Received: 10 March 2022 | Revised: 18 May 2022 | Accepted: 5 June 2022

DOI: 10.1002/pds.5486

ORIGINAL ARTICLE

WILEY

Antibacterial-associated acute kidney injury among older adults: A post-marketing surveillance study using the FDA adverse events reporting system

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Abstract

Purpose: Antibacterials induce a differential risk of acute kidney injury (AKI) in older adults. This study investigated the reporting risk of AKI associated with antibacterials using the individual case safety reports (ICSRs) submitted to the Food and Drug Administration Adverse Event Reporting System (FAERS) database.

Methods: A case/non-case method was used to assess AKI risk associated with antibacterials between 1 January 2000 and 30 September 2021. Cases were ICSRs for antibacterials with AKI as preferred terms included in the Medical Dictionary of Regulatory Activities (MedDRA) system organ classes 'Renal and urinary disorders' disorders. The analyses were completed on a de-duplicated data set containing only the recent version of the ICSR. Signals were defined by a lower 95% confidence interval (CI) of reporting odds ratio (ROR) ≥ 2, proportional reporting ratio (PRR) ≥ 2, information component (IC) > 0, Empirical Bayes Geometric Mean (EBGM) > 1 and reports ≥4. Sensitivity analyses were conducted a priori to assess the robustness of signals.

Results: A total of 3 680 621 reports on ADEs were retrieved from FAERS over the study period, of which 92 194 were antibacterial reports. Gentamicin, sulfamethoxazole, trimethoprim and vancomycin consistently gave strong signals of disproportionality on all four disproportionality measures and across the different sensitivity analyses: gentamicin (ROR = 2.95[2.51–3.46]), sulfamethoxazole (ROR = 2.97[2.68–3.29]), trimethoprim (ROR = 2.81[2.29–3.46]) and vancomycin (ROR = 3.35[3.08–3.64]).

Conclusion: Signals for gentamicin, sulfamethoxazole, trimethoprim and vancomycin were confirmed by using antibacterials as a comparator, adjusting for drug-related competition bias and event-related competition bias.

KEYWORDS

adverse event, antibiotics, data signal, elderly, reporting odds ratio

Plain language summary

This study investigated the reporting risk of AKI associated with antibacterials using the individual case safety reports (ICSRs) submitted to the Food and Drug Administration Adverse Event Reporting System (FAERS) database. A case/non-case method was used to assess AKI risk

associated with antibacterials between 1 January 2000 and 30 September 2021. The analyses were completed on a de-duplicated data set containing only the recent version of the ICSR. A total of 3 680 621 reports on ADEs were retrieved from FAERS over the study period, of which 92 194 were antibacterial reports. We found significant disproportionate reporting risk of AKI associated with gentamicin, sulfamethoxazole, trimethoprim and vancomycin when compared to all other drugs and all other antibacterials. No significant disproportionate reporting risk of AKI associated with newer antibacterial agents, such as telavancin and dalbavancin, was detected.

Key Points

- This study investigated the reporting risk of AKI associated with several old and new antibacterials in older adults.
- The newer glycopeptides, telavancin and dalbavancin generated no disproportionality signals, while vancomycin generated a much stronger signal.
- The application of Frequentist, Bayesian and sensitivity analyses strengthened the rigour of our findings.

1 | INTRODUCTION

Antibacterials are frequently used and play a vital role in treating serious infectious diseases. However, most antibacterial research focuses on the drugs' benefits with much lesser attention to the harm they cause to the patients.[1] On the other hand, clinicians need valuable information to balance the benefits and harm while prescribing antibacterials to their patients.

Older adults are considered a 'special' population demographic due to their differences from younger adults in terms of pharmacokinetics, comorbidity, polypharmacy and increased vulnerability to adverse drug events.[2] Several studies have already indicated the increased vulnerability of older adults to adverse drug events (ADEs). In one Irish cohort study, 78% of 931 community-dwelling older adults (70 years and above) experienced at least one ADE during the 6 months of the study period.[3] In another prospective cohort, there was an ADE incidence of 14% among 2916 long-term care nursing home residents in Massachusetts over 12 months.[4] In their Dutch cross-sectional survey of hospitalised over 70-year-olds, Mannesse et al.[5] found that 23.6% of the admissions were due to ADEs. Although these studies do not specifically attribute this rise in ADEs to antibacterials, the need to strengthen antibacterial ADE surveillance among older adults cannot be emphasised.

