META-ANALYSIS

Safety of sulfamethoxazole–trimethoprim for the treatment of bacterial infection in outpatient settings: A systematic review and meta-analysis with active comparator disproportionality analysis

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Aims: Sulfamethoxazole–trimethoprim (SMX-TMP) is a widely used antibiotic for treating bacterial infections, but its safety in adult outpatients remains understudied. This systematic review and meta-analysis evaluated the safety profile of SMX-TMP and identified critical research gaps. The pharmacovigilance study aimed to validate and extend findings from meta-analyses to better understand the real-world safety of SMX-TMP.

Methods: We searched MEDLINE and Embase up to 12 August 2024, to identify studies comparing adverse drug events (ADEs) following SMX-TMP *vs.* other antibiotics in adult outpatients. Meta-analyses were performed where data allowed. A pharmacovigilance study using the Food and Drug Administration Adverse Event Reporting System was conducted to supplement our findings.

Results: Our review, which included 43 studies, found SMX-TMP had a nearly 3-fold higher risk of rash compared to other antibiotics (pooled risk ratio 2.56, 95% confidence interval [1.69, 3.89], $I^2 = 0\%$, $n = 4458$ participants, 24 randomized control trials). Pharmacovigilance data confirmed a higher frequencies of skin disorders and other ADEs compared to various comparator drugs. Compared to azithromycin, SMX-TMP was associated with a 5-fold increase in Stevens–Johnson syndrome, a 3-fold increase in toxic epidermal necrolysis, and a 10-fold increase in drug reaction with eosinophilia and systemic symptoms. Additionally, SMX-TMP showed a 10-fold increase in reports of pancytopenia, a 6-fold increase in neutropenia, a 4-fold increase in both thrombocytopenia and aplastic anaemia, a 56-fold increase in hyperkalaemia, and a 10-fold increase in hyponatraemia.

Conclusion: Our meta-analyses and pharmacovigilance study suggested SMX-TMP was associated with increased risk of ADEs compared to other antibiotics including amoxicillin/clavulanate, azithromycin and nitrofurantoin. Further robust research is essential to confirm these safety signals and guide clinical practice.

1 | INTRODUCTION

Adverse drug events (ADEs) are significant concerns in healthcare, contributing to significant morbidity and mortality, leading to patient harm, prolonged hospital stays and increased healthcare costs.[1,2] Sulfamethoxazole–trimethoprim (SMX-TMP), commonly referred to as cotrimoxazole, was first approved for use in Canada in 1968, followed by the USA in 1973 and is known for its efficacy in treating bacterial infections and its cost-effectiveness compared to other antibiotics such as ciprofloxacin.[3–5] This combination antibiotic has broad-spectrum activity against various bacterial pathogens, including *Moraxella catarrhalis, Streptococcus pneumoniae, Proteus mirabilis, Klebsiella pneumoniae* and *Escherichia coli*.[6] Current Food and Drug Administration (FDA)-approved indications include treatment of chronic bronchitis, traveller's diarrhoea, urinary tract infections (UTIs), *Pneumocystis carinii* pneumonia, *Pneumocystis jirovecii* pneumonia and toxoplasmosis.[7]

SMX-TMP use has been associated with many ADEs ranging from mild to life-threatening in severity.[8,9] Several studies indicated that SMX-TMP exhibits a higher incidence of ADEs compared to fluoroquinolones when used for the treatment of similar infections.[10] Furthermore, this antibiotic combination has been linked to ADEs unrelated to its intended use, and prescribers often underestimate the risk associated with this medication.[9] The product monograph for SMX-TMP has reported potential associations with skin disorders such as rash and severe cutaneous adverse reactions (SCARs), including Stevens–Johnson syndrome (SJS), toxic epidermal necrolysis (TEN), and drug reaction with eosinophilia and systemic symptoms (DRESS).[11] Additionally, SMX-TMP has been linked with blood disorders, including thrombocytopenia, neutropenia, aplastic anaemia and pancytopenia.[12–14] Previous literature suggests SMX-TMP use can deplete folic acid stores in the human body, increasing the risk for myelosuppression in patients.[4,15] SMX-TMP has also been linked to metabolic disorders, including hyponatraemia and hyperkalaemia.[11,16,17] Other ADEs, including liver disorders such as hepatic disorders and renal disorders have also been reported.[11,18,19]

