses also strengthen the study. To date, there is only one systematic review conducted in the general population of Asia-Pacific countries regarding risk factors for carriage of community-acquired MRSA (CA-MRSA). The paediatric population with age less than or equal to 6 months was found to be one of the significant risk factors, which echoes with our study result. Our study took a step forward to investigate the paediatric population as our study target and focused on four common resistant bacteria in the community, which is more comprehensive for understanding the carriage of bacteria. Most of the systematic reviews and meta-analyses in PubMed studied AMR bacterial carriage among adult populations in non-Asia-Pacific regions such as Africa and Europe. Our study focused specifically on the Asia-Pacific paediatric population can help complement the missing pooled evidence. Moreover, as the number of studies included in the meta-analysis is limited, a funnel plot was not performed, as it would not reliably identify publication bias, if any.
Conclusions

The findings of this meta-analysis and narrative review of epidemiological studies support that there are several significant risk factors associated with carriage of AMR bacteria in the Asian-Pacific paediatric population. To combat the issue of antimicrobial resistance and utilize antibiotics more appropriately in the future, these risk factors should be considered, and measures should be taken to mitigate associated carriage.

Funding

This study was funded by a research grant from the Food and Health Bureau, The Government of the Hong Kong Special Administrative Region (Ref. no. PR-HKCH-4).

Transparency declarations

None to declare.

Supplementary data

Figures S1 and S2 and Tables S1 to S3 are available as Supplementary data at JAC-AMR Online.

