Journal Pre-proof

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PII: S2213-2198(25)00048-0

DOI: https://doi.org/10.1016/j.jaip.2025.01.007

Reference: JAIP 5808

To appear in: *The Journal of Allergy and Clinical Immunology: In Practice*

Received Date: 24 July 2024

Revised Date: 22 December 2024

Accepted Date: 2 January 2025

Impact of parent-reported antibiotic allergies on paediatric Antimicrobial Stewardship Programs

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There are no funding sources to declare for this review and no conflicts of interest to declare for each of the authors.

Word Count- Abstract: 253 - Main Text: 4099

ABSTRACT

Background:

Antimicrobial stewardship (AMS) is crucial for optimising antimicrobial use and restraining emergence of antimicrobial resistance. The overall increase in reported antibiotic allergies in children can pose a significant barrier to AMS, but its impact on clinical AMS care in children has not been addressed.

Objective:

Compare the clinical outcomes for children with a reported antibiotic allergy label (AAL) with those with no AAL reviewed by AMS.

Method:

A retrospective cohort study conducted in a paediatric tertiary hospital, capturing 1590 inpatient admissions reviewed under the AMS between 2017-2019. Logistic, log-binomial and Cox regression analyses were undertaken. Data collected included documented AAL, antibiotic prescriptions, principal diagnosis, admitting specialty, hospital length of stay, intensive care admissions and hospital readmissions.

Results:

All 1590 paediatric patients were prescribed at least one antibiotic. AALs were recorded in 6.6% of patients; majority were beta-lactam (82%), mostly penicillins (71%). AALs increased with age ($p<0.001$); no gender effect was seen. Patients with AALs received more quinolones ($p<0.001$), lincosamides ($p=0.001$), aminoglycosides ($p<0.001$), and metronidazole ($p=0.015$), than patients with no AALs. In contrast, children with no AAL received more penicillin ($p<0.001$). Children with any AAL had marginally longer hospital length of stay, median (IQR) 7.0 (4.0, 15.0) days, than those without (median (IQR) 5.0 (3.75, 11.0) days, $p=0.027$).

Conclusion:

This study is the first to show how AALs impact clinical outcomes in children under an AMS program. With recent advances in delabelling, early intervention in cases of AAL should target children under AMS services who are in immediate need of optimal antibiotic management.

What is already known about this topic?

Antimicrobial stewardship aims to reduce inappropriate antibiotic use, preserving treatment options. Parent reported β-lactam allergies, affecting 5% of children globally, are overreported and are frequently inaccurate (over 90%), causing adverse outcomes and significantly impeding antimicrobial stewardship initiatives.

What does this article add to our knowledge?

This study, explores the negative impact of antibiotic allergy labels in children, specifically reviewed under antimicrobial stewardship, evidenced by longer hospital stays and increased prescribing of reserved antibiotics, creating a barrier to antimicrobial management.

How does this study impact current management guidelines?

Antimicrobial stewardship optimises antimicrobial use and mitigates the emergence of antimicrobial resistance. Early assessment of these labels could enhance children's health and children under AMS review should be the primary focus for paediatric delabeling services.

Key Words

Antibiotic allergy, antimicrobial stewardship, drug allergy, paediatrics

Abbreviations

AAL -	Antibiotic Allergy Labels
AMS -	Antimicrobial Stewardship
BL-AAL -	Beta-lactam Antibiotic Allergy Labels
C. diff. -	*Clostridioides difficile*
ICU -	Intensive Care Unit
ID -	Infectious Diseases
MRSA -	Methicillin-Resistant *Staphylococcus aureus*

Introduction

With the increase in antimicrobial resistance and rate of antimicrobial drug development slowing, antimicrobial stewardship (AMS) is paramount in optimizing the use of antimicrobials, preventing the development of resistance and improving patient outcomes.[1] While AMS principles align in both adult and paediatric settings it is important to understand that paediatric antimicrobial stewardship has to manage physiological and pathological differences unique to children, with fewer medications available and dramatic differences to therapeutic options from neonates to adolescents.[2, 3] Patient reported allergy to beta-lactam antibiotics, especially penicillins, is the most encountered drug allergy and is a substantial and growing public health concern;[4] however, it is often misdiagnosed and associated with adverse outcomes. AMS is the concept of reducing inappropriate antibiotic use, preserving therapeutic options and decreasing antibiotic resistance.[5] It was first introduced by the Infectious Diseases Society of America in 2007.[6] Antibiotic overuse and resistance have become a major public health issue globally.[7] The prevalence of antibiotic allergy reporting remains high at between 10% to 35% of the adult population, although this can vary based on country and social demographics.[8, 9] Such reporting can lead to the restriction of the prescribing of first-line antibiotics and an increased reliance on alternative antimicrobials, which can be less effective and linked to increased rates of antimicrobial resistance.[10, 11] Antibiotic allergy labels (AALs) contribute to 20% - 50% of inappropriate antibiotic use in American acute care hospitals.[12]

Although adults have the highest rate of self-reported antibiotic allergy, it's frequently acquired during childhood.[13] Moreover, there has been a noticeable rise in paediatric-reported antibiotic allergies over the past decade,[13] particularly in those aged five years or greater.[14] In Australia, 6-10% of children have reported antibiotic allergies [15] with over 90% of these reports being inaccurate.[16] Most of these children will have an AAL against a beta-lactam antibiotic.[14, 17] The symptoms suggestive of an allergic reaction such as hives, rash or other benign symptoms, seen in children, can often be due to a bacterial or viral infection and this can be mistaken for an allergy to the antibiotic prescribed.[18] Just as in adults, there is a negative impact of these labels on clinical outcomes in children, evidenced by longer hospital stays and increased use of alternative, less effective antibiotics.[19] Overall, AALs both within the adult and paediatric population create a barrier to AMS with both clinical and economic implications, however data specifically relating to AMS, especially for paediatrics, are sparse.[20]

Methods

Study Design and Population

We conducted a retrospective single-centre cohort study of paediatric inpatients (n=1590) admitted to the sole paediatric tertiary care teaching hospital in Western Australia, who were seen by the AMS Service between October 2017 and April 2019. Not all patients who received antibiotics during their hospital stay were reviewed by the AMS service. Selection for AMS review was based on the need for broad-spectrum or intravenous antimicrobials to treat the patient's underlying condition. Children with multiple antibiotic allergies were not given preference for AMS review. AMS rounds were conducted three times a week, with new admissions prioritized for initial screening on each round day. Patients whose admission reason did not suggest antimicrobial use were not further investigated for allergy or antimicrobial use. For patients selected for review, their medication charts were assessed for both antibiotic use and documented allergy status. This selection process likely biased the reviewed cases toward patients with higher acuity or more severe presentations.. Patients in the emergency department, same-day surgical wards, or intensive care units are not included in the AMS round. AMS pharmacists provided lists of all children reviewed on a monthly basis, including any parent reported antibiotic allergies, to the Immunology Department. The AMS round does not include an AAL assessment service, but can refer to the Immunology Department for formal AAL assessment.

The study included 1,737 inpatient admissions to a paediatric tertiary hospital. After removing 122 repeat admissions during the study period, the dataset was reduced to 1,615, and further to 1,590 individual patients after excluding 25 patients due to charts being unavailable for review, no antibiotics prescribed upon further review, or incorrectly provided admission dates (Figure E1 – Online Repository).

The cohort study captured data on all patients admitted under speciality units, categorised as general medical, general surgical and oncology (including haematology). Data collected included patient demographic characteristics, documented antibiotic labels, principal diagnosis on admission, antibiotics prescribed, admitting speciality unit, hospital length of stay, and readmissions within 4 weeks and 6 months of discharge, excluding hospital transfers, day procedures, and emergency department reviews.

AAL refers to any antibiotic listed in the 'allergies and adverse drug reaction' section of the patient's medication chart. Data on the AAL, culprit medication, and alleged symptoms were collected from medical notes, charts, and allergy forms. Symptoms were classified as: (1) anaphylaxis, (2) angioedema, (3) rash, (4) gastrointestinal upset, and (5) nonspecific symptoms (e.g., headache). while symptoms numbered 1-3 were considered allergic symptoms, symptoms 4 and 5 were classified as non-allergic, non-immunological reactions.

Study groups were classified on the presence or absence of a documented AAL. Patients were further classified with an AAL into 'β-lactam' and 'non-β-lactam' labels where β-lactam labels, penicillin, cephalosporin, carbapenem, or monobactam labels were subclassified.

Statistical Methods

Baseline characteristics are presented as counts and percentages for categorical variables related to the presence of antibiotic and β-lactam allergy labels (BL-AAL). Associations of sex, age group (0-5, 5-10, >10 years), specialty (medical, surgical, oncology), and principal diagnosis which was determined using the following criteria (minor medical - short term mild or moderate symptoms, rarely leading to serious complications; major medical - significant symptoms, requiring specialised medical care, with higher risk of serious complications; minor surgical - less complex with minimal risk, with shorter recovery period; major surgical - complex surgery with significant risk, with shorter recovery period; and oncology) with having AAL were analysed using logistic regression. Both univariate and multivariable (using stepwise deletion with a 5% significance level) prevalence odds ratios (POR) with 95% confidence intervals (95% CI) are reported.

The impact of an AAL (any antibiotic or β-lactam) on hospital outcomes was assessed. Cox proportional hazards regression analyzed hospital length of stay, with discharge considered the event and in-hospital deaths censored. Hazard ratios (HRs) with 95% confidence intervals (CIs) reflect the discharge rate of AAL patients relative to those without. Logistic regression was used for binary outcomes, including Medical Emergency Team (MET) calls, Intensive Care Admissions (ICU) admission, and 4-week readmissions including for infection, with odds ratios (ORs) and 95% CIs. Linear regression assessed the number of antibiotics prescribed, with mean differences and 95% CIs presented. Multivariable models were adjusted for significant demographic factors found to be independently significant after a stepwise selection process. Namely, Cox models of hospital length of stay are stratified by Speciality. Regression models are adjusted for age, sex and/or principal diagnosis if independently significant: Hospital stay and readmission outcomes adjusted for principal diagnosis; MET call and ICU admission outcomes adjusted for age and principal diagnosis; number of antibiotics prescribed adjusted for age, sex and principal diagnosis.

Log-binomial regression was used to explore potential associations between antibiotic allergy status (any antibiotic allergy label, any β-lactam allergy label, and any penicillin allergy label) and receipt of antibiotics categorized within broad spectrum groupings: penicillins, quinolones, cephalosporins, aminoglycosides, lincosamides, nitroimidazole, macrolides, glycopeptides, and carbapenems. Risk ratios (RRs) with 95% CIs are presented. Specific antibiotic use within the broad-spectrum groupings is presented descriptively.

Statistical analysis was undertaken using SPSS statistical software (IBM SPSS Statistics, Armonk, NY) and via the R environment for statistical computing [21] (https://www.R-project.org/).

Ethical Approval

Ethical Approval was granted by the Child and Adolescent Health Service Human Research Ethics Committee (RGS3057) and Reciprocal Approval was granted by Edith Cowan Human Research Ethics Committee (2019-00279).

Results

Demographic and cohort characteristics

A total of 1590 patients were analysed, and Table 1 outlines the demographics of these patients, identified by any antibiotic allergy label or β-lactam allergy label. In total, 59% were male and the mean age was 5.7 years (range 0-19 years) with 49% under five years. The specialities were divided into general medical (50.2%), general surgical (41.0%), and oncology (8.8%); with principal diagnosis defined as minor surgical (28.8%), major surgical (5.8%), minor medical (33.4%), major medical (25.5%) and oncology (6.5%)[19]. Length of stay had a median (interquartile range) of 6 (4-11) days.

All 1590 patients were receiving at least one antibiotic (mean number of antibiotics 2.2, SD 1.32). Route of administration was intravenous antibiotics in 82.9% of patients, oral antibiotics in 15.9% and topical, inhaled, or intramuscular in 1.1%. The prescribed antibiotics were penicillins (71.1%), cephalosporins (48.3%), glycopeptides (27.5%), aminoglycosides (13.4%), carbapenems (7.3%), sulfamethoxazole/trimethoprim (7.0%), and macrolides (6.5%).

Antibiotic allergy labels

Antibiotic allergy labels were reported in 105 of patients (6.6% of cohort: 7.9% of female patients and 6.5% of male patients; Table 1). Of these, eighty (76.1%) patients reported one antibiotic allergy, 20 (19.0%) reported two, and 5 (4.8%) reported multiple allergies (range 3-5). β-lactam antibiotics were the most reported allergy with 79.0% (n=83) of patients reporting penicillin allergy and 20.9% (n=22) reporting a cephalosporin allergy. Non-β-lactam allergy was reported in 23.8% (n=25) of labelled patients, with vancomycin the most reported at 12.3% (n=13) and sulfamethoxazole/trimethoprim at 6.6% (n=7) (Figure 1). Most reported reactions for the 105 with an AAL were rash 70.5%, gastrointestinal upset 11.4%, angioedema 6.6%, with only 2.8% reported anaphylaxis. Mild non-specific symptoms listed as 'other' were reported in 32% of patients and in 21% of cases more than one symptom was reported.

The association of age and sex with antibiotic allergy labels

The odds of observing AAL at admission increased with increasing age at admission (Table 2; OR [95% CI] 5-9.99 years vs 0-4.99 years: 2.89 [2.44-6.64]; OR [95% CI] >10 years vs 0-4.99 years: 4.02 [9.66-5.03]; $p<0.001$), in line with the increasing prevalence (ages 0-4.99 years 3.1%, 5-9.99 years 8.5%, ≥10 years 11%). This association remained statistically significant after adjusting for principal diagnosis (Table 2; OR [95% CI] 5-9.99 years vs 0-4.99 years: 3.34 [1.90-5.89]; OR [95% CI] >10 years vs 0-4.99 years: 5.24 [3.13-8.79]; $p<0.001$). β-lactam allergy, was particularly observed relatively more frequently with increasing age (Table 2; OR [95% CI] 5-9.99 years vs 0-4.99 years: 2.9 [1.5-5.2]; OR [95% CI] >10 years vs 0-5 years: 4.0 [2.4-6.6]). Observed rates of antibiotic allergy were similar for males and females.

The association with admitting speciality or principal diagnosis and antibiotic allergy labels

Prevalence of AAL differed across specialties with an AAL more likely to be noted for oncology admissions and relatively fewer labels recorded for general surgical admissions (general surgical 4.5%, general medical 7.5%, oncology 11.4%), however, this relationship did not remain after adjusting for age, sex and principal diagnosis (Table 2). In terms of principal diagnosis, patients with a principal diagnosis of oncology were more likely to be labelled compared to those with a diagnosis of major surgical (POR, 4.66; 95% CI 1.29-16.8; $p=0.02$). This remained significant after adjustment for age and sex (POR, 3.62; 95% CI 0.98-13.4; $p=0.05$; Table 2).

The association of antibiotic allergy labels with antibiotic prescriptions

Overall rates of broad spectrum (restricted) antibiotic prescriptions varied significantly across the allergy groupings (Table 3, Online Repository Table E1, $p<0.001$). Compared to patients with no AAL, patients with any AAL were more likely to receive second-line antimicrobials such as quinolones ($p<0.001$), aminoglycosides ($p<0.001$), lincosamides ($p=0.001$), and metronidazole ($p=0.015$), as well as more likely to be prescribed a broad-spectrum cephalosporin ($p<0.001$). In contrast, children without an AAL received more β-lactam antibiotics including benzylpenicillin and piperacillin/tazobactam (Table 3, Figure 2). Of note, differential rates of second-line antimicrobial and cephalosporin prescription were more marked in comparisons of β-lactam allergy label versus no BL-AAL (Table 3, Figure 2).

The association of antibiotic allergy labels with prolonged hospital stay

Hospital lengths of stay for children with an AAL (median [IQR] 7.0 [4.0, 15.0] days) were marginally longer than for children with no AAL (median [IQR] 5.0 [3.25, 11.0] days) and similarly for children with a β-lactam allergy label (median [IQR] 7.0 [4.0, 16.0] days) compared to children with no AAL (median [IQR] 5.0 [3.25, 11.0] days) (Table 4 and Online Repository Table E2: Hazard Ratio (HR) adjusted for age and specialty: AAL vs no AAL HR 0.79, 95% CI 0.65, 0.97, p=0.02; BL-AAL vs no BL-AAL HR 0.79, 95% CI 0.64, 0.99, p=0.04). We have endeavoured to address potential biases by stratification and covariate adjustment of the Cox models. Analyses for any antibiotic allergy label or any beta-lactam allergy label indicate variable levels of association between antibiotic labelling and length of hospital stay across the different subgroups (speciality, principal diagnosis, age, sex), with longer duration of stay for the labeled children more evident in those subgroups where antibiotic labelling predicted greater odds for receiving a reserved antimicrobial (Online Repository Figure E2 and Table E3). The association of antibiotic allergy labelling with duration of hospital admission lost significance when additionally considering the relationship between antibiotic prescription and duration, with children receiving a broad-spectrum antibiotic staying for significantly longer times (p<0.001). Notably, patients prescribed a reserved antimicrobial had a statistically significantly longer length of hospital stay than patients not receiving a broad-spectrum antibiotic (adjusting for age and specialty HR 0.45, 95% CI 0.40-0.51).

The association of antibiotic allergy labels and clinical outcomes

Approximately 12% of children were readmitted to hospital, with half of the readmissions related to infection. There was no association between antibiotic labelling and risk of readmission within 4 weeks post discharge for any reason (any AAL vs no AAL: OR 0.78, 95% CI 0.36-1.56, p=0.5) nor for risk of 4-week readmission for infection (AAL vs no AAL: OR 0.86, 95% CI 0.24-2.34, p=0.8). There were also no significant associations noted with either any allergy labeling or β-lactam labelling in terms of a MET Call during admissions and ICU admissions, nor the amount of antibiotics prescribed to each group (p≥0.4, Table 4 and Online Repository Tables E4-E8).

Comparative analysis of between AMS and General Inpatient children

We undertook systematic comparative analysis of this study focusing on AMS patients and our previous study from 2018, reporting on the general inpatient population[19]. Key demographic differences were that general inpatients had a higher percentage of patients admitted under general surgery (52.2% vs. 41.0%; p<0.001), whereas the AMS cohort saw significantly more patients admitted under general medicine (50.2% vs. 26.6%; p<0.001). Oncology admissions were also slightly higher in the second cohort (8.8% vs. 6.2%; Online Repository Table E9). Both studies reported a significant increase of AAL reporting with increasing age at admission with the general inpatient study >10 years vs 0-5 year (OR 2.82; 95% CI 1.67-4.78; p<0.001) and the latter >10 years vs 0-5 years (OR 5.24; 95% CI 3.13-8.79; p<0.001); the AMS cohort also found significant increase for the <10 years groups (5-9.99 years vs 0-4.99 years: OR 2.89; 95% CI 2.44-6.64; p<0.001: Online Repository Table E9). β-lactam antibiotics were the most commonly reported antibiotic allergy in both cohorts (85.2%; 79.0%), with penicillin being the most frequent, followed by cephalosporins. The AMS cohort reported significantly higher unspecified penicillin allergies (OR 2.788, 95% CI 1.315–6.434, p=0.004) and allergies to piperacillin-tazobactam (OR 5.005, 95% CI 1.885–16.734, p<0.001), while general inpatient had more penicillin V allergies (OR 0.029, 95% CI 0.001–0.175, p<0.001; Figure 3).

In the earlier general inpatient study we reported that only 0.3% of children with a reported AAL had more than one AAL. In the AMS cohort, this had risen to 19.0%, with 4.7% reporting more than two allergies. Both studies found a significant relationship between antibiotic allergy labels (AALs) and alternative prescribing, with similar classes of antibiotics prescribed. Patients with AALs received more macrolides (p=0.045[1]), aminoglyclosides (p<0.001[2]) quinolones (p=0.01[1]; p<0.001[2]), lincosamides (p<0.001[1]; p=0.001[2]), and nitroimidazoles (p=0.009[1]; p=0.015[2]) than those without AALs. Of note, the AMS cohort reported a higher use of different antibiotics within those classes. (Online Repository Tables E10-E11). Both studies, after adjusting for age, sex, principal diagnosis and speciality, found those patients with an AAL were associated with an increased length of stay, for general inpatients 5 days versus 3.8 days(OR 1.59; 95% CI 1.03-2.28; p=0.04), compared with the AMS cohort 7 days versus 5 days (HR 0.79, 95% CI 0.65, 0.97, p=0.02; Online Repository Table E12)

<u>Discussion</u>

This is the first study to examine the impact of AAL in hospitalised children who were reviewed by an AMS programme. Children, managed under the AMS, differ from general medical inpatients, as they all received antibiotics during their admission, and often have needs for more complex and prolonged antimicrobial therapies, while commonly having fewer therapeutic options[22].

Antibiotic allergies were recorded in 6.6% of children within this cohort, which is higher to the 5.3% reported in our previous study.[19] This compares with internationally reported prevalence in children of around 5%, but is significantly lower than AAL reporting in the adult population reported at between 5-35%.[20] In our paediatric AMS study β-lactam antibiotics were the most reported allergy with penicillin allergy reported in 84% of patients, whereas only 23% of patients reported a non β-lactam allergies. This is comparable with national and international data [13, 19, 23] where paediatric inpatients have a higher prevalence of β-lactam allergy than adults. A high proportion of AMS patients were admitted under general medical specialites compared to our previous study of general inpatients. This could be attributed that antimicrobial prescriptions are enriched within a medical cohort which include neonates, immunocompromised children, children with underlying complex conditions and critical care patients. [25]

We observed an increase of antibiotic allergy labels with age, our previous study demonstrated an increase in antibiotic allergy labels in >10 years, while this current study shows this trend across all age groups. The increase of these labels within these age groups may hinder appropriate antimicrobial selection in a cohort with fewer therapeutic options available, potentially resulting in suboptimal treatment regimens and subsequent adverse events.[2, 3, 19] It is also reported within the literature that antibiotic allergy is more prevalent in female patients in all antibiotic classes and age groups apart from the first decade of life where more boys than girls carry AAL.[11] However, within our cohort, no gender effect was seen, which may be due to a smaller sample size, or may be because higher rates of reporting in the female adult population is due to higher rates of antibiotic utilizations or other biological factors that emerge in adulthood.[19]

Alternative prescribing has been widely reported within adult populations with approximately 50% of patients with AAL having poorer concordance with prescribing patterns than those without and higher use of restricted antibiotics,[8, 22] however there is limited data in paediatrics. Naurekas et al. (2023) found that children with osteomyelitis and a penicillin allergy were more likely to be prescribed clindamycin instead of a first-generation cephalosporin, despite high clindamycin resistance and recommendations for cefazolin. Similarly, Joerger et al. (2023) reported that children with antibiotic allergies and respiratory infections were more often given broad-spectrum antibiotics and had a higher chance of returning to the hospital due to adverse events. [26, 27] Antimicrobial resistance is an emerging global threat and children are becoming increasingly affected.[2] Our study is novel in that the focus is children reviewed under AMS, which aims to reduce inappropriate antibiotic use, preserve therapeutic options, and decrease antibiotic resistance. We found that AAL significantly influenced prescribing practices, with children who had AAL being much more likely to be prescribed restrictive alternatives such as quinolones, lincosamides, aminoglycosides, and metronidazole. They were also more frequently given broad-spectrum cephalosporins, while children without AAL were more likely to receive β-lactam antibiotic. Compared to the study by Lucas et al. (2018) conducted in a general inpatient cohort, our findings revealed similar alternative antibiotic classes prescribed. However, the AMS cohort showed a higher use of specific antibiotics within those classes.[19] Variance in alternative antibiotic use in adults and children may be influenced by many factors including adults being more likely to have multiple AAL, reducing prescribing options, therefore the higher incidence of multiple allergies reported within this cohort may have influenced this greater utilisation, as seen in adults.[11]

In our pediatric cohort, antibiotic allergy labels were associated with longer hospital stays, with children labeled as allergic to beta-lactams staying a median of 7.0 days compared to 5.0 days for those without such labels. This increase was significantly greater than that reported by Lucas et al. (2018) in a general inpatient population (mean 5.0 days vs. 3.8 days; p<0.001) together with similar findings reported by Sousa-Pinto et al. (2018), who observed a difference of 5.0 versus 4.0 days (p=0.03).[28] Whilst the reasons for increased lengths of stay remains unclear it could be attributed to such alternative antibiotic use in these children, where the antibiotics may be less effective or have more adverse reactions. However, we also found a correlation with children prescribed broad-spectrum antibiotics showing significantly longer stays (p<0.001) which has not previously been reported (Online Repository Figure E2).

Whilst a correlation between AAL and readmission rates at 4 weeks and 6 months has been widely reported in adult studies [20] it has not been observed in the paediatric population.[13, 19, 23] Our study concurs with current paediatric data and we found there was no correlation between AAL and readmission at 4 weeks or 6 months within our cohort. This may be due to paediatric patients having lower readmission rates than adults generally.[19] We also found there was no increase in MET Calls during admission or ICU admissions for patients with AAL (Table 4 and Online Repository Tables E4-E8). Kaminsky et al. (2023) conducted a matched cohort study on children with pneumonia and found that, in addition to the previously observed alternative prescribing patterns, children with an AAL were more likely to be hospitalized, require intensive care, and experience respiratory failure. This suggests that the pediatric population may be showing trends similar to those reported in adults.[29]

Over 90% of our cohort reported mild to moderate IgE and non-IgE mediated reations, the majority of which were rashes, with less than 3% reporting an anaphylaxis. These reactions can often be attributed to a bacterial or viral infection and not the antibiotic prescribed.[18]

Diagnostic assessment and identification is paramount in children, and the process of removing AAL is now acknowledged as a vital element of AMS initiatives which aim to minimize inappropriate antibiotic usage and safeguard therapeutic choices.[23, 30] Until recently, diagnostic guidelines for assessing β-lactam allergy in children were based on adult data. However, emerging studies show that children with low-risk historical reactions to an oral, but not intravenous, penicillin can be safely and accurately delabeled through direct oral provocation challenges.[31] Lucas et al. (2024) concured that skin testing did not aid the diagnosis of beta-lactam antibiotic allergy in children and those with an immediate and non-immediate history of reaction, excluding anaphylaxis and SCAR, can be safely delabeled through direct oral challenge. Mill et al. (2016) found that over 90% of children with a mild history of oral amoxicillin reactions were safely delabeled using this method. Labrosse et al. (2020) and Ibanez et al. (2023) agreed, noting that routine skin tests are poor predictors of β-lactam allergy in children [33-35]

In our AMS cohort, 47/76 patients (61%) had mild reactions to oral penicillin, and 29/76 (39%) to intravenous penicillin. By contrast, Lucas et al. (2018) in a general inpatient population found that 55/62 patients (89%) reacted mildly to oral penicillin, with only 2/62 (3%) reacting to IV penicillin (Figure 3). Furthermore, multiple AALs were previously rare, with only 0.3% of children reporting more than one allergy in 2018, but in this study, 19% reported at least two allergies, and 4.7% had multiple. This indicates more complex antibiotic allergies in the AMS cohort, making direct oral challenges and delabeling less feasible and highlighting the need for specialised allergy services.[19]

There are limitations to this study as it was a single centre, retrospective study using medical chart review, which relies on accurate data collection from staff during admission. Using reported allergy documentation from charts to classify reactions can be inaccurate, however, gathering data from multiple sources such as medical charts, records, and allergy notification forms enabled cross-referencing and verification. Although our study was performed at a single centre, it is the sole tertiary paediatric centre for the entire state of Western Australia, serving a population of 2.95 million. In relation to the length of stay data which shows a marginally significant increase for those with an allergy label and we have addressed potential biases by stratification and covariate adjustment of the Cox models, however, we acknowledge there may still be residual confounding (see Online Repository Figure E2).

This is the first study to examine the negative impact of AAL for children reviewed under the AMS programe. We identified key difference between this AMS study and previously reported studies, addressing AAL impact, in general paediatric cohort. Early identification and assessment of AAL could improve the healthcare of children reviewed under AMS and should be a primary focus for paediatric delabeling services. The incidence of these labels in children has risen over the past decade, often persisting into adulthood. Proper assessment of AAL in childhood can ensure lifelong benefits and that children enter adulthood either label-free or with a clear understanding of their allergy, improving access to optimal antimicrobial treatment and reducing the clinical and economic impact throughout their healthcare jouney.

Declaration of generative AI and AI-assisted technologies in the writing process

During the preparation of this work the authors used AI, in order to improve English and rephrase some sentences to enhance readability and improve clarity. After using this tool, the authors reviewed and edited the content as needed and take full responsibility for the content of the publication.

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Figure 1. Antibiotic Allergy Labels

Figure 2. Bar plots of the proportion of patients taking different antibiotic groups categorized by antibiotic allergy label, with p-values

Figure 3. Comparison of Reported Antibiotic Allergies Between the Studies

TABLE 1. Demographic summaries categorised by any antibiotic or β-lactam allergy label.

Variable	Overall	No antibiotic allergy label	Any antibiotic allergy label	Any β-lactam allergy label
	(n= 1590)	**(n = 1485)**	**(n = 105)**	**(n = 86)**
Age, mean (SD) years	5.7 (5.2)	5.5 (5.1)	7.4 (4.8)	9.0 (4.8)
Age group, n (%)				
0-4.99 y	782 (49.2)	758 (96.9)	24 (3.1)	18 (2.3)
5-9.99 y	357 (22.5)	327 (91.5)	30 (8.5)	23 (6.5)
>10 y	451 (28.3)	400 (88.7)	51 (11.3)	45 (10.0)
Sex, n (%)				
Female	654 (41.1)	606 (92.7)	48 (7.3)	37 (5.7)
Male	936 (58.9)	879 (94.0)	57 (6.0)	49 (5.2)
Speciality, n (%)				
General Medical	798 (50.2)	738 (92.5)	60 (7.5)	50 (6.3)
General Surgical	652 (41.0)	623 (95.5)	29 (4.5)	24 (3.7)
Oncology	140 (8.8)	124 (88.6)	16 (11.4)	12 (8.6)
Principle Diagnosis, n (%)				
Minor Surgical	458 (28.8)	441 (96.3)	17 (3.7)	12 (2.6)
Major Surgical	92 (5.8)	89 (96.7)	3 (3.3)	2 (2.2)
Minor Medical	531 (33.4)	485 (91.3)	46 (8.7)	40 (7.5)
Major Medical	406 (25.5)	381 (93.8)	25 (6.2)	22 (5.4)
Oncology	103 (6.5)	89 (86.4)	14 (13.6)	10 (9.7)

TABLE 2. Prevalence odds ratios from univariate and multivariable logistic regression modelling of demographic associations with presence of antibiotic allergy labelling at admission.

	Any antibiotic allergy label								Any β-lactam allergy label							
	Univariate				**Multivariate**				**Univariate**				**Multivariate**			
Variable	**POR**	**95% CI**	**Pairwise *P* value**	**Overall *P* value**	**POR**	**95% CI**	**Pairwise *P* value**	**Overall *P* value**	**POR**	**95% CI**	**Pairwise *P* value**	**Overall *P* value**	**POR**	**95% CI**	**Pairwise *P* value**	**Overall *P* value**
Age group				<0.001				<0.001				<0.001				<0.001
5-9.99 vs 0.4.99 y	2.89	1.66-5.03	<0.001		3.34	1.90-5.89	<0.001		2.92	1.55-5.48	0.001		3.49	1.84-6.65	<0.001	
>10 vs 0-4.99 y	4.02	2.44-6.64	<0.001		5.24	3.13-8.79	<0.001		4.70	2.68-8.23	<0.001		6.34	3.56-11.3	<0.001	
Sex																
Female vs Male	1.22	0.82-1.81	0.3			Not significant			1.08	0.70-1.68	0.7			Not significant		
Speciality				0.004		Not significant						0.02		Not significant		
General Medical vs General Surgical	1.75	1.11-2.76	0.02						1.75	1.06-2.88	0.03					
Oncology vs General Surgical	2.77	1.46-5.25	0.002						2.45	1.19-5.03	0.01					
Principle Diagnosis				< 0.001				<0.001				0.001				<0.001
Major Medical vs Major Surgical	1.95	0.57-6.59	0.3		1.89	0.55-6.49	0.3		2.58	0.59-11.16	0.2		2.53	0.58-11.1	0.2	
Minor Medical vs Major Surgical	2.81	0.85-9.24	0.09		2.23	0.67-7.46	0.2		3.67	0.87-15.43	0.08		2.89	0.68-12.4	0.2	
Minor Surgical vs Major Surgical	1.14	0.32-3.98	0.02		0.63	0.18-2.24	0.5		1.21	0.26-5.50	0.8		0.65	0.14-3.00	0.6	
Oncology vs Major Surgical	4.66	1.29-16.80	0.02		3.62	0.98-13.4	0.05		4.83	1.03-22.69	0.05		3.75	0.78-18.0	0.1	

CI, confidence interval; *POR* prevalence odds ratio

TABLE 3. Counts and percentages (along with risk ratios, 95% CI, and *P* values) of patients prescribed specific antibiotics, categorised by whether they were also labeled with an antibiotic, β-lactam or penicillin allergy labels.

Antibiotic received	**Any antibiotic label**					**Any β-lactam label**					**Penicillin label**				
	NAAL	**AAL**	**RR**	**95%CI**	**P**	**NBLAL**	**BLAL**	**RR**	**95%CI**	**P**	**NPAL**	**PAL**	**RR**	**95%CI**	**P**
	N = 1485	N = 105				N = 1504	N = 86				N = 1514	N = 76			
	n (%)	n (%)				n (%)	n (%)				n (%)	n (%)			
Penicillin	1088 (73.3)	43 (41.0)	0.56	0.43-0.69	<0.001	1103 (73.3)	28 (32.6)	0.44	0.32-0.59	<0.001	1111 (73.4)	20 (26.3)	0.36	0.24-0.50	<0.001
Amoxicillin	88 (5.9)	2 (1.9)				88 (5.9)	2 (2.3)				89 (5.9)	1 (1.3)			
Benzylpenicillin	179 (12.1)	1 (1.0)				179 (11.9)	1 (1.2)				180 (11.9)	0 (0.0)			
Flucloxacillin	158 (10.6)	8 (7.6)				161 (10.7)	5 (5.8)				163 (10.8)	3 (3.9)			
Piperacillin/ tazobactam	732 (49.3)	35 (33.3)				743 (49.4)	24 (27.9)				749 (49.5)	18 (23.7)			
Quinolone	73 (4.9)	16 (15.2)	3.1	1.80-4.97	<0.001	75 (5.0)	14 (16.3)	3.26	1.84-5.33	<0.001	76 (5.0)	13 (17.1)	3.41	1.88-5.62	<0.001
Ciprofloxacin	68 (4.6)	11 (10.5)				69 (4.6)	10 (11.6)				70 (4.6)	9 (11.8)			
Moxifloxacin	5 (0.3)	6 (5.7)				6 (0.4)	5 (5.8)				6 (0.4)	5 (6.6)			
Cephalosporin	707 (47.6)	61 (58.1)	1.22	1.01-1.43	0.022	713 (47.4)	55 (64.0)	1.35	1.12-1.57	<0.001	714 (47.2)	54 (71.1)	1.51	1.27-1.73	<0.001
Cefepime	25 (1.7)	10 (9.5)				26 (1.7)	9 (10.5)				26 (1.7)	9 (11.8)			
Ceftazidime	19 (1.3)	13 (12.4)				20 (1.3)	12 (14.0)				21 (1.4)	11 (14.5)			
Ceftriaxone	485 (32.7)	29 (27.6)				488 (32.4)	26 (30.2)				488 (32.2)	26 (34.2)			
Cephalexin	68 (4.6)	7 (6.7)				69 (4.6)	6 (7.0)				69 (4.6)	6 (7.9)			
Aminoglycoside	184 (12.4)	29 (27.6)	2.23	1.55-3.06	<0.001	190 (12.6)	23 (26.7)	2.12	1.41-2.99	<0.001	192 (12.7)	21 (27.6)	2.18	1.43-3.11	<0.001
Amikacin	4 (0.3)	2 (1.9)				4 (0.3)	2 (2.3)				4 (0.3)	2 (2.6)			
Gentamicin	132 (8.9)	3 (2.9)				133 (8.8)	2 (2.3)				133 (8.8)	2 (2.6)			
Tobramycin	48 (3.2)	24 (22.9)				53 (3.5)	19 (22.1)				55 (3.6)	17 (22.4)			
Lincosamide	82 (5.5)	13 (12.4)	2.24	1.23-3.73	0.004	83 (5.5)	12 (14.0)	2.53	1.36-4.25	0.001	85 (5.6)	10 (13.2)	2.34	1.18-4.09	0.006
Clindamycin	82 (5.5)	13 (12.4)				83 (5.5)	12 (14.0)				85 (5.6)	10 (13.2)			
Nitroimidazole	64 (4.3)	10 (9.5)	2.21	1.09-3.97	0.015	65 (4.3)	9 (10.5)	2.42	1.16-4.43	0.009	65 (4.3)	9 (11.8)	2.76	1.32-5.02	0.003
Metronidazole	64 (4.3)	10 (9.5)				65 (4.3)	9 (10.5)				65 (4.3)	9 (11.8)			
Macrolide	93 (6.3)	10 (9.5)	1.52	0.76-2.68	0.19	94 (6.2)	9 (10.5)	1.67	0.81-3.01	0.12	94 (6.2)	9 (11.8)	1.91	0.92-3.41	0.049
Azithromycin	90 (6.1)	9 (8.6)				90 (6.0)	9 (10.5)				90 (5.9)	9 (11.8)			
Glycopeptide	414 (27.9)	23 (21.9)	0.79	0.52-1.10	0.2	420 (27.9)	17 (19.8)	0.71	0.44-1.05	0.12	422 (27.9)	15 (19.7)	0.71	0.42-1.07	0.14
Vancomycin	414 (27.9)	23 (21.9)				420 (27.9)	17 (19.8)				422 (27.9)	15 (19.7)			
Carbapenem	107 (7.2)	9 (8.6)	1.19	0.57-2.14	0.6	108 (7.2)	8 (9.3)	1.3	0.60-2.39	0.46	110 (7.3)	6 (7.9)	1.09	0.44-2.17	0.84
Meropenem	107 (7.2)	9 (8.6)				108 (7.2)	8 (9.3)				110 (7.3)	6 (7.9)			

AAL, antibiotic allergy label; *BLAL*, β-lactam allergy label; *CI*, confidence interval; NAAL, no antibiotic allergy label; *NBLAL*, no β-lactam allergy label; *RR* risk ratio

Table 4. Antibiotic labelling as a predictor of clinical outcomes and other analyses.

		Univariate			Multivariate *		
		Effect measure	**95% CI**	**p-value**	**Effect measure**	**95% CI**	**p-value**
		HR			**HR**		
Hospital length of stay	AAL vs NAAL	0.84	0.69, 1.03	0.089	0.80	0.65, 0.97	0.026
	BLAAL vs NBLAAL	0.83	0.67, 1.03	0.091	0.80	0.64, 0.99	0.044
		OR			**OR**		
MET call during admission	AAL vs NAAL	0.65	0.04, 3.12	0.7	1.36	0.31, 4.06	0.6
	BLAL vs NBLAL	0.49	0.15, 1.19	0.2	1.07	0.17, 3.77	>0.9
ICU admission	AAL vs NAAL	0.50	0.17, 1.12	0.13	0.64	0.22, 1.51	0.4
	BLAL vs NBLAL	0.49	0.15, 1.19	0.2	0.63	0.19, 1.61	0.4
4-wk readmission	AAL vs NAAL	1.25	0.65, 2.23	0.5	0.78	0.36, 1.56	0.5
	BLAL vs NBLAL	1.03	0.47, 2.00	>0.9	0.72	0.29, 1.57	0.4
4-wk readmission with infection	AAL vs NAAL	1.45	0.55, 3.20	0.4	0.92	0.33, 2.17	0.9
	BLAL vs NBLAL	1.21	0.36, 3.05	0.7	0.86	0.24, 2.34	0.8
		Δ			**Δ**		
Number of antibiotics prescribed	AAL vs NAAL	0.02	-0.25, 0.28	0.9	0.05	-0.20, 0.30	0.7
	BLAAL vs NBLAAL	0.02	-0.27, 0.31	0.9	0.06	-0.21, 0.33	0.7

^ Cox models of hospital length of stay are stratified by Speciality.

* Regression models are adjusted for age, sex and/or principal diagnosis if independently significant: Hospital stay and readmission outcomes adjusted for principal diagnosis; MET call and ICU admission outcomes adjusted for age and principal diagnosis; Number of antibiotics prescribed adjusted for age, sex and principal diagnosis.

Abbreviations: *AAL*, antibiotic allergy label; *BLAL*, β-lactam allergy label; *NAAL*, no antibiotic allergy label; *NBLAL*, no β-lactam allergy label; *CI*, confidence interval; *HR*, hazard ratio, estimated by Cox regression; *OR*, odds ratio, estimated from logistic regression; Δ, difference in means, estimated by linear regression; *ICU*, intensive care unit.

Figure 1.

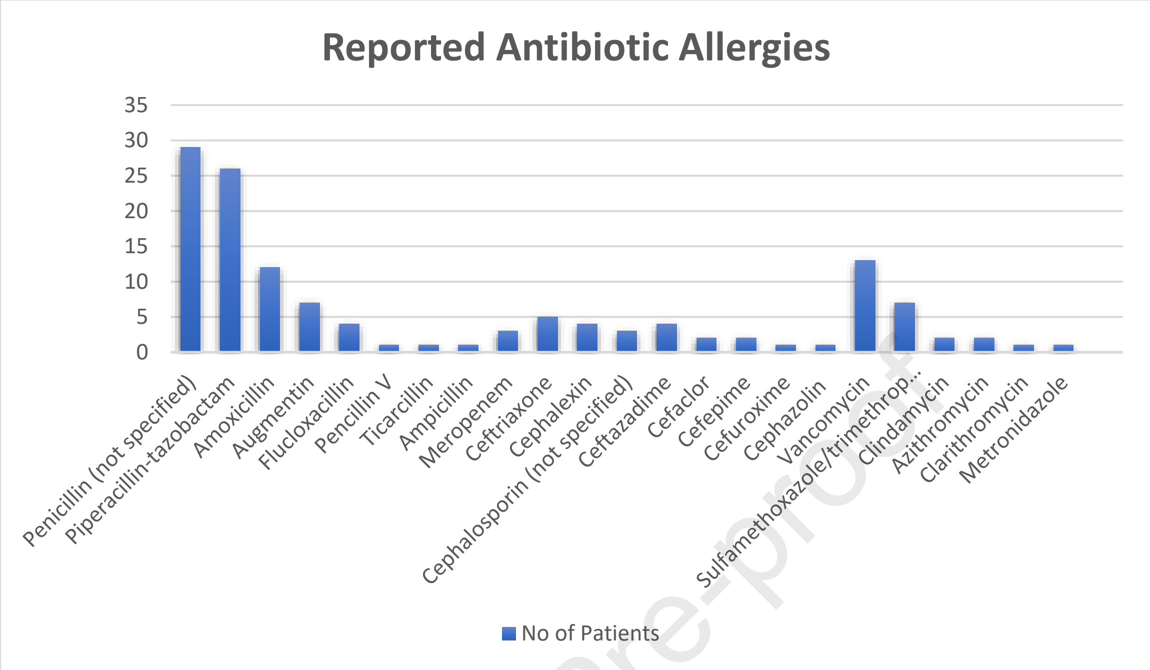

Reported Antibiotic Allergies
35
30
25
20
15
10
5
0
Penicillin (not specified)
Piperacillin-tazobactam
Amoxicillin
Augmentin
Flucloxacillin
Pencillin V
Ticarcillin
Ampicillin
Meropenem
Ceftriaxone
Cephalexin
Cephalosporin (not specified)
Ceftazadime
Cefaclor
Cefepime
Cefuroxime
Cephazolin
Vancomycin
Sulfamethoxazole/trimethrop...
Clindamycin
Azithromycin
Clarithromycin
Metronidazole
No of Patients

Figure 2

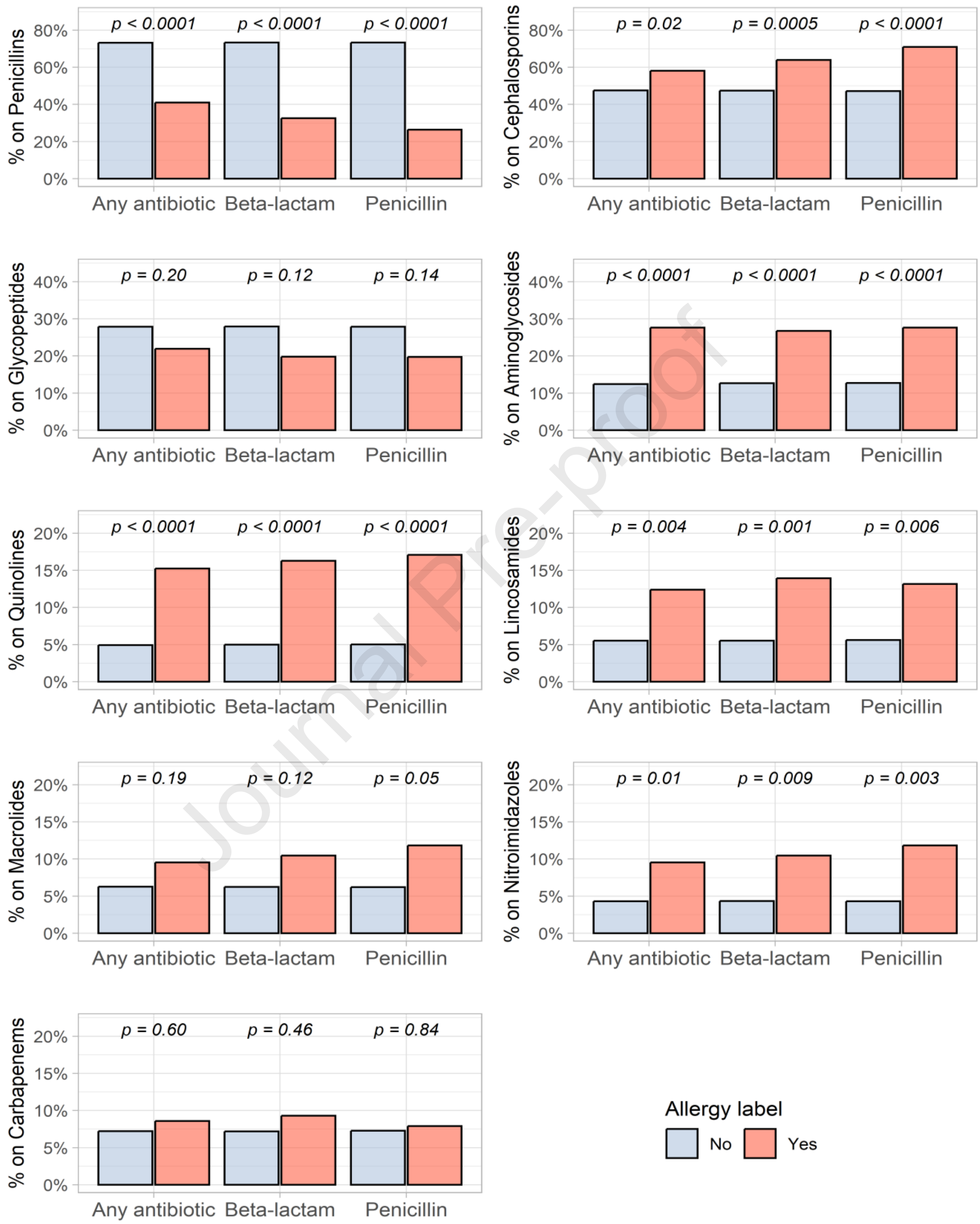
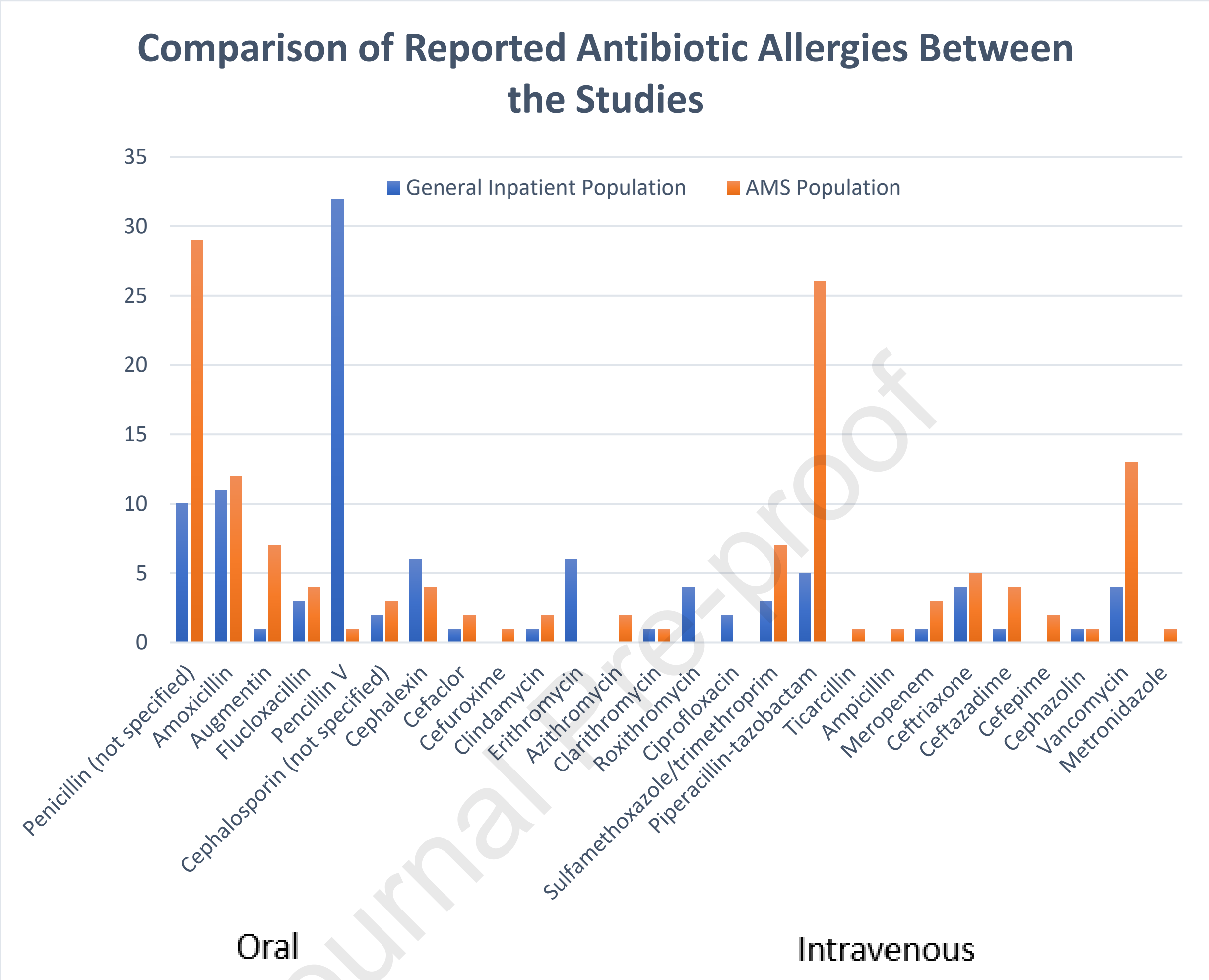
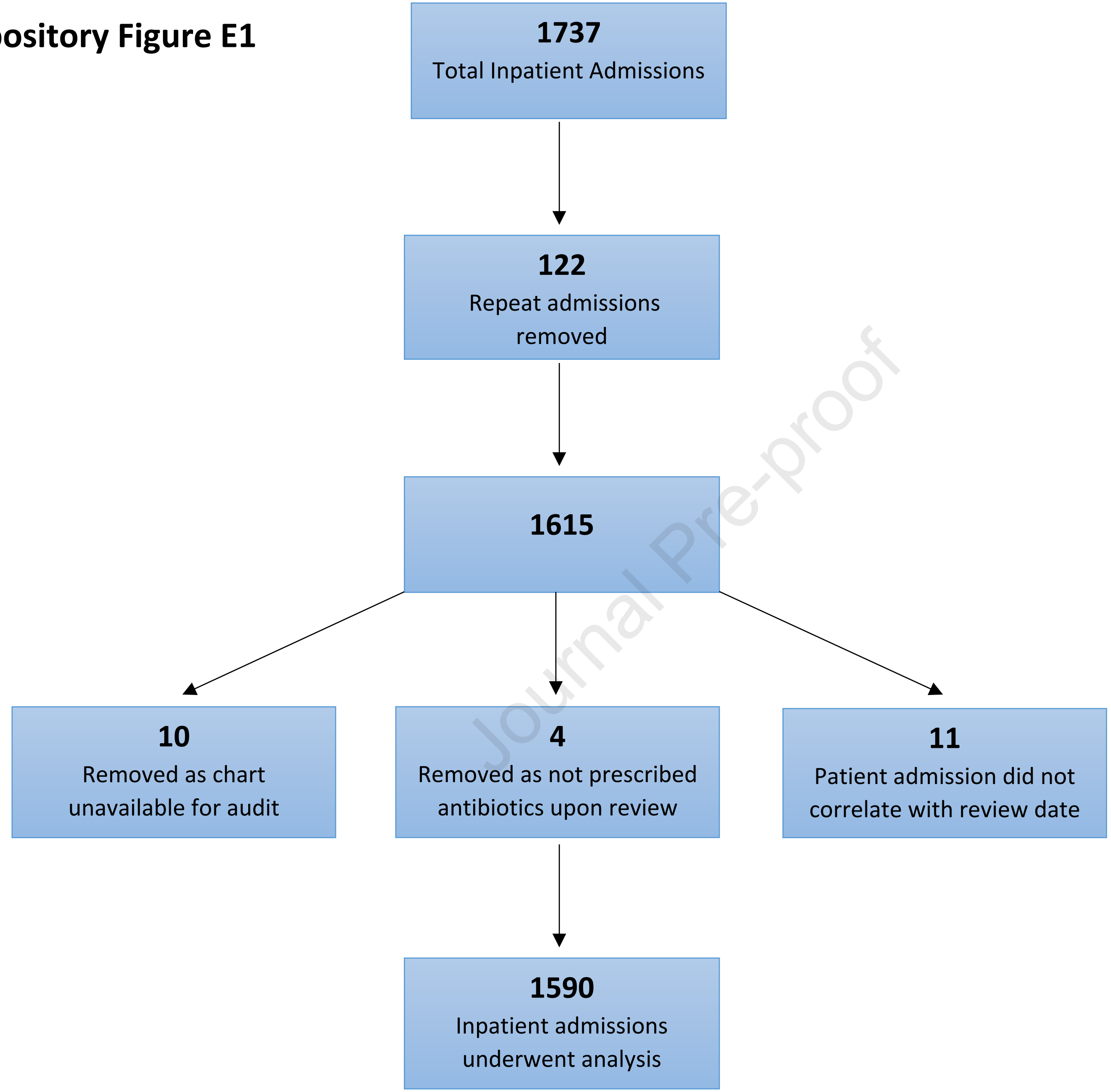

% on Penicillins
p < 0.0001
p < 0.0001
p < 0.0001
% on Cephalosporins
p = 0.02
p = 0.0005
p < 0.0001
% on Glycopeptides
p = 0.20
p = 0.12
p = 0.14
% on Aminoglycosides
p < 0.0001
p < 0.0001
p < 0.0001
% on Quinolines
p < 0.0001
p < 0.0001
p < 0.0001
% on Lincosamides
p = 0.004
p = 0.001
p = 0.006
% on Macrolides
p = 0.19
p = 0.12
p = 0.05
% on Nitroimidazoles
p = 0.01
p = 0.009
p = 0.003
% on Carbapenems
p = 0.60
p = 0.46
p = 0.84
Any antibiotic
Beta-lactam
Penicillin
Allergy label
No
Yes

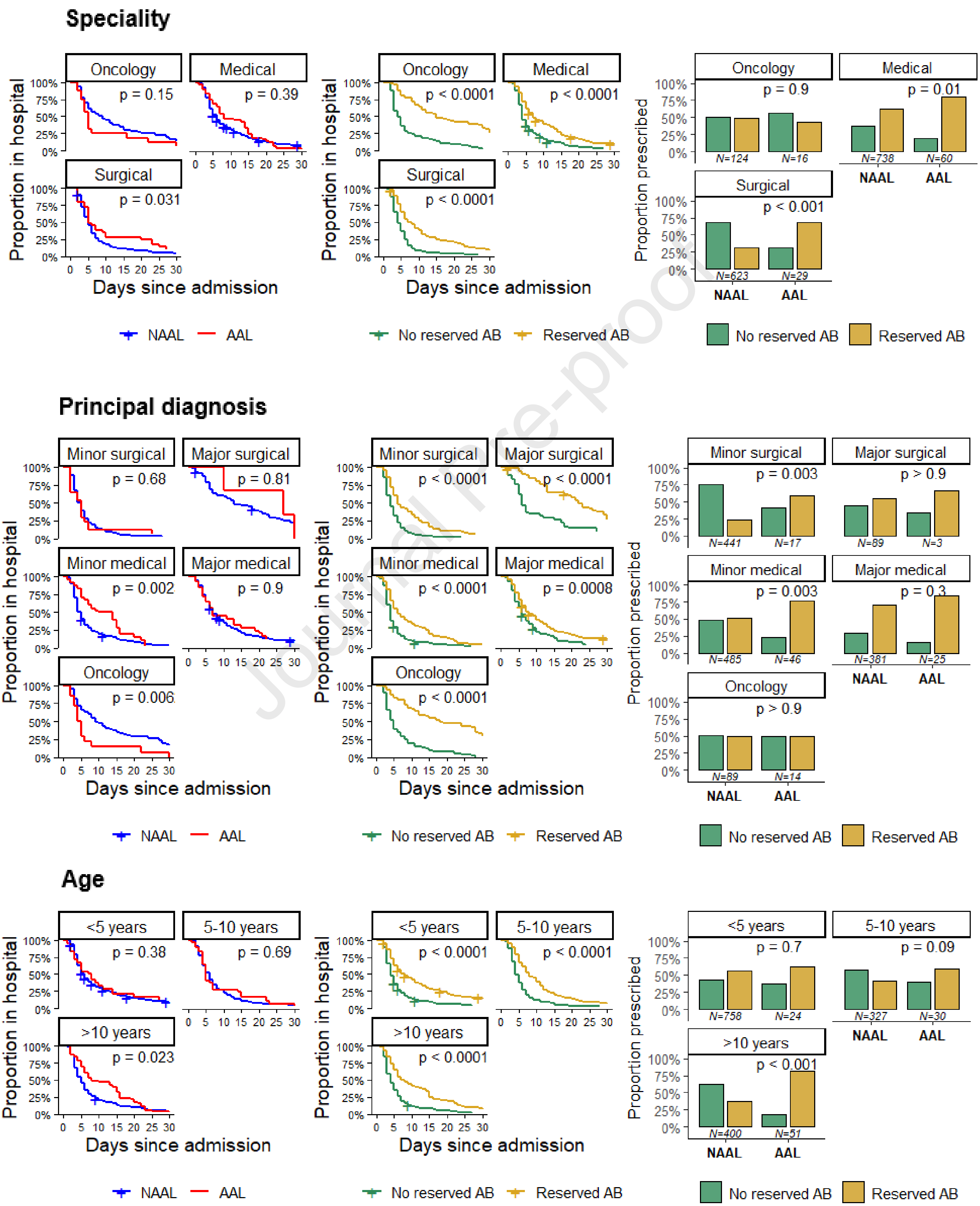
Figure 3

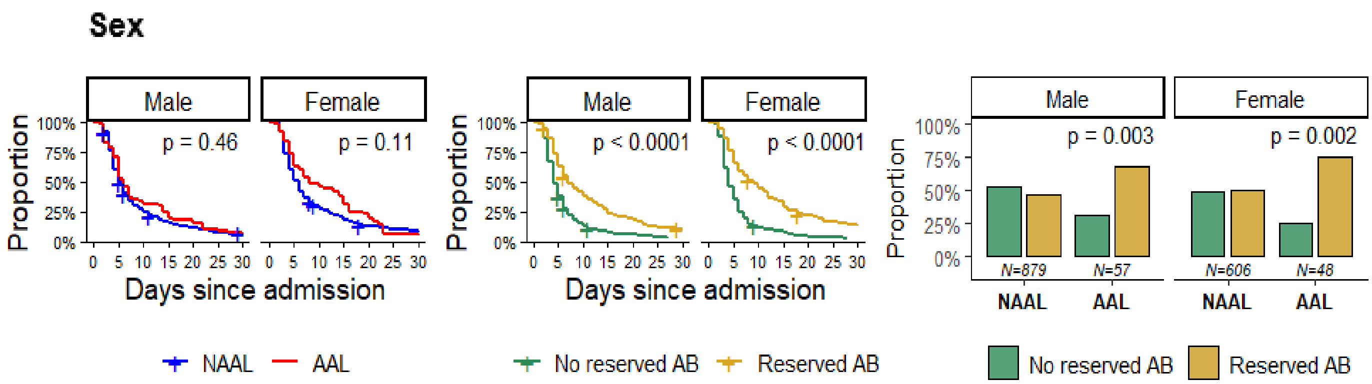

Comparison of Reported Antibiotic Allergies Between the Studies
General Inpatient Population
AMS Population
35
30
25
20
15
10
5
0
Penicillin (not specified)
Amoxicillin
Augmentin
Flucloxacillin
Pencillin V
Cephalosporin (not specified)
Cephalexin
Cefaclor
Cefuroxime
Clindamycin
Erithromycin
Azithromycin
Clarithromycin
Roxithromycin
Ciprofloxacin
Sulfamethoxazole/trimethroprim
Piperacillin-tazobactam
Ticarcillin
Ampicillin
Meropenem
Ceftriaxone
Ceftazadime
Cefepime
Cephazolin
Vancomycin
Metronidazole
Oral
Intravenous

Online Repository Figure E1



Online Repository Figure E2




Sex
Male
Female
p = 0.46
p = 0.11
Proportion
100%
75%
50%
25%
0%
0 5 10 15 20 25 30
Days since admission
NAAL
AAL
p < 0.0001
p < 0.0001
No reserved AB
Reserved AB
p = 0.003
p = 0.002
N=879
N=57
N=606
N=48

Online Repository Table E1. Full set of antibiotic prescription analyses that relate to Table 3

	Any Antibiotic Allergy					B-lactam Allergy					Penicillin Allergy				
AB	No	Yes	RR	CI	P	No	Yes	RR	CI	P	No	Yes	RR	CI	P
Amikacin	4 (0.3)	2 (1.9)	7.07	0.99-35.81	0.023	4 (0.3)	2 (2.3)	8.74	1.22-44.17	0.012	4 (0.3)	2 (2.6)	9.96	1.40-50.23	0.007
Amoxicillin	88 (5.9)	2 (1.9)	0.32	0.053-0.99	0.11	88 (5.9)	2 (2.3)	0.40	0.066-1.23	0.19	89 (5.9)	1 (1.3)	0.22	0.013-0.98	0.13
Azithromycin	90 (6.1)	9 (8.6)	1.41	0.68-2.56	0.30	90 (6.0)	9 (10.5)	1.75	0.84-3.15	0.092	90 (5.9)	9 (11.8)	1.99	0.96-3.56	0.036
Bactrim	102 (6.9)	9 (8.6)	1.25	0.60-2.25	0.51	104 (6.9)	7 (8.1)	1.18	0.51-2.26	0.66	105 (6.9)	6 (7.9)	1.14	0.46-2.28	0.75
Benzylpenicillin	179 (12.1)	1 (1.0)	0.079	0.0045-0.34	0.011	179 (11.9)	1 (1.2)	0.098	0.0056-0.42	0.02	180 (11.9)	0 (0.0)	-	-	-
Cefazolin	102 (6.9)	7 (6.7)	0.97	0.42-1.88	0.94	102 (6.8)	7 (8.1)	1.20	0.52-2.31	0.63	102 (6.7)	7 (9.2)	1.37	0.59-2.61	0.40
Cefepime	25 (1.7)	10 (9.5)	5.66	2.65-11.10	<0.001	26 (1.7)	9 (10.5)	6.05	2.75-12.03	<0.001	26 (1.7)	9 (11.8)	6.90	3.15-13.64	<0.001
Cefotaxime	76 (5.1)	0 (0.0)	-	-	-	76 (5.1)	0 (0.0)	-	-	-	76 (5.0)	0 (0.0)	-	-	-
Ceftazidime	19 (1.3)	13 (12.4)	9.68	4.80-18.89	<0.001	20 (1.3)	12 (14.0)	10.49	5.14-20.46	<0.001	21 (1.4)	11 (14.5)	10.43	5.02-20.42	<0.001
Ceftriaxone	485 (32.7)	29 (27.6)	0.85	0.60-1.13	0.30	488 (32.4)	26 (30.2)	0.93	0.65-1.26	0.67	488 (32.2)	26 (34.2)	1.06	0.75-1.42	0.72
Cefuroxime	1 (0.1)	0 (0.0)	-	-	-	1 (0.1)	0 (0.0)	-	-	-	1 (0.1)	0 (0.0)	-	-	-
Cephalexin	68 (4.6)	7 (6.7)	1.46	0.62-2.86	0.33	69 (4.6)	6 (7.0)	1.52	0.60-3.11	0.31	69 (4.6)	6 (7.9)	1.73	0.69-3.53	0.18
Ciprofloxacin	68 (4.6)	11 (10.5)	2.29	1.18-4.00	0.007	69 (4.6)	10 (11.6)	2.53	1.26-4.50	0.004	70 (4.6)	9 (11.8)	2.56	1.23-4.64	0.005
Clindamycin	82 (5.5)	13 (12.4)	2.24	1.23-3.73	0.004	83 (5.5)	12 (14.0)	2.53	1.36-4.25	0.001	85 (5.6)	10 (13.2)	2.34	1.18-4.09	0.006
Daptomycin	1 (0.1)	1 (1.0)	14.14	0.56-355.98	0.06	2 (0.1)	0 (0.0)	-	-	-	2 (0.1)	0 (0.0)	-	-	-
Ertapenem	1 (0.1)	1 (1.0)	14.14	0.56-355.98	0.06	1 (0.1)	1 (1.2)	17.49	0.70-439.76	0.042	2 (0.1)	0 (0.0)	-	-	-
Erythromycin	4 (0.3)	1 (1.0)	3.54	0.18-23.64	0.26	5 (0.3)	0 (0.0)	-	-	-	5 (0.3)	0 (0.0)	-	-	-
Flucloxacillin	158 (10.6)	8 (7.6)	0.72	0.33-1.32	0.34	161 (10.7)	5 (5.8)	0.54	0.20-1.15	0.17	163 (10.8)	3 (3.9)	0.37	0.092-0.93	0.078
Fosfomycin	1 (0.1)	0 (0.0)	-	-	-	1 (0.1)	0 (0.0)	-	-	-	1 (0.1)	0 (0.0)	-	-	-
Gentamicin	132 (8.9)	3 (2.9)	0.32	0.08-0.83	0.048	133 (8.8)	2 (2.3)	0.26	0.044-0.80	0.058	133 (8.8)	2 (2.6)	0.30	0.05-0.91	0.086
Isoniazid	3 (0.2)	0 (0.0)	-	-	-	3 (0.2)	0 (0.0)	-	-	-	3 (0.2)	0 (0.0)	-	-	-
Linezolid	4 (0.3)	0 (0.0)	-	-	-	4 (0.3)	0 (0.0)	-	-	-	4 (0.3)	0 (0.0)	-	-	-
Meropenem	107 (7.2)	9 (8.6)	1.19	0.57-2.14	0.60	108 (7.2)	8 (9.3)	1.30	0.60-2.39	0.46	110 (7.3)	6 (7.9)	1.09	0.44-2.17	0.84
Metronidazole	64 (4.3)	10 (9.5)	2.21	1.09-3.97	0.015	65 (4.3)	9 (10.5)	2.42	1.16-4.43	0.009	65 (4.3)	9 (11.8)	2.76	1.32-5.02	0.003

Moxifloxacin	5 (0.3)	6 (5.7)	16.97	5.19-58.04	<0.001	6 (0.4)	5 (5.8)	14.57	4.28-47.49	<0.001	6 (0.4)	5 (6.6)	16.60	4.88-53.97	<0.001
Rifampicin	10 (0.7)	0 (0.0)	-	-	-	10 (0.7)	0 (0.0)	-	-	-	10 (0.7)	0 (0.0)	-	-	-
Tazocin	732 (49.3)	35 (33.3)	0.68	0.50-0.87	0.005	743 (49.4)	24 (27.9)	0.56	0.39-0.77	0.001	749 (49.5)	18 (23.7)	0.48	0.30-0.69	<0.001
Teicoplanin	2 (0.1)	0 (0.0)	-	-	-	2 (0.1)	0 (0.0)	-	-	-	2 (0.1)	0 (0.0)	-	-	-
Tobramycin	48 (3.2)	24 (22.9)	7.07	4.44-10.94	<0.001	53 (3.5)	19 (22.1)	6.27	3.78-9.89	<0.001	55 (3.6)	17 (22.4)	6.16	3.63-9.82	<0.001
Vancomycin	414 (27.9)	23 (21.9)	0.79	0.52-1.10	0.20	420 (27.9)	17 (19.8)	0.71	0.44-1.05	0.12	422 (27.9)	15 (19.7)	0.71	0.42-1.07	0.14
Augmentin Duo	138 (9.3)	2 (1.9)	0.20	0.034-0.63	0.025	139 (9.2)	1 (1.2)	0.13	0.0072-0.55	0.038	140 (9.2)	0 (0.0)	-	-	-
Penicillin VK	9 (0.6)	1 (1.0)	1.57	0.086-8.25	0.67	10 (0.7)	0 (0.0)	-	-	-	10 (0.7)	0 (0.0)	-	-	-

AB, Antibiotic; *CI*, confidence interval; *P, P-values; RR, risk ratio*

Online Repository Table E2. Cox regression analyses of length of stay (LOS) at hospital

	Univariate			Multivariate Any Antibiotic Label			Multivariate β-lactam Label		
	HR	**95% CI**	**p-value**	**HR**	**95% CI**	**p-value**	**HR**	**95% CI**	**p-value**
Age			(0.001)						
5-10 yrs. vs >5 yrs.	1.20	1.06, 1.36	0.005		NS			NS	
>10 yrs. vs >5 yrs.	1.21	1.08, 1.36	0.001						
Sex									
Female	0.92	0.83, 1.01	0.086		NS			NS	
Principal Diagnosis			(<0.001)						
Major medical vs major surgical	1.47	1.17, 1.85	<0.001	1.48	1.18, 1.86	<0.001	1.48	1.18, 1.86	<0.001
Minor medical vs major surgical	2.16	1.73, 2.70	<0.001	2.21	1.77, 2.77	<0.001	2.21	1.77, 2.77	<0.001
Minor surgical vs major surgical	2.63	2.10, 3.30	<0.001	2.64	2.11, 3.31	<0.001	2.63	2.10, 3.31	<0.001
Oncology	1.27	0.96, 1.68	0.10	1.28	0.96, 1.69	0.088	1.28	0.96, 1.69	0.088
Any Antibiotic Allergy Label									
Yes vs No	0.84	0.69, 1.02	0.075	0.79	0.65, 0.97	0.022		NA	
Any β-lactam label									
Yes vs No	0.82	0.66, 1.02	0.077		NA		0.79	0.64, 0.99	0.038

HR = Hazard Ratio, CI = Confidence Interval

Results presented as hazard ratio (HR) and 95% confidence intervals. Note that hazard ratios below 1 indicate a longer duration of hospital stay relative to reference level, and hazard ratios above 1 indicate a shorter length of stay. NS – not significant following model selection, NA – not applicable as this variable was not considered in the multivariable analysis.

Table E3: Stratified analyses of duration of hospital stay and receipt of a reserved antimicrobial, with hazard ratios (HR < 1 corresponds to relatively longer duration) and odds ratios (OR > 1 corresponds to relatively increased prescription rates) respectively.

		Duration of hospital stay				Prescription of reserved AB	
Subgroup		**Hazard ratio AAL : NAAL**	**P^**	**Hazard ratio Reserved AB : No reserved AB**	**P^**	**Odds Ratio AAL : NAAL**	**P***
Specialty							
	Oncology	1.48 (0.87,2.49)	0.2	0.30 (0.21,0.44)	<0.001	0.80 (0.27,2.29)	0.8
	Medical	0.89 (0.68,1.15)	0.4	0.56 (0.48,0.64)	<0.001	2.35 (1.27,4.70)	0.05
	Surgical	0.66 (0.45,0.97)	0.03	0.45 (0.38,0.53)	<0.001	4.88 (2.24,11.45)	<0.001
Principal Diagnosis							
	Minor surgical	0.91 (0.55,1.50)	0.7	0.48 (0.39,0.60)	<0.001	4.57 (1.71,12.87)	<0.001
	Major surgical	0.87 (0.27,2.78)	0.8	0.35 (0.22,0.54)	<0.001	1.63 (0.15,35.88)	>0.9
	Minor medical	0.63 (0.46,0.85)	0.002	0.53 (0.44,0.63)	<0.001	2.97 (1.52,6.25)	0.02
	Major medical	0.97 (0.65,1.46)	0.9	0.69 (0.55,0.86)	<0.001	2.10 (0.78,7.34)	0.2
	Oncology	2.23 (1.25,3.98)	0.006	0.23 (0.15,0.37)	<0.001	1.02 (0.32,3.22)	>0.9
Age							
	<5 years	0.83 (0.55,1.25)	0.4	0.48 (0.41,0.55)	<0.001	1.26 (0.56,3.04)	0.6
	5-10 years	0.93 (0.64,1.36)	0.7	0.49 (0.40,0.61)	<0.001	2.05 (0.97,4.51)	0.1
	>10 years	0.71 (0.53,0.95)	0.02	0.49 (0.40,0.59)	<0.001	7.61 (3.77,17.10)	<0.001
Sex							
	Male	0.90 (0.69,1.18)	0.5	0.51 (0.45,0.58)	<0.001	2.46 (1.40,4.46)	0.009
	Female	0.78 (0.58,1.05)	0.1	0.44 (0.37,0.51)	<0.001	2.88 (1.51,5.88)	<0.001

Online Repository Table E4. Logistic regression results for MET call during current admission

	Univariate			**Multivariate Any Antibiotic Label***			**Multivariate β-lactam label***		
	OR[1]	**95% CI[1]**	**p-value**	**OR[1]**	**95% CI[1]**	**p-value**	**OR[1]**	**95% CI[1]**	**p-value**
Age			(0.002)						
5-10 yrs. vs <5 yrs.	0.32	0.11, 0.76	0.019	0.38	0.13, 0.94	0.055	0.39	0.13, 0.96	0.060
>10 yrs. v <5 yrs	0.31	0.11, 0.69	0.008	0.39	0.14, 0.92	0.045	0.40	0.15, 0.94	0.052
Sex									
Female v Male	1.45	0.79, 2.65	0.2		NS			NS	
Principal Diagnosis			(0.003)						
Major medical vs major surgical	1.62	0.54, 6.96	0.4	1.67	0.56, 7.20	0.4	1.68	0.56, 7.22	0.4
Minor medical vs major surgical	0.57	0.17, 2.58	0.4	0.65	0.19, 2.96	0.5	0.66	0.20, 2.99	0.5
Minor surgical vs major surgical	0.33	0.08, 1.62	0.13	0.50	0.12, 2.53	0.4	0.50	0.12, 2.51	0.4
Oncology vs major surgical	1.51	0.36, 7.55	0.6	1.84	0.43, 9.30	0.4	1.87	0.44, 9.47	0.4
Any Antibiotic Allergy Label									
Yes vs No	1.04	0.25, 2.91	>0.9	1.36	0.31, 4.06	0.6		NA	
Any β-lactam label									
Yes vs No	0.83	0.13, 2.75	0.8		NA		1.07	0.17, 3.77	>0.9

[1]*OR = Odds Ratio, CI = Confidence Interval*

* Regression models adjusted for age, sex and/or principal diagnosis if independently significant.

Online Repository Table E5. Logistic regression results for assessing predictors of PICU stay at current admission

	Univariate			Multivariate Any Antibiotic Label*			Multivariate β-lactam label*		
	OR[1]	**95% CI[1]**	**p-value**	**OR[1]**	**95% CI[1]**	**p-value**	**OR[1]**	**95% CI[1]**	**p-value**
Age			(<0.001)						
5-10 yrs vs <5 yrs	0.52	0.32, 0.82	0.006	0.79	0.47, 1.28	0.3	0.79	0.47, 1.27	0.3
>10 yrs v <5 yrs	0.37	0.22, 0.59	<0.001	0.54	0.32, 0.89	0.019	0.54	0.32, 0.89	0.018
Sex									
Female v Male	1.42	1.00, 2.01	0.048		NS			NS	
Principal Diagnosis			(<0.001)						
Major medical vs major surgical	0.40	0.24, 0.67	<0.001	0.40	0.24, 0.68	<0.001	0.40	0.24, 0.68	<0.001
Minor medical vs major surgical	0.10	0.05, 0.18	<0.001	0.11	0.06, 0.19	<0.001	0.11	0.06, 0.19	<0.001
Minor surgical vs major surgical	0.10	0.05, 0.19	<0.001	0.12	0.06, 0.23	<0.001	0.12	0.06, 0.23	<0.001
Oncology vs major surgical	0.13	0.05, 0.32	<0.001	0.15	0.05, 0.36	<0.001	0.15	0.05, 0.35	<0.001
Any Antibiotic Allergy Label									
Yes vs No	0.50	0.17, 1.12	0.13	0.66	0.22, 1.55	0.4		NA	
Any β-lactam label									
Yes vs No	0.49	0.15, 1.19	0.2		NA		0.65	0.19, 1.67	0.4

[1]*OR = Odds Ratio, CI = Confidence Interval*

* Regression models adjusted for age, sex and/or principal diagnosis if independently significant.

Online Repository Table E6. Logistic regression results for assessing predictors of 4-wk readmission

	Univariate			Multivariate Any Antibiotic Label*			Multivariate β-lactam label*		
	OR[1]	**95% CI[1]**	**p-value**	**OR[1]**	**95% CI[1]**	**p-value**	**OR[1]**	**95% CI[1]**	**p-value**
Age			(>0.9)						
5-10 yrs. vs <5 yrs.	1.04	0.69, 1.54	0.8		NS			NS	
>10 yrs. vs <5 yrs.	0.95	0.65, 1.38	0.8						
Sex									
Female v Male	0.94	0.68, 1.29	0.7		NS			NS	
Principal Diagnosis			(<0.001)						
Major medical vs major surgical	1.02	0.49, 2.31	>0.9	1.03	0.50, 2.34	>0.9	1.03	0.50, 2.35	>0.9
Minor medical vs major surgical	0.71	0.34, 1.61	0.4	0.72	0.35, 1.63	0.4	0.72	0.35, 1.64	0.4
Minor surgical vs major surgical	0.46	0.21, 1.07	0.056	0.46	0.21, 1.08	0.057	0.46	0.21, 1.08	0.058
Oncology vs major surgical	16.8	7.49, 41.2	<0.001	17.3	7.67, 42.6	<0.001	17.2	7.67, 42.4	<0.001
Any Antibiotic Allergy Label									
Yes vs No	1.25	0.65, 2.23	0.5	0.78	0.36, 1.56	0.5		NA	
Any β-lactam label									
Yes vs No	1.03	0.47, 2.00	>0.9		NA		0.72	0.29, 1.57	0.4

[1]*OR = Odds Ratio, CI = Confidence Interval*

* Regression models adjusted for age, sex and/or principal diagnosis if independently significant.

Online Repository Table E7. Logistic regression results for assessing predictors of 4-wk readmission with infection

	Univariate			Multivariate Any Antibiotic Label*			Multivariate β-lactam label*		
	OR	**95% CI**	**p-value**	**OR**	**95% CI**	**p-value**	**OR**[1]	**95% CI**	**p-value**
Age			(0.4)						
5-10 yrs. vs <5 yrs.	1.44	0.83, 2.46	0.2		NS			NS	
>10 yrs. vs <5 yrs.	1.28	0.75, 2.16	0.4						
Sex									
Female v Male	1.18	0.76, 1.84	0.5		NS			NS	
Principal Diagnosis			(<0.001)						
Major medical vs major surgical	2.52	0.72, 15.9	0.2	2.53	0.72, 16.0	0.2	2.53	0.73, 16.0	0.2
Minor medical vs major surgical	1.56	0.44, 9.91	0.6	1.56	0.44, 9.95	0.6	1.57	0.44, 9.98	0.6
Minor surgical vs major surgical	1.20	0.33, 7.73	0.8	1.20	0.33, 7.74	0.8	1.20	0.33, 7.75	0.8
Oncology vs major surgical	19.1	5.37, 122	<0.001	19.3	5.40, 124	<0.001	19.3	5.42, 124	<0.001
Any Antibiotic Allergy Label									
Yes vs No	1.45	0.55, 3.20	0.4	0.92	0.33, 2.17	0.9		NA	
Any β-lactam label									
Yes vs No	1.21	0.36, 3.05	0.7		NA		0.86	0.24, 2.34	0.8

[1]*OR = Odds Ratio, CI = Confidence Interval*

* Regression models adjusted for age, sex and/or principal diagnosis if independently significant.

Online Repository Table E8. Linear regression results assessing predictors of the number of antibiotics prescribed during admission

	Univariate			Multivariate Any Antibiotic Label*			Multivariate β-lactam label*		
	Δ	**95% CI**	**p-value**	**Δ**	**95% CI**	**p-value**	**Δ**	**95% CI**	**p-value**
Age			(<0.001)						
5-10 yrs. vs <5 yrs.	-0.59	-0.75, -0.43	<0.001	-0.38	-0.54, -0.22	<0.001	-0.38	-0.54, -0.22	<0.001
>10 yrs. vs <5 yrs.	-0.67	-0.82, -0.52	<0.001	-0.41	-0.56, -0.26	<0.001	-0.41	-0.56, -0.26	<0.001
Sex									
Female v Male	0.15	0.02, 0.28	0.029	0.13	0.01, 0.26	0.035	0.13	0.01, 0.26	0.034
Principal Diagnosis			(<0.001)						
Major medical vs major surgical	0.18	-0.10, 0.46	0.2	0.20	-0.08, 0.48	0.2	0.20	-0.08, 0.48	0.2
Minor medical vs major surgical	-0.44	-0.71, -0.16	0.002	-0.36	-0.63, -0.09	0.010	-0.36	-0.63, -0.09	0.010
Minor surgical vs major surgical	-1.0	-1.3, -0.73	<0.001	-0.82	-1.1, -0.53	<0.001	-0.82	-1.1, -0.53	<0.001
Oncology vs major surgical	-0.04	-0.39, 0.31	0.8	0.06	-0.29, 0.41	0.7	0.06	-0.29, 0.41	0.7
Any Antibiotic Allergy Label									
Yes vs No	0.02	-0.25, 0.28	0.9	0.05	-0.20, 0.30	0.7		NA	
Any β-lactam label									
Yes vs No	0.02	-0.27, 0.31	0.9		NA		0.06	-0.21, 0.33	0.7

***Δ** Difference in means, estimated by linear regression; CI = Confidence Interval*
* Regression models adjusted for age, sex and/or principal diagnosis if independently significant.

Table E9. Demographic summaries categorised by any antibiotic or β-lactam allergy label across both studies

	General Inpatient Population (2018)				AMS Population (2024)				
Variable	**Overall**	**No AAL**	**Any AAL**	**Any β-lactam allergy label**	**Overall**	**No AAL**	**Any AAL**	**Any β-lactam allergy label**	**Overall p-values**
	(n=1672)	**(n=1584)**	**(n=88)**	**(n=75)**	**(n= 1590)**	**(n = 1485)**	**(n = 105)**	**(n = 86)**	
Age group, n (%)									0.009
0-4.99 y	738 (44.1)	714 (96.8)	24 (3.3)	19 (2.6)	782 (49.2)	758 (96.9)	24 (3.1)	18 (2.3)	
5-9.99 y	435 (26.0)	416 (95.6)	19 (4.4)	18 (4.1)	357 (22.5)	327 (91.5)	30 (8.5)	23 (6.5)	
>10 y	499 (29.8)	454 (91.0)	45 (9.0)	38 (7.6)	451 (28.3)	400 (88.7)	51 (11.3)	45 (10.0)	
Sex, n (%)									0.67
Female	701 (41.9)	657 (93.7)	44 (6.3)	37 (5.3)	654 (41.1)	606 (92.7)	48 (7.3)	37 (5.7)	
Male	971 (58.1)	927 (95.5)	44 (4.5)	38 (3.9)	936 (58.9)	879 (94.0)	57 (6.0)	49 (5.2)	
Speciality, n (%)									<0.001
General Medical	444 (26.6)	428 (96.4)	16 (3.6)	15 (3.4)	798 (50.2)	738 (92.5)	60 (7.5)	50 (6.3)	
General Surgical	873 (52.2)	836 (95.8)	37 (4.2)	30 (3.4)	652 (41.0)	623 (95.5)	29 (4.5)	24 (3.7)	
Oncology	103 (6.2)	93 (90.3)	10 (9.7)	8 (7.8)	140 (8.8)	124 (88.6)	16 (11.4)	12 (8.6)	
Other	252 (15.1)	227 (90.1)	25 (9.9)	22 (8.7)	0	0	0	0	
Principle Diagnosis, n (%)									<0.001
Minor Surgical	645 (38.6)	611 (94.7)	34 (5.3)	26 (4.0)	458 (28.8)	441 (96.3)	17 (3.7)	12 (2.6)	
Major Surgical	68 (4.1)	67 (98.5)	1 (1.5)	1 (1.5)	92 (5.8)	89 (96.7)	3 (3.3)	2 (2.2)	
Minor Medical	678 (40.6)	647 (95.4)	31 (4.6)	29 (4.3)	531 (33.4)	485 (91.3)	46 (8.7)	40 (7.5)	
Major Medical	180 (10.8)	165 (91.7)	15 (8.3)	14 (7.8)	406 (25.5)	381 (93.8)	25 (6.2)	22 (5.4)	
Oncology	101 (6)	94 (93.1)	7 (6.9)	5 (5.0)	103 (6.5)	89 (86.4)	14 (13.6)	10 (9.7)	

Table E10. Counts and percentages (along with risk ratios, 95% CI and *P* values) of patients prescribed specific antibiotics, categorised by whether they were also prescribed with an antibiotic, β-lactam or penicillin allergy labels for General Inpatient Population

	Any Antibiotic Allergy					B-lactam Allergy					Penicillin Allergy				
	No	Yes	RR	CI	P	No	Yes	RR	CI	P	No	Yes	RR	CI	P
Penicillin															
Amoxicillin	185 (26.2)	3 (6.5)	0.25	0.08-0.75	0.003	187 (26.3)	1 (2.63)	0.10	0.01-0.69	0.001	188 (5.9)	1 (26.0)	Cannot Calculate*		0.003
Quinolone															
Ciprofloxacin	9 (1.3)	4 (8.7)	6.79	2.17-21.22	0.006	10 (1.4)	3 (7.9)	5.61	0.96-3.96	0.09	12 (1.7)	1 (4.0)	2.41	0.33-17.84	0.36
Ofloxacin	10 (1.4)	4 (8.7)	3.67	1.99-18.75	0.008	11 (1,5)	3 (13.2)	3.60	1.48-17.53	0.03	13 (1.8)	1 (4.0)	2.23	0.30-16.37	0.38
Cephalosporin															
Ceftriaxone	67 (9.4)	7 (15.2)	1.60	0.78-3.28	0.20	67 (9.4)	7 (18.4)	1.95	0.96-3.96	0.09	67 (9.2)	7 (28.0)	3.03	1.55-5.91	0.08
Lincosomide															
Clindamycin	11 (1.6))	7 (15.2)	9.73	1.58-8.49	0.009	12 (1.7)	6 (15.8)	9.36	3.71-23.57	<0.001	13 (1.8)	5 (20.0)	2.41	0.33-17.84	0.36
Nitromidazole															
Metronidazole	25 (3.6)	6 (13,0)	3.67	1.58-8.49	0.009	26 (3.6)	5 (13.2)	3.60	1.46-8.85	0.02	27 (3.7)	4 (16.0)	4.29	1.62-11.33	0.02
Macrolide															
Azithromycin	28 (4.0)	5 (10.9)	2,73	0.78-3.28	0.045	28 (3.9)	5 (13.2)	3.34	1.37-8.17	0.02	30 (4.1)	3 (12.0)	2.90	0.95-8.86	0.09

RR – Risk Ratio; CI – 95% Confidence Interval; P – *P*-value
*The RR cannot be calculated with an entry of 0

Table E11. Counts and percentages (along with risk ratios, 95% CI and P values) of patients prescribed specific antibiotics, categorised by whether they were also prescribed with an antibiotic, β-lactam or penicillin allergy labels for AMS Population.

	Any Antibiotic Allergy					B-lactam Allergy					Penicillin Allergy				
	No	Yes	RR	CI	P	No	Yes	RR	CI	P	No	Yes	RR	CI	P
Penicillin															
Amoxicillin	88 (5.9)	2 (1.9)	0.32	0.053-0.99	0.11	88 (5.9)	2 (2.3)	0.40	0.066-1.23	0.19	89 (5.9)	1 (1.3)	0.22	0.013-0.98	0.13
Benzylpenicillin	179 (12.1)	1 (1.0)	0.079	0.0045-0.34	0.011	179 (11.9)	1 (1.2)	0.098	0.0056-0.42	0.02	180 (11.9)	0 (0.0)	-	-	-
Flucloxacillin	158 (10.6)	8 (7.6)	0.72	0.33-1.32	0.34	161 (10.7)	5 (5.8)	0.54	0.20-1.15	0.17	163 (10.8)	3 (3.9)	0.37	0.092-0.93	0.078
Piperacillin/ Tazobactam	732 (49.3)	35 (33.3)	0.68	0.50-0.87	0.005	743 (49.4)	24 (27.9)	0.56	0.39-0.77	0.001	749 (49.5)	18 (23.7)	0.48	0.30-0.69	<0.001
Quinolone															
Ciprofloxacin	68 (4.6)	11 (10.5)	2.29	1.18-4.00	0.007	69 (4.6)	10 (11.6)	2.53	1.26-4.50	0.004	70 (4.6)	9 (11.8)	2.56	1.23-4.64	0.005
Moxifloxacin	5 (0.3)	6 (5.7)	16.97	5.19-58.04	<0.001	6 (0.4)	5 (5.8)	14.57	4.28-47.49	<0.001	6 (0.4)	5 (6.6)	16.60	4.88-53.97	<0.001
Cephalosporin															
Cefepime	25 (1.7)	10 (9.5)	5.66	2.65-11.10	<0.001	26 (1.7)	9 (10.5)	6.05	2.75-12.03	<0.001	26 (1.7)	9 (11.8)	6.90	3.15-13.64	<0.001
Ceftazidime	19 (1.3)	13 (12.4)	9.68	4.80-18.89	<0.001	20 (1.3)	12 (14.0)	10.49	5.14-20.46	<0.001	21 (1.4)	11 (14.5)	10.43	5.02-20.42	<0.001
Ceftriaxone	485 (32.7)	29 (27.6)	0.85	0.60-1.13	0.30	488 (32.4)	26 (30.2)	0.93	0.65-1.26	0.67	488 (32.2)	26 (34.2)	1.06	0.75-1.42	0.72
Cephalexin	68 (4.6)	7 (6.7)	1.46	0.62-2.86	0.33	69 (4.6)	6 (7.0)	1.52	0.60-3.11	0.31	69 (4.6)	6 (7.9)	1.73	0.69-3.53	0.18
Aminoglycoside															
Amikacin	4 (0.3)	2 (1.9)	7.07	0.99-35.81	0.023	4 (0.3)	2 (2.3)	8.74	1.22-44.17	0.012	4 (0.3)	2 (2.6)	9.96	1.40-50.23	0.007
Gentamicin	132 (8.9)	3 (2.9)	0.32	0.08-0.83	0.048	133 (8.8)	2 (2.3)	0.26	0.044-0.80	0.058	133 (8.8)	2 (2.6)	0.30	0.05-0.91	0.086
Tobramycin	48 (3.2)	24 (22.9)	7.07	4.44-10.94	<0.001	53 (3.5)	19 (22.1)	6.27	3.78-9.89	<0.001	55 (3.6)	17 (22.4)	6.16	3.63-9.82	<0.001
Lincosomide															
Clindamycin	82 (5.5)	13 (12.4)	2.24	1.23-3.73	0.004	83 (5.5)	12 (14.0)	2.53	1.36-4.25	0.001	85 (5.6)	10 (13.2)	2.34	1.18-4.09	0.006
Nitomidazole															
Metronidazole	64 (4.3)	10 (9.5)	2.21	1.09-3.97	0.015	65 (4.3)	9 (10.5)	2.42	1.16-4.43	0.009	65 (4.3)	9 (11.8)	2.76	1.32-5.02	0.003
Macrolide															
Azithromycin	90 (6.1)	9 (8.6)	1.41	0.68-2.56	0.30	90 (6.0)	9 (10.5)	1.75	0.84-3.15	0.092	90 (5.9)	9 (11.8)	1.99	0.96-3.56	0.036
Glycopeptide															
Vancomycin	414 (27.9)	23 (21.9)	0.79	0.52-1.10	0.20	420 (27.9)	17 (19.8)	0.71	0.44-1.05	0.12	422 (27.9)	15 (19.7)	0.71	0.42-1.07	0.14
Carbapenem															
Meropenem	107 (7.2)	9 (8.6)	1.19	0.57-2.14	0.60	108 (7.2)	8 (9.3)	1.30	0.60-2.39	0.46	110 (7.3)	6 (7.9)	1.09	0.44-2.17	0.84

RR-Risk Ratio; CI – 95% Confidence Interval; P – p-value

Table E12**.** Antibiotic labelling as a predictor of clinical outcomes and other analyses across both studies

		General Inpatient Population (2018)						AMS Population (2024)					
		Univariate			Multivariate *			Univariate			Multivariate *		
Outcome	**Comparison**	**OR**	**95% CI**	**p-value**	**OR**	**95% CI**	**p-value**	**Effect measure**	**95% CI**	**p-value**	**Effect measure**	**95% CI**	**p-value**
								HR			**HR**		
Hospital length of stay	AAL vs NAAL	1.71	1.16-2.53	0.007	1.59	1.03-2.28	0.04	0.83	0.68, 1.02	0.070	0.79	0.65, 0.97	0.022
	BLAL vs NBLAL	1.90	1.24-2.89	0.003	1.62	1.05-2.50	0.03	0.82	0.66, 1.02	0.075	0.79	0.64, 0.99	0.040
								OR			**OR**		
MET call during admission	AAL vs NAAL	1.83	0.55-6.11	0.33	1.27	0.35-4.58	0.72	0.65	0.04, 3.12	0.7	1.36	0.31, 4.06	0.6
	BLAL vs NBLAL	2.18	0.65-7.30	0.21	1.47	0.41-5.36	0.56	0.49	0.15, 1.19	0.2	1.07	0.17, 3.77	>0.9
ICU admission	AAL vs NAAL							0.50	0.17, 1.12	0.13	0.64	0.22, 1.51	0.4
	BLAL vs NBLAL	1.70	1.01-2.85	0.045	1.42	0.76-2.66	0.27	0.49	0.15, 1.19	0.2	0.63	0.19, 1.61	0.4
4-wk readmission	AAL vs NAAL	1.55	0.88-2.74	0.13	1.31	0.66-2.59	0.44	1.25	0.65, 2.23	0.5	0.78	0.36, 1.56	0.5
	BLAL vs NBLAL							1.03	0.47, 2.00	>0.9	0.72	0.29, 1.57	0.4
4-wk readmission with infection	AAL vs NAAL	2.12	0.94-4.78	0.07	1.63	0.68-3.94	0.28	1.45	0.55, 3.20	0.4	0.92	0.33, 2.17	0.9
	BLAL vs NBLAL	2.12	0.89-5.06	0.09	1.69	0.66-4.33	0.28	1.21	0.36, 3.05	0.7	0.86	0.24, 2.34	0.8
								RR			**RR**		
Number of antibiotics prescribed +	AAL vs NAAL	1.60	1.02-2.50	0.04	1.20	0.71-2.00	0.50	1.01	0.85, 1.20	0.9	1.06	0.89, 1.25	0.5
	BLAL vs NBLAAL	1.53	0.94-2.49	0.09	1.16	0.67-2.02	0.59	1.015	0.83, 1.23	0.9	1.06	0.88,1.26	0.5

Abbreviations: *AAL*, antibiotic allergy label; *BLAL*, β-lactam allergy label; *NAAL*, no antibiotic allergy label; *NBLAL*, no β-lactam allergy label; *CI*, confidence interval; *HR*, hazard ratio, estimated by Cox regression; *OR*, odds ratio, estimated from logistic regression; *Δ*, difference in means, estimated by linear regression; *ICU*, intensive care unit.

*Adjusting for patient age, sex, principal diagnosis and specialty if statistically significant.

+ Analyses carried out on the subset of patients who were currently on antibiotics (N=749) in General Inpatient Population.

Online Repository Figure E1. Study Population Screening Process

Online Repository Figure E2. Demographic subgroup analyses of any allergy labelling as a predictor of both length of hospital stay (LOS) and receipt of a reserved antimicrobial (non-cephalosporin/non-penicillin broad spectrum antibiotic), and receipt of a reserved antimicrobial as a predictor of LOS.