Despite >50 years of use, the evidence on SMX-TMP safety has not been comprehensively studied and remains incompletely characterized. Data on SMX-TMP safety primarily come from small observational studies and case reports, offering a lower level of evidence compared to randomized controlled trials and large-scale cohort studies. Therefore, assessing the true incidence and severity of adverse effects associated with SMX-TMP in diverse outpatient populations is challenging. While SMX-TMP is primarily prescribed for treating bacterial infections, existing systematic reviews and meta-analyses predominantly examine its safety and efficacy in the treatment of fungal infections (*P. jirovecii*) and parasitic infections (toxoplasma, *Plasmodium falciparum*) especially in patients with HIV/AIDS. This has resulted in a significant gap in the literature regarding the safety of SMX-TMP when used for bacterial infections in outpatient settings.

To address this significant gap and identify critical areas for future research, we conducted a systematic review and meta-analysis to summarize current evidence on the association between SMX-TMP use for bacterial infections and the risk of ADEs in outpatient settings. A pharmacovigilance study using the FDA Adverse Event Reporting System (FAERS) database was conducted to further extend and validate findings from the meta-analyses.

2 | METHODS

2.1 | Protocols and registration

We adhered to the Preferred Reporting Items for Systematic Reviews and Meta-Analysis (PRISMA)[20] (Table S1). This review was registered with the International Prospective Systematic Reviews Registry (PROSPERO) under the number CRD42023488122.

2.2 | Eligibility criteria

Eligibility criteria for study selection included: (i) studies published in the English language on adult outpatients aged 18 and older treated with SMX-TMP or with other antibiotics with a similar indication of use (e.g., nitrofurantoin, ciprofloxacin, amoxicillin/clavulanic acid); and (ii) comparative studies, including pharmacovigilance studies, cross-sectional studies, case–control studies, cohort studies and randomized control trials (RCTs). The following exclusion criteria were used: (i) editorials, case reports, case series, reviews, and grey literature such as institutional reports, unpublished theses and conference abstracts; (ii) studies on pregnant and lactating patients; (iii) studies including inpatients or patients taking multiple medications or patients diagnosed with HIV or AIDS; and (iv) any studies on SMX-TMP use as a prophylactic agent or for treatment of fungal and parasitic infections.

2.3 | Search strategy

A comprehensive literature search of the bibliographic databases MEDLINE (Ovid) and Embase was conducted up to 12 August 2024, for comparative studies reporting the following outcomes of interest associated with SMX-TMP use for the treatment of bacterial infections in outpatient settings: skin disorders (e.g., rash, SJS, TEN, DRESS), metabolic and nutrition disorders (e.g., hyponatraemia and hyperkalaemia), blood disorders (e.g., pancytopenia, aplastic anaemia, neutropenia and thrombocytopenia), renal disorders and hepatic

disorders. We have chosen to explore these ADEs outlined in the SMX-TMP product monograph because of their potential severity, including life-threatening consequences or the need for hospitalization. Searching 2 or more databases provides >95% coverage of the relevant references.[21] The search strategy included database-specific keywords and Medical Subject Headings (MeSH) terms to ensure all relevant literature was captured. Synonyms for SMX-TMP, such as cotrimoxazole, and commercialized brand names such as Bactrim and Septra were used in the search strategy. Further, synonymous terms used to describe outcomes of interest were also incorporated into the search strategy. Details of the search strategy used for Medline and Embase can be found in Tables S2 and S3, respectively.

2.4 | Study selection

We used Covidence systematic review software (Veritas Health Innovation, Melbourne, Australia) for study selection. Two screening levels were conducted to identify relevant literature: (i) title and abstract screening; and (ii) full-text review. Two independent reviewers (R.P. and L.E.) independently screened the titles and abstracts of all records identified in the systematic search to assess their eligibility for inclusion in the review. The full texts of potentially relevant studies were retrieved, and full texts were assessed independently by the same reviewers for eligibility based on pre-established inclusion and exclusion criteria. Consensus or a third reviewer (F.T.M.) resolved disagreements at both screening levels.