References

1. Willyard C. The drug-resistant bacteria that pose the greatest health threats. Nature 2017; 543: 15.
2. Maragakis LL, Perencevich EN, Cosgrove SE. Clinical and economic burden of antimicrobial resistance. Expert Rev Anti Infect Ther 2008; 6: 751–63.
3. ReAct Group. Why Are Children More Vulnerable to Resistant Infections? https://www.reactgroup.org/news-and-views/news-and-opinions/year-2019/why-are-children-more-vulnerable-to-amr/.
4. Williams PCM, Isaacs D, Berkley JA. Antimicrobial resistance among children in sub-Saharan Africa. Lancet Infect Dis 2018; 18: e33–44.
5. Medernach RL, Logan LK. The growing threat of antibiotic resistance in children. Infect Dis Clin North Am 2018; 32: 1–17.
6. Higgins JPT, Thomas J, Chandler J et al. Cochrane Handbook for Systematic Reviews of Interventions. Cochrane, 2021. www.training.cochrane.org/handbook.
7. Forster AJ, Oake N, Roth V et al. Patient-level factors associated with methicillin-resistant Staphylococcus aureus carriage at hospital admission: a systematic review. Am J Infect Control 2013; 41: 214–20.
8. Melsen WG, Boatsma MC, Rovers MM et al. The effects of clinical and statistical heterogeneity on the predictive values of results from meta-analyses. Clin Microbial Infect 2014; 20: 123–9.
9. Adler A, Givan-Lavi N, Moses AE et al. Carriage of community-associated methicillin-resistant Staphylococcus aureus in a cohort of infants in southern Israel: risk factors and molecular features. J Clin Microbial 2010; 48: 531–8.
10. Lee NY, Song JH, Kim S et al. Carriage of antibiotic-resistant pneumococci among Asian children: a multinational surveillance by the Asian Network for Surveillance of Resistant Pathogens (ANSORP). Clin Infect Dis 2001; 32: 1463–9.
11. Chen C-J, Hsu K-H, Lin T-Y et al. Factors associated with nasal colonization of methicillin-resistant Staphylococcus aureus among healthy children in Taiwan. J Clin Microbial 2011; 49: 131–7.
12. Hu J, Sun X, Huang Z et al. Streptococcus pneumoniae and Haemophilus influenzae type b carriage in Chinese children aged 12–18 months in Shanghai, China: a cross-sectional study. BMC Infect Dis 2016; 16: 149.
13. Dyr OJ, Hoa NQ, Trung NV et al. High prevalence of antibiotic resistance in commensal Escherichia coli among children in rural Vietnam. BMC Infect Dis 2012; 12: 92.
14. Pathak A, Marothi Y, Iyer RV et al. Nasal carriage and antimicrobial susceptibility of Staphylococcus aureus in healthy preschool children in Ujjain, India. BMC Pediatr 2010; 10: 100.
15. Dey S, Rosales-Klintz S, Shouche S et al. Prevalence and risk factors for nasal carriage of Staphylococcus aureus in children attending anganwaries (preschools) in Ujjain, India. BMC Res Notes 2013; 6: 265.
16. Schlesinger Y, Yalahom S, Raveh D et al. Methicillin-resistant Staphylococcus aureus nasal colonization in children in Jerusalem: community vs. chronic care institutions. Isr Med Assoc J 2003; 5: 847–51.
17. Lo W-T, Wang C-C, Lin W-J et al. Changes in the nasal colonization with methicillin-resistant Staphylococcus aureus in children: 2004-2009. PLoS One 2010; 5: e15791.
18. Chiu SS, Ho PL, Chow FK et al. Nasopharyngeal carriage of antimicrobial-resistant Streptococcus pneumoniae among young children attending 79 kindergartens and day care centers in Hong Kong. Antimicrob Agents Chemother 2001; 45: 2765–70.
19. Biber A, Abuelaish I, Rahav G et al. A typical hospital-acquired methicillin-resistant Staphylococcus aureus clone is widespread in the community in the Gaza strip. PLoS One 2012; 7: e42864.
20. Erami M, Soltani B, Taghavi Ardakani A et al. Nasal carriage and resistance pattern of multidrug resistant Staphylococcus aureus among healthy children in Kashan, Iran. Iran Red Crescent Med J 2014; 16: e21346.
21. Lo W-T, Lin W-J, Tseng M-H et al. Dissemination of methicillin-resistant Staphylococcus aureus among healthy children in Northern Taiwan. J Med Sci 2010; 30: 47–53.
22. Pan H-H, Huang Y-C, Chen C-J et al. Prevalence of and risk factors for nasal methicillin-resistant Staphylococcus aureus colonization among children in central Taiwan. J Microbial Immunol Infect 2019; 52: 45–53.
23. Soltani B, Taghavi Ardakani A, Moravveji A et al. Risk factors for methicillin-resistant Staphylococcus aureus nasal colonization of healthy children. Jundishapur J Microbial 2014; 7: e20025.
24. Shaky P, Barrett P, Diwan V et al. Antibiotic resistance among Escherichia coli isolates from stool samples of children aged 3 to 14 years from Ujjain, India. BMC Infect Dis 2013; 13: 477.
25. Chen C-H, Kuo K-C, Hwang K-P et al. Risk factors for and molecular characteristics of methicillin-resistant Staphylococcus aureus nasal colonization among healthy children in southern Taiwan, 2005–2010. J Microbial Immunol Infect 2019; 52: 929–36.
26. Chan KC, Ip M, Chong PS et al. Nasopharyngeal colonisation and antimicrobial resistance of Streptococcus pneumoniae in Hong Kong children younger than 2 years. Hong Kong Med J 2018; 24 Suppl 6: 4–7.
27. Kuo C-Y, Hwang K-P, Hsieh Y-C et al. Nasopharyngeal carriage of Streptococcus pneumoniae in Taiwan before and after the introduction of a conjugate vaccine. Vaccine 2011; 29: 5171–7.
28. Lu PL, Chin LC, Peng CF et al. Risk factors and molecular analysis of community methicillin-resistant Staphylococcus aureus colonization. J Clin Microbiol 2005; 43: 132–9.
29. Boost MV, O’Donoghue MM, Dooley JS. Prevalence of carriage of antimicrobial-resistant strains of Streptococcus pneumoniae in primary school children in Hong Kong. Epidemiol Infect 2001; 127: 49–55.
30. Stoesser N, Kayaheuang S, Vongsouvath M et al. Colonization with Enterobacteriaceae producing ESBLs in children attending pre-school...
childcare facilities in the Lao People’s Democratic Republic. J Antimicrob Chemother 2015; 70: 1893–7.

31 Hedon K, Pettersson C, Cars H et al. Infection prevention at day-care centres: feasibility and possible effects of intervention. Scand J Prim Health Care 2006; 24: 44–9.

32 Nesti MM, Goldbaum M. Infectious diseases and daycare and pre-school education. J Pediatr (Rio J) 2007; 83: 299–312.

33 Infections in child care centres. Paediatr Child Health 2000; 5: 495–8.

34 Mantis NJ, Rol N, Cotterly B. Secretory IgA and mucosal homeostasis in the gut. Mucosal Immunol 2011; 4: 603–11.

35 Peterson R, Cheah WY, Grinier J et al. Glycoconjugates in human milk: protecting infants from disease. Glycobiology 2013; 23: 1425–38.