In one systematic review and meta-analysis, it was found that older adults (65 years and above) had a 15.1% (95% CI = 12.8%–17.3%) risk of developing AKI when exposed to aminoglycosides and 19.1% (95% CI = 15.4%–22.7%) when exposed to glycopeptides.[6] In a recent study, Dylis et al.[7] described the association between high Charlson's comorbidity index score with antibacterial prescriptions not adhering to guidelines, resulting in untoward ADEs among the older adults with multiple comorbidities. Due to the large body of evidence associating older age with increased risk of ADEs, the attention to accurate identification of antibacterial associated ADEs among older adults is becoming vital for the quality use of medicines. Accurate information and knowledge will always be essential in managing infections in hospitals and communities[1] and mitigates the burden of ADEs such as AKI on patients and economy.

Several studies have described some association of AKI with increased hospital stay and hospitalisation costs.[8–10] Hospital stay increases by an average of 3.2–7.4 days for patients with AKI when compared to patients without AKI.[9] According to Ker et al.,[10] England experiences more than 40 000 excess deaths among AKI patients every year. Annual inpatient costs associated with AKI range from US $5.4 billion to US$24.0 billion in the US,[8] more than 200 million Canadian dollars[9] and about £1.02 billion in England.[10]

Several studies have also highlighted how physicians are challenged by the lack of information on the variable nature and frequency of ADEs associated with each antibacterial or class of antibacterials.[11–13] The identification of antibacterial ADEs, like any other drug adverse events, starts with detecting a signal of a potential hazard, which can further be investigated using either observational studies or clinical trials.[1]

This study aimed to detect signals of acute kidney injury (AKI) associated with antibacterials among older adults aged 65 years and above.[14] The post-marketing surveillance reports collected by the Food and Drug Administration (FDA) Adverse Event Reporting System (FAERS) were used.[15]

2 | METHODS

2.1 | Data Source

We used the Elsevier PharmaPendium to access the curated FAERS data, and the use of PharmaPendium for drug safety research is

described elsewhere.[16,17] The FAERS data, which is also publicly available, is a collection of adverse event reports submitted by consumers, manufacturers and healthcare professionals, to the US Food and Drug Administration.[16] The individual case safety reports (ICSR) include information, such as drug, administration route, the active ingredient and the drugs reported in the incident. In addition, each ICSR contains a named primary suspect drug with at least one ADE, and other drugs used by the patient may be included.[18]

2.2 | Study design

Disproportionality analysis was performed to investigate AKI reporting with antibacterials from 1 January 2000 to 30 September 2021, using the FAERS data. All included reports were from patients at least 65 years of age when taking the antibacterial. Duplicate reports were excluded using the case number, and only the latest version of each report was included in the study.

2.3 | Antibacterial exposure definition

Antibacterial exposure was defined as the systemic exposure to an antibacterial agent administered orally, intramuscularly or intravenously. The antibacterials were identified using generic names, with those listed as primary suspect drugs evaluated for inclusion in the study. Antibacterials with less than three AKI ADE reports were excluded from the analysis.[19]

2.4 | Adverse event definition

AKI was defined using the preferred term 'acute kidney injury' only from the system organ class 'Renal and urinary disorders' disorders, MedDRA, version 24.0.

2.5 | Statistical analysis

A disproportionality analysis was conducted by computing the proportional reporting ratio (PRR),[20] reporting odds ratio (ROR),[19] the empirical Bayes geometric mean (EBGM)[19] and the information component (IC),[21] at 95% confidence interval. The analyses were implemented on a de-duplicated data set and deemed significant if the lower limit of the 95% confidence interval (CI) is at least 2 for ROR, greater than zero for IC, at least 1 for EBGM score, at least 2 for PRR, with χ^2 at of least 4.[17] In all situations, antibacterials were included for analysis if at least three suspected cases of AKI ADE were reported.[20]

Analyses were done as follows:

1. The main analysis was done on the unrestricted data, where each antibacterial was compared with all other drugs.

TABLE 1 Characteristics of the case reports

Characteristic Primary suspect antimicrobial by class	N = 92 194 N (%)
Aminoglycoside	3569 (3.80)
Antimycobacterial	2425 (2.60)
Carbapenem	4950 (5.40)
Cefalosporin	8604 (9.31)
Fluoroquinolone	30 706 (33)
Glycopeptide	5303 (5.71)
Lipopeptide	2325 (2.50)
Macrolide	9737 (10.60)
Metronidazole	3978 (4.30)
Monobactam	762 (0.80)
Nitrofuran	1259 (1.40)
Oxazolidinone	4271 (4.60)
Penicillin	6466 (7.10)
Phosphonic acid	181 (0.20)
Polymyxin	87 (<0.10)
Sulfamethoxazole	2776 (3.00)
Tetracycline	4102 (4.40)
Trimethoprim	693 (0.80)
Grand total	92 194
Gender, *n* (%)	
Female	47 929 (52.0)
Male	42 547 (46.1)
Unknown	1718 (1.9)
Age, Median (IQR)	75 (70–81)
Reporter occupation, *n* (%)	
Consumer	16 561 (18.0)
Health Professional[a]	26 885 (29.2)
Lawyer	183 (0.2)
Pharmacist	12 352 (13.4)
Physician	23 874 (25.9)
Registered Nurse	30 (<0.1)
Unknown	12 309 (13.4)
Report type, *n* (%)	
Direct[b]	13 117 (14)
Expedited[c]	66 052 (72)
Periodic[d]	13 025 (14)

[a]Health professionals included reporters who did not specify their health profession, for example pharmacist or doctor, but indicated that they are professionals.
[b]Direct reports are reports submitted directly to the US Food and Drug Administration without going through the manufacturers. It is usually new, important information on serious reactions that are not anticipated.
[c]An expedited report is a manufacturer's report that contains at least one adverse event not currently described in the product labelling.
[d]Periodic reports are non-expedited reports submitted by manufacturers to the FDA quarterly for the first three years after approval.

2. Analyses were repeated using the unrestricted data with all other antibacterials as the comparator.
3. Further sensitivity analyses to investigate the influence of different confounders were done as follows:
   a. To minimise event-related bias, AKI reports from diabetic patients prescribed antibacterials were excluded due to the strong association of diabetes and AKI.[22]
   b. Non-steroidal anti-inflammatory drugs (NSAIDs) like ibuprofen, diclofenac or naproxen are known common causes of AKI.[23] Reports, where NSAIDs were co-prescribed with antibacterials were removed to minimise co-prescription bias on AKI. Several other drugs are strongly associated with AKI (see Appendix A1).[24] Reports where any of these drugs were prescribed together with an antibacterial, were removed to minimise co-prescription bias on AKI. Anti-hypertensives (ACE inhibitors and ARBs), anti-cancer drugs (cisplatin, carboplatin and methotrexate) and antiretroviral drugs (tenofovir, indinavir and ritonavir) are all strongly associated with AKI.[25–27] Reports containing antibacterials prescribed to patients on these drugs were also removed to minimise co-prescription bias towards AKI.

Signal consistency was based on the number of statistically significant disproportionality signals that emerged across the analyses. The following scale was used to classify the disproportionate signal as weak, moderate, or strong:: <2/4 = weak; 2/4 to 3/4 = moderate; and 4/4 = strong.

3 | RESULTS

3.1 | Descriptive analysis

A total of 3 680 621 reports on ADEs for older adults of 65 years and above were retrieved from FAERS over the study period, of which 92 194 were antibacterial reports. Table 1 shows the characteristics of the study population in the ICSRs. Females constituted 53% of the antibacterial-associated ADEs, higher than males. The median age reported was 75 years (IQR = 70–81). Thirty per cent of the antibacterial ADEs reports were made by physicians, with 21% by consumers, 15% by pharmacists and 26% by other health professionals. The most frequently reported antibacterials were ciprofloxacin (12%) and levofloxacin (12%). Forty-seven antibacterials were associated with at least three AKI adverse events each. Among them were nine cephalosporins (9.31%), six fluoroquinolones (33%), four each for carbapenems (5.4%) and macrolides (10.6%), three each for penicillin (7.1%), glycopeptides (5.71%), tetracyclines (4.4%) and aminoglycosides (3.8%) and two antimycobacterial (2.6%). Other classes were represented by a single antibacterial or none.

3.2 | Main analysis

Table 2 shows all antibacterials that generated a positive disproportional reporting signal with any four methods without any restrictions applied to the dataset. Twenty antibacterials showed a positive signal on at least one of the four methods. Eight antibacterials, including amoxicillin, ciprofloxacin, clarithromycin, colistin, gentamicin, sulfamethoxazole, trimethoprim and vancomycin, showed strong signals of disproportionality across all four methods. The strongest signals were obtained from vancomycin, thus PRR = 5.69(5.26–6.15), ROR = 5.73 (5.30–6.21), IC = 2.36 (2.26–2.46), and EBGM score = 5.05 (4.96–5.15).

3.3 | Analyses of restricted data

Restrictions were applied using other antibacterials as a comparator, controlling for other prescribed drugs and controlling for diabetes mellitus.

Table 3 summarises disproportionality outcomes for RORs after using all other antibacterials as a comparator, controlling for other prescribed drugs and controlling for diabetes mellitus. Gentamicin, sulfamethoxazole, trimethoprim and vancomycin continued to show strong signals following all sensitivity analyses. At the same time, amoxicillin, ciprofloxacin, colistin and clarithromycin lost their ROR signals using all other antibacterials as a comparator and after controlling for other prescribed drugs. The signals generated were almost half of the main analyses. For example, in the main analysis, amoxicillin ROR = 2.75 (2.50–3.04) compared with ROR = 1.50 (1.35–1.66) when antibacterials were used as a comparator.

4 | DISCUSSION

In this study, four methods were used to detect signals of disproportional reporting of AKI due to antibacterials among the elderly population. The methods included two Frequentist and two Bayesian methods.

Almost 60% of AKI among older adults is due to therapeutic drugs, including antibacterials.[28] According to Pierson-Marchandise et al.,[29] antibacterials for systemic use were more frequently associated with AKI than any other drug class. Aminoglycosides (gentamicin and amikacin), vancomycin and beta-lactams (cefazolin and ceftriaxone) were the causes of AKI in most patients in the study conducted by Khalili et al.[30]

Among the aminoglycosides analysed, only gentamicin showed a positive disproportionality signal (Figure 1) with a ROR of 5.45 (95% CI = 4.65–6.38). This is consistent with previous findings that aminoglycosides in general, and mainly gentamicin, cause AKI in about 26% to 30% of patients being treated and contribute significantly to overall drug-induced AKI.[31,32]

Several authors have established that when used as monotherapy, the incidence of vancomycin-associated AKI is 7.4%–10.9%.[30,33] Unfortunately, not much information about ADEs associated with 'newer' antibacterials is known. However, out of the three glycopeptides included in this study, the newer glycopeptides, telavancin and dalbavancin generated no disproportionality signals, while vancomycin generated a much stronger signal (Figure 1, ROR = 5.73; 95% CI = 5.30–6.21).

TABLE 2 Disproportionality analyses on acute kidney injury on unrestricted data

Antibacterial agent	Chi Squared (χ^2)	PRR (95% CI)	ROR (95% CI)	IC (95% CI)	EBGM (95% CI)
Amoxicillin	452.6	**2.74 (2.49–3.02)**	**2.75 (2.50–3.04)**	**1.40 (1.27–1.53)**	**2.61 (2.37–2.86)**
Cephalexin	8.3	1.49 (1.13–1.96)	1.49 (1.13–1.96)	**0.56 (0.18–0.94)**	**1.44 (1.1–1.86)**
Cefepime	36.1	2.11 (1.64–2.70)	2.11 (1.64–2.71)	**1.04 (0.70–1.38)**	**1.98 (1.55–2.49)**
Ceftazidime	8.2	1.50 (1.13–1.98)	1.50 (1.13–1.98)	**0.57 (0.18–0.96)**	**1.45 (1.1–1.88)**
Ceftriaxone	101.4	2.08 (1.80–2.41)	2.08 (1.80–2.41)	**1.02 (0.82–1.22)**	**2 (1.74–2.3)**
Ciprofloxacin	592.7	**2.65 (2.44–2.87)**	**2.66 (2.45–2.89)**	**1.35 (1.24–1.46)**	**2.53 (2.34–2.74)**
Clarithromycin	342.4	**2.74 (2.45–3.06)**	**2.75 (2.46–3.07)**	**1.40 (1.25–1.55)**	**2.6 (2.33–2.89)**
Clindamycin	80.9	2.02 (1.73–2.36)	2.02 (1.73–2.37)	**0.98 (0.77–1.20)**	**1.95 (1.66–2.26)**
Colistin	56.0	**5.10 (3.17–8.21)**	**5.11 (3.17–8.22)**	**2.22 (1.61–2.83)**	**4.81 (2.77–5.14)**
Daptomycin	69.1	2.19 (1.81–2.65)	2.19 (1.81–2.65)	**1.09 (0.83–1.35)**	**2.08 (1.72–2.49)**
Doripenem	6.00	1.98 (1.13–3.45)	1.98 (1.13–3.45)	**0.95 (0.19–1.72)**	**1.68 (1–2.67)**
Gentamicin	562.1	**5.44 (4.65–6.36)**	**5.45 (4.65–6.38)**	**2.30 (2.10–2.50)**	**5.04 (4.95–5.14)**
Levofloxacin	41.9	1.48 (1.31–1.66)	1.48 (1.31–1.67)	**0.55 (0.38–0.71)**	**1.46 (1.3–1.63)**
Linezolid	54.0	1.83 (1.55–2.15)	1.83 (1.55–2.15)	**0.84 (0.62–1.07)**	**1.77 (1.5–2.07)**
Meropenem	8.8	1.45 (1.13–1.87)	1.46 (1.13–1.87)	**0.53 (0.18–0.87)**	**1.42 (1.1–1.79)**
Rifampin	66.2	2.00 (1.69–2.37)	2.00 (1.69–2.38)	**0.97 (0.73–1.20)**	**1.92 (1.62–2.26)**
Sulfamethoxazole	1351.0	**5.27 (4.78–5.82)**	**5.30 (4.80–5.85)**	**2.26 (2.14–2.39)**	**5.04 (4.94–5.13)**
Tobramycin	4.15	1.33 (1.01–1.74)	1.33 (1.01–1.74)	**0.40 (0.02–0.78)**	**1.3 (0.99–1.68)**
Trimethoprim	311.7	**5.24 (4.27–6.44)**	**5.25 (4.27–6.45)**	**2.26 (1.99–2.52)**	**5.03 (4.94–5.14)**
Vancomycin	2393.4	**5.69 (5.26–6.15)**	**5.73 (5.30–6.21)**	**2.36 (2.26–2.46)**	**5.05 (4.96–5.15)**

Note: Proportional reporting ratio lower 95% CI >2.0; Reporting Odds Ratio lower 95% CI >2.0; Information Component lower 95% CI >0; Empirical Bayesian Geometric Mean score lower 95% CI >1.0. The bold numbers are positive disproportionate reporting signals.

TABLE 3 Sensitivity analyses on acute kidney injury

Antibacterial agent	Main analysis ROR (95% CI)	All other antimicrobials as comparator ROR (95% CI)	ROR without co-prescription bias[a] (95% CI)	ROR without event bias[b] (95% CI)	Signal[c]
Amoxicillin	2.75 (2.50–3.04)	1.50 (1.35–1.66)	1.49 (1.34–1.65)	2.75 (2.49–3.03)	Moderate
Ciprofloxacin	2.66 (2.45–2.89)	1.46 (1.34–1.59)	1.47 (1.35–1.60)	2.64 (2.43–2.86)	Moderate
Clarithromycin	2.75 (2.46–3.07)	1.48 (1.32–1.66)	1.44 (1.28–1.61)	2.74 (2.45–3.06)	Moderate
Colistin	5.11 (3.17–8.22)	2.71 (1.68–4.36)	2.72 (1.69–4.37)	5.05 (3.14–8.13)	Moderate
Gentamicin	5.45 (4.65–6.38)	2.95 (2.51–3.46)	2.91 (2.47–3.42)	5.57 (4.76–6.52)	Strong
Sulfamethoxazole	5.30 (4.80–5.85)	2.97 (2.68–3.29)	2.98 (2.68–3.30)	5.28 (4.78–5.84)	Strong
Trimethoprim	5.25 (4.27–6.45)	2.81 (2.29–3.46)	2.84 (2.30–3.49)	5.22 (4.25–6.41)	Strong
Vancomycin	5.73 (5.30–6.21)	3.35 (3.08–3.64)	3.37 (3.09–3.66)	5.74 (5.30–6.21)	Strong

[a]Co-prescription bias was considered when an antibacterial was co-prescribed with any of the drugs listed in Appendix A1. These drugs are already known causes of AKI.
[b]Event bias was considered when an antibacterial was prescribed to an older adult with diabetes mellitus. This condition is already strongly associated with AKI.
[c]Signal consistency was based on the number of statistically significant disproportionality signals that emerge across the analyses: <2/4 = weak; 2/4 to 3/4 = moderate; and 4/4 = strong. Light grey = negative signals; Moderate Light grey = positive signal.

AKI is not established as a common ADE for beta-lactam antibacterials. However, according to Moenster et al.,[34] the potential for beta-lactams to cause AKI in ascending order is monobactams, penicillins, cephalosporins and carbapenems. In contrast, Morales-Alvarez[35] stated that these antibacterials are well-recognised nephrotoxins that cause AKI by direct proximal tubule toxicity. In this study, amoxicillin is the only beta-lactam that reached the signal detection threshold for all four methods. Four cephalosporins (cephalexin, cefepime, ceftazidime and ceftriaxone) and two carbapenems (doripenem and meropenem) reached the signal detection threshold for IC and EBGM only (Table 2).

Of the four macrolides tested, only clarithromycin reached the signal detection threshold for all four methods (Table 2 and Figure 1). Persico et al.[36] stated that macrolide-associated AKI is usually delayed by 10 days to 6 weeks post-antibiotic treatment. This may explain possible under-reporting and subsequently poor signal detection when data sources such as FAERS are used as the source of

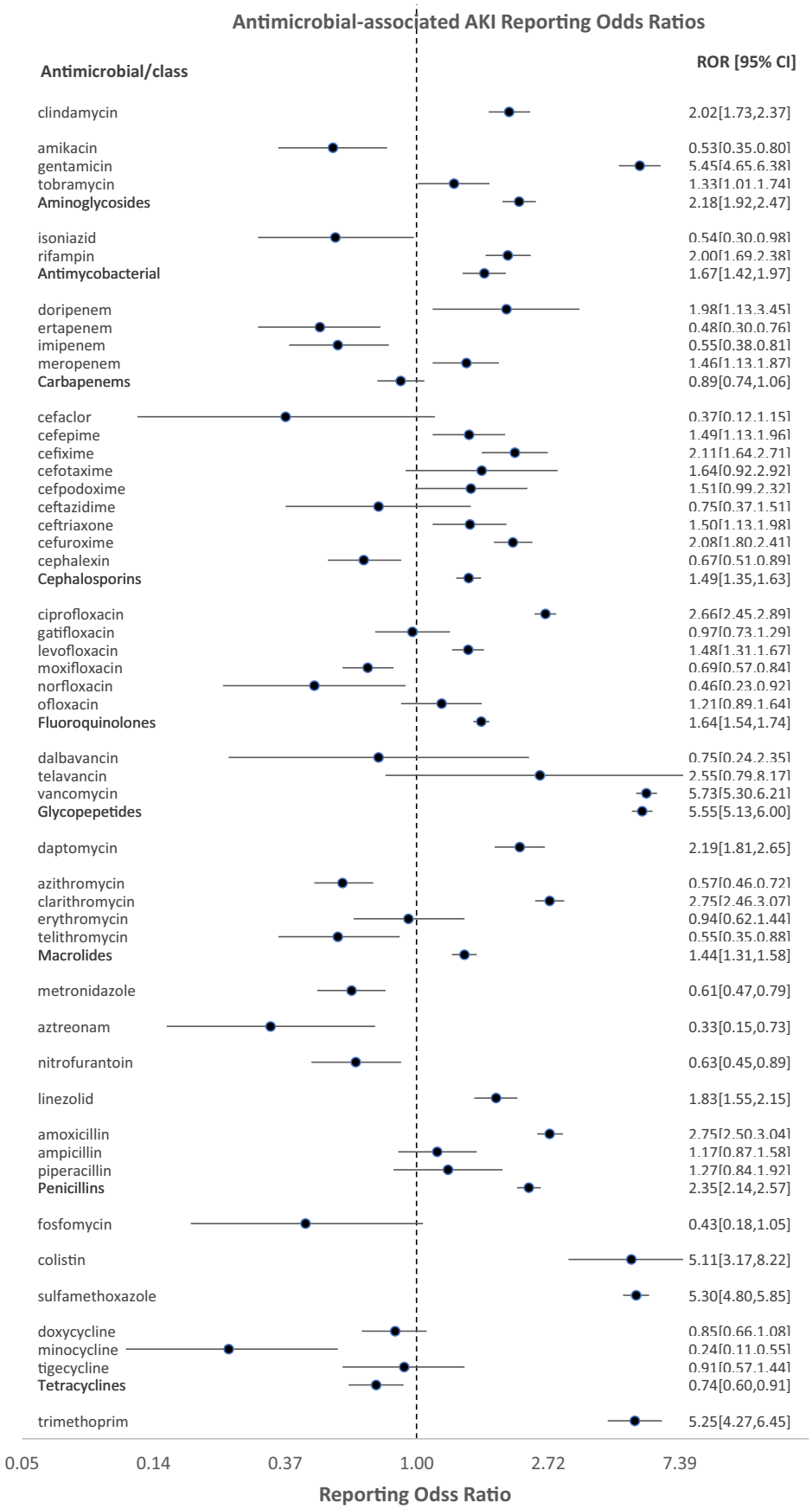

FIGURE 1 Reporting odds ratios for AKI with antimicrobials/antimicrobial class on the unrestricted data

information. Fluoroquinolone-induced AKI is not common in general. However, ciprofloxacin can cause AKI by tubular damage.[35] In one study, the risk ratio for AKI due to ciprofloxacin was 2.76 (95% CI = 2.03–3.76).[37] Of the six fluoroquinolones tested in this study, ciprofloxacin and levofloxacin reached the signal detection threshold for all four and only two analyses, respectively (Table 2).

Trimethoprim and sulfamethoxazole inhibit tubular secretion of creatinine, leading to increased serum creatinine levels.[35] Polymyxins are also known as nephrotoxins that cause AKI by direct proximal tubule cytotoxicity.[35] In this study, trimethoprim, sulfamethoxazole and colistin reached the signal detection threshold for all four methods. Several studies have described the association of trimethoprim and sulfamethoxazole, as single drugs or in combination, with AKI. In a large cohort study by Crellin et al.,[38] trimethoprim was an independent risk factor for AKI, with a 72% increase in odds of AKI among patients aged 65 and over when compared to amoxicillin. Sulfa-containing medications, such as sulfamethoxazole, can cause crystal-induced nephropathy.[39] The combined effect of inhibition of tubular secretion of creatinine by trimethoprim and crystal-induced nephropathy by sulfamethoxazole explains the increased risk of cotrimoxazole-associated AKI[40,41] and the strong disproportionality signals for trimethoprim and sulfamethoxazole found in this study.

The PRR and ROR, both frequentist methods, detected signals from similar and significantly fewer ($p = 0.0071$) antibacterials than Bayesian methods, the IC and EBGM, as shown in Table 2. In their analysis, Poluzzi et al.[42] summarised that Bayesian methods have lower sensitivity and frequentist methods have lower specificity when the originally published thresholds are applied. Similarly, an earlier study by Van Puijenbroek et al.[43] found out that both PRR and ROR detected more disproportionate signals than IC. However, our study used more stringent thresholds for the frequentist methods (PRR and ROR lower 95% confidence interval of at least 2.0), consistent with recently published literature.[44] Our findings show that with improved signal detection thresholds, the specificity for frequentist methods can be improved (Table 2).

Following sensitivity analyses, the signals generated noticeably reduced when all other antibacterials were used as a comparator and when other AKI-associated drugs were removed compared with the main analysis (Table 3). Using all other antibacterials as a comparator group mitigates confounding by indication, resulting in amoxicillin, ciprofloxacin, clarithromycin and colistin dropping below the signal detection threshold. When controlled for diabetes mellitus, there was no significant reduction in signals generated compared with the main analysis.

This study demonstrated that at least two methods, a Frequentist and a Bayesian method, should be employed when investigating ADEs using disproportionality analysis. In addition, sensitivity analysis should be performed to reduce the background noise to mitigate false signals.

4.1 | Limitations

A major limitation for signal detection using reporting disproportionality analysis is that a positive signal does not infer causality. It should always be followed by well-structured observational studies or randomised controlled trials. Although sensitivity analysis was done in this study, unknown confounders may still exist and skew the findings. The ADEs were reported spontaneously and voluntarily; therefore, the analysis is prone to selection bias. We did not investigate a dose-dependent or a temporal relationship with AKI, which are important considerations in older adults.

5 | CONCLUSION

A combination of Frequentist and Bayesian methods, together with sensitivity analyses, helped to separate strong signals of disproportionality from weak signals. Gentamicin, sulfamethoxazole, trimethoprim and vancomycin showed strong signals after using antibacterials as a comparator, adjusting for drug-related competition bias and event-related competition biases. The strongest signals for AKI emerged from vancomycin. This study detected no disproportionality signals from newer antibacterials like dalbavancin and telavancin.

AUTHOR CONTRIBUTIONS

TC (Bath) and PN contributed to study concept and design; TC (Bath) PN, TC (Otago) contributed to statistical analysis;all authors contributed to interpretation of data and critical revision of the manuscript for important intellectual content;: TC (Bath), PN contributed to drafting of the manuscript; PN contributed to study supervision.

ACKNOWLEDGMENT

Open access funding enabled and organized by Projekt DEAL.

CONFLICT OF INTEREST

The authors have no conflicts of interest to declare.

ETHICS STATEMENT

The Departmental Research and Ethics Officer at the University of Bath assessed the ethical implications of research activity (EIRA) and approved this study on behalf of the University of Bath's Research, Integrity, and Ethics committee. Approval number EIRA 1 No. 4048.

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How to cite this article: Chinzowu T, Chyou T-Y, Nishtala PS. Antibacterial-associated acute kidney injury among older adults: A post-marketing surveillance study using the FDA adverse events reporting system. *Pharmacoepidemiol Drug Saf*. 2022;31(11):1190-1198. doi:10.1002/pds.5486

APPENDIX 1

Drugs associated with AKI

Bisacodyl, cetirizine hydrochloride, codeine phosphate, colchicine, cyclizine hydrochloride, dexamethasone, diazepam, dihydrocodeine tartrate, domperidone, glycerol trinitrate, haloperidol, hyoscine N-butylbromide, loperamide hydrochloride, loratadine, lorazepam, metoclopramide hydrochloride, morphine hydrochloride, morphine sulphate, ondansetron, prednisone, prochlorperazine, promethazine hydrochloride, quetiapine, risperidone, temazepam, triazolam, zopiclone, ibuprofen, diclofenac, naproxen, anti-hypertensives (ACE inhibitors and ARBs), anti-cancer drugs (cisplatin, carboplatin, and methotrexate), and antiretroviral drugs (tenofovir, indinavir and ritonavir).