2.5 | Data extraction

Data were extracted from included studies and managed using Microsoft Excel. Extracted data included study characteristics (e.g., author, study design and sample size), data collection procedures and statistical analysis methods used, patient demographics and baseline characteristics (e.g., sex, age and gender), details of SMX-TMP exposure (e.g., dosage and duration of treatment), type of adverse event reported, as well as the number of ADEs associated and any relevant measures of effect (e.g., odds ratios, relative risks or hazard ratios). When the measure of association was not reported, we calculated unadjusted risk ratios using the Mantel–Haenszel chi-squared test.

2.6 | Risk of bias assessment

Four reviewers, grouped into 2 pairs (R.P. and L.E., F.A. and A.J), independently assessed the risk of bias for each included study. Any disagreements were resolved by consensus or a fifth reviewer (F.T.M.). Version 2 of the Cochrane Risk of Bias for Randomized Trials (RoB 2) tool was used to appraise RCTs.[22] If an RCT exhibited indications for concern in the randomization process, deviations from the intended intervention, missing outcome data, inadequacy in measuring the outcome, or selective reporting, it was classified as having an overall high

risk of bias. If the RCT did not provide sufficient information to make a definite judgement in these bias domains, the study was classified as having an unclear risk of bias. If a study scored a high or unclear risk of bias in 1 domain, the overall article was classified as high or unclear risk of bias, respectively. If a study was classified as low risk across all domains, the overall article had a low risk of bias. For cohort studies, the Risk of Bias in Non-randomized Studies—of Exposures (ROBINS-E) tool was used.[23] The modified Downs and Black checklist was used to appraise case–control and cross-sectional studies (Downs and Black 1998).[24] These studies were assigned scores ranging from 0 to 28 and categorized into 4 quality levels: excellent (scores 26–28), good (scores 20–25), fair (scores 15–19) and poor (scores ≤14). All reviewers who completed the risk of bias assessment convened to ensure uniformity and clarify uncertainties throughout the evaluation process. Details regarding the grading of RCTs, cohort studies and other observational studies are provided in Tables S4, S5 and S6.

2.7 | Data synthesis and analysis

We calculated the summary risk ratios and 95% confidence intervals (CIs) using the random effects model (Der Simonian and Laird method) to address variability within and between studies.[25] We considered that this model was the most appropriate for calculating the summary estimate because of the diverse range of countries, populations, comparators and study periods included in our review. A meta-analysis was completed if 3 studies or more were available for an outcome of interest. Pooled estimates were also obtained for 2 studies where the results were sufficiently similar.[26] We applied a 0.5 continuity correction to include data from a study in which 1 of the arms had zero events. This continuity correction allows for the inclusion of zero-event trials while maintaining analytic consistency.[27] Including zero total event trials in meta-analyses maintains analytic consistency and incorporates all available data.[27] The heterogeneity was quantified using the I^2 statistic, which indicates the percentage of variability in effect estimates attributed to heterogeneity rather than sampling error (chance). If the I^2 statistic exceeded 50%, we considered the heterogeneity to be high.[23] Subgroup analysis was conducted, and funnel plots were created and visually inspected with the eyeball test to assess publication bias in cases where at least 10 studies were included in a meta-analysis.

All analyses were performed using RevMan 5.4 Review Manager software.[28] Quantitative data were combined through meta-analysis using RevMan 5.4 Review Manager software.

2.8 | Analysis of pharmacovigilance FAERS data

We used FAERS Quarterly Data Extract Files from the first quarter of 2004 to the fourth quarter of 2023 to collect reports of ADEs reported following SMX-TMP use. The FAERS database adheres to the International Safety Reporting Guidelines established by the International Council for Harmonization (ICH). ADEs are categorized

according to the Medical Dictionary for Regulatory Activities (MedDRA), an international standard medical terminology used for encoding adverse event information related to medicinal products. MedDRA preferred terms were used to identify outcomes of interest. Additionally, both the generic and brand name were used to study drugs of interest. Duplicate cases were identified and removed based on the unique Case ID associated with each report. Only the most recently reported case was included. Additionally, only case reports designated as primary suspects were included in the study.

Active comparators included drugs with similar indications for the treatment of the same condition or drugs commonly used as alternatives in clinical practice. The drugs selected as active comparators were nitrofurantoin, amoxicillin/clavulanate and azithromycin. We selected these antibiotics as comparator groups because they share several similar indications of use with SMX-TMP, including treatment of uncomplicated UTIs, which is 1 of the most common indications for SMX-TMP, particularly in women. Additionally, amoxicillin/clavulanate and azithromycin are commonly used for respiratory tract infections and skin and soft tissue infections, both of which are also treated with SMX-TMP.

To identify safety signals, researchers have proposed using qualitative methods, which involve the case-by-case evaluation of individual safety reports, and quantitative methods that leverage data mining techniques with real-world data from large spontaneous reporting database.[29] Disproportionality analysis is a data mining technique based on comparison of reporting proportions between the study drug and all drugs in the spontaneous reporting database combined to detect potential safety signal.[30] While this commonly used data mining technique has proven effective in identifying potential safety signals associated with newly marketed drugs that have limited safety data from randomized trials, it is not suitable for determining causality or accurately quantifying the risk of ADEs. This is due to the inherent limitations of spontaneous reporting systems, such as the presence of confounding factors and incomplete capture of critical variables needed to address these confounders, and the common issue of underreporting.[31] Therefore, to reduce concern about confounding by the indication, we used an active-comparator restricted disproportionality analysis.[32] This method restricts the reference group to reports that include a clinically relevant active comparator, thereby improving the performance of disproportionality analysis when using spontaneous reporting databases to identify safety signals. By employing this approach, we also seek to reduce the incidence of false positive signals resulting from disproportionate reporting.[33] It is important to note that the active comparator disproportionality analysis closely resembles the active new user design, which is widely recognized as the gold standard for cohort studies evaluating post-marketing drug safety.[34]

SAS (Version 8.3, SAS Studio, Cary, NC, USA) was used to perform all statistical analyses. A logistic regression was used to calculate the reporting odds ratio (ROR) and 95% CI for SMX-TMP reports in comparison to the azithromycin, amoxicillin/clavulanic acid and nitrofurantoin reports.

3 | RESULTS

3.1 | Study selection

In total, 20 720 studies were retrieved from the databases EMBASE and MEDLINE (Figure 1). There were 2377 duplicates removed, leaving 18 238 studies to undergo title and abstract screening. Following this level of screening, 526 studies were sought for full-text retrieval. A total of 484 studies were excluded during the full-text review, with the most common reasons for exclusion being wrong study design ($n = 193$), non-English language ($n = 75$) and wrong outcomes ($n = 62$; Figure 1). After completing full-text screening, 43 studies were included in the review.

3.2 | Included studies

Of the 43 studies included in the review, 33 studies (77%) reported on skin disorders, 9 (21%) reported on blood disorders, 3 (7%) reported on metabolic and nutritional disorders, 3 (7%) reported on immune system disorders and 4 studies (9%) reported on other ADEs including renal disorders, hepatic disorders and musculoskeletal disorders. Of the 43 studies included in the review, 33 (77%) were RCTs, 3 (7%) were cohort studies, 3 (7%) were case–control studies, 3 (7%) were cross-sectional studies and 1 (2%) was a case-crossover study. All 33 RCTs were published prior to 2000, with study populations ranging from 36 to 938 subjects. The median age of individuals included in this review was 36.7 years, with 93.8% of them being female.

3.3 | Skin disorders

Skin disorders were reported in 33 studies (24 RCTs and 9 observational studies), comprising a total of 1 551 121 participants. These studies included patients who either received SMX-TMP or an antibiotic with the same indication. Pre-existing sulfa allergy was not specifically assessed or reported in individuals who presented with rash. Compared to other antibiotics, SMX-TMP was associated with a greater risk of rash (pooled risk ratio [RR] 2.56, 95% CI [1.69–3.89], $I^2 = 0$, $n = 4458$ participants, 24 RCTs; Figure 2). There was no suggestion of publication bias in this meta-analysis (Figure S1). Characteristics of the studies included in the meta-analysis are shown in Table 1. In subgroup analyses, SMX-TMP was also associated with a higher risk of rash when compared to quinolone (pooled RR 4.19, 95% CI [2.30–7.64], $I^2 = 0\%$, $n = 2309$ participants, 11 RCTs; Figure 3A) or to nitrofurantoin (pooled RR 6.36, 95% CI [1.13–35.77], $I^2 = 0\%$, $n = 552$ participants, 2 RCTs; Figure 3D). A higher risk of rash was also observed when penicillin or other sulfonamide-TMP combinations were used as the comparator group, but the difference did not reach statistical significance (Figure 3B,C).
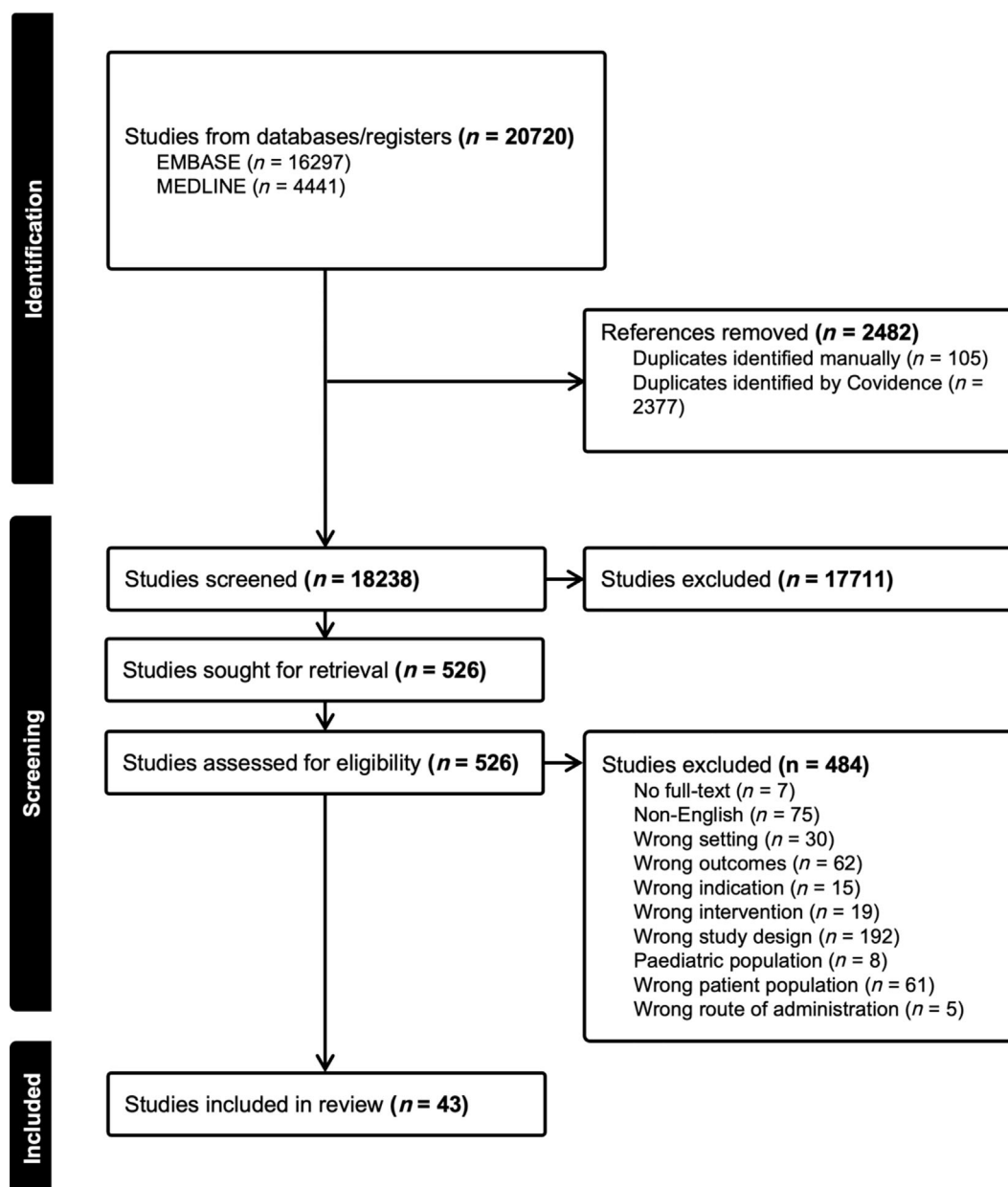
FIGURE 1 PRISMA flow diagram of study selection from the databases MEDLINE and EMBASE. (Indexed from 1946 to 12 August 2024).

SCARs, including SJS and TEN, were reported in 2 studies: 1 retrospective population-based cohort study and 1 case-crossover study. The retrospective population-based study, conducted in 1 169 033 adult outpatient women with uncomplicated UTI using the IBM MarketScan Commercial Database from 1 July 2006 to 30 September 2015 quantified the risk of adverse events associated with antibiotic treatment for urinary tract infection. This study showed that the rate of SJS events was higher among SMX-TMP users compared to nitrofurantoin users; however, the hazard ratio could not be estimated due to low case counts.[59] The case-crossover study assessing the risk of SJS/TEN associated with different antibiotic classes in Japanese patients showed a higher 28-day risk of SJS/TEN (odds ratio 18.11, 95% CI [5.62–91.36])

for SMX-TMP. However, a similar risk was also observed for penicillins (odds ratio 19.56, 95% CI [8.66–54.00]).[60] A summary of the studies reporting SJS/TEN as an outcome can be found in Table S7.

3.4 | SMX-TMP and blood disorders

Nine studies reported blood disorders (5 RCTs and 4 observational studies), comprising a total of 21 959 participants.[37,39,48,61–66] Thrombocytopenia, anaemia and leucopenia were each reported in 3 studies,[37,39,48,61,64,65] while eosinophilia and agranulocytosis were each reported in 2 studies.[48,62–64] Compared to quinolones users,

Study or Subgroup	SMX-TMP		Other Antibiotics		Risk ratio	Risk ratio	Risk of Bias
	Events	Total	Events	Total	IV, Random, 95% CI	IV, Random, 95% CI	A B C D E
Andrewes et al., 1981	1	24	0	24	3.00 [0.13 , 70.16]		? ? ? + +
Block et al., 1987	4	122	3	122	1.33 [0.30 , 5.83]		− + + + +
Brown et al., 1982	3	477	3	461	0.97 [0.20 , 4.76]		− − − + −
Cooper et al., 1980	4	43	4	44	1.02 [0.27 , 3.83]		+ + ? + ?
Corrado et al., 1990	3	86	0	124	10.06 [0.53 , 192.26]		+ + − + ?
Crochiolo, 1990	1	35	0	38	3.25 [0.14 , 77.25]		+ ? − + ?
Giamarellou et al., 1983	1	28	0	28	3.00 [0.13 , 70.64]		+ + − + ?
Gleckman, 1975	1	118	3	122	0.34 [0.04 , 3.27]		+ + + + +
Grubbs et al., 1992	8	100	2	103	4.12 [0.90 , 18.93]		+ + + + +
Haase et al., 1984	2	21	0	22	5.23 [0.27 , 102.87]		+ + − + ?
Hooton et al. , 1995	1	47	0	49	3.13 [0.13 , 74.85]		+ + − + +
Hooton et al., 1991	1	40	1	43	1.07 [0.07 , 16.62]		+ + − + ?
Iravani et al., 1981	1	64	0	71	3.32 [0.14 , 80.15]		+ ? − + +
Iravani et al., 1991	10	196	2	204	5.20 [1.15 , 23.45]		+ + ? + +
Irivani et al., 1999	9	238	3	239	3.01 [0.83 , 10.99]		+ + ? + +
Lemieux, 1974	2	17	0	22	6.39 [0.33 , 124.91]		+ + ? − ?
Lovestad et al., 1979	3	43	1	41	2.86 [0.31 , 26.40]		+ + + + +
Pisani et al