36 Parnanen K, Karkman A, Hultman J et al. Maternal gut and breast milk microbiota affect infant gut antibiotic resistome and mobile genetic elements. Nat Commun 2018; 9: 3891.

37 Cacho NT, Lawrence RM. Innate immunity and breast milk. Front Immunol 2017; 8: 584.

38 Ygberg S, Nilsson A. The developing immune system - from foetus to toddler. Acta Paediatr 2012; 101: 120–7.

39 Bashar S, Surendran N, Pichichero M. Immune responses in neonates. Expert Rev Clin Immunol 2014; 10: 1171–84.

40 Regev-Yochay G, Raz M, Carmeli Y et al. Parental Staphylococcus aureus carriage is associated with staphylococcal carriage in young children. Pediatr Infect Dis J 2009; 28: 960–5.

41 Siegel SJ, Weiser JN. Mechanisms of bacterial colonization of the respiratory tract. Annu Rev Microbiol 2015; 69: 425–44.

42 Regev-Yochay G, Trzcinski K, Thompson CM et al. Interference between Streptococcus pneumoniae and Staphylococcus aureus: in vitro effects of hydrogen peroxide-mediated killing. J Bacteriol 2006; 188: 4996–5001.

43 Ebruke C, Diane MM, Walter B et al. High genetic diversity of Staphylococcus aureus strains colonising the nasopharynx of Gambian villagers before widespread use of pneumococcal conjugate vaccines. BMC Microbiol 2016; 16: 38.

44 Sandiumenge A, Diaz E, Rodriguez A et al. Impact of diversity of antibiotic use on the development of antimicrobial resistance. J Antimicrob Chemother 2006; 57: 1197–204.

45 Flaherty JP, Weinstein RA. Nosocomial infection caused by antibiotic-resistant organisms in the intensive-care unit. Infect Control Hosp Epidemiol 1996; 17: 236–48.

46 Prestinaci F, Pezzotti P, Pantosti A. Antimicrobial resistance: a global multifaceted phenomenon. Pathog Glob Health 2015; 109: 309–18.

47 Struelens MJ. The epidemiology of antimicrobial resistance in hospital acquired infections: problems and possible solutions. BMJ 1998; 317: 652–4.

48 Kupfer M, Jatzwauk L, Monecke S et al. MRSA in a large German university hospital: male gender is a significant risk factor for MRSA acquisition. GMS Krankenh Hyg Interdiszip 2010; 5: Doc11.

49 Jallion S, Berthenet K, Garlanca C. Sexual dimorphism in innate immunity. Clin Rev Allergy Immunol 2019; 56: 308–21.

50 Mollena FP, Richardus JH, Behrendt M et al. Transmission of methicillin-resistant Staphylococcus aureus to household contacts. J Clin Microbial 2010; 48: 202–7.

51 Bryce A, Hay AD, Lane IF et al. Global prevalence of antibiotic resistance in paediatric urinary tract infections caused by Escherichia coli and association with routine use of antibiotics in primary care: systematic review and meta-analysis. BMJ 2016; 352: i939.

52 Sugianli AK, Ginting F, Parwati I et al. Antimicrobial resistance among uropathogens in the Asia-Pacific region: a systematic review. JAC Antimicrob Resist 2021; 3: diab003.

53 White A, Hughes JM. Critical importance of a One Health approach to antimicrobial resistance. EcoHealth 2019; 16: 404–9.

54 Wong JW, Ip M, Tang A et al. Prevalence and risk factors of community-associated methicillin-resistant Staphylococcus aureus carriage in Asia-Pacific region from 2000 to 2016: a systematic review and meta-analysis. Clin Epidemiol 2018; 10: 1489–501.

55 Uzuner A, Ilki A, Akman M et al. Nasopharyngeal carriage of penicillin-resistant Streptococcus pneumoniae in healthy children. Turk J Pediatr 2007; 49: 370–8.

56 Öksüz Ş, Şencan I, Yıldırım M et al. The investigation of nasal MRSA carriage and colonization of nasopharyngeal pathogens at a primary school in Düzce. Turk J Med Sci 2007; 37: 359–65.

57 Shetty V, Trumbull K, Hegde A et al. Prevalence of community-acquired methicillin-resistant Staphylococcus aureus nasal colonization among children. J Clin Diag Res 2014; 8: DC12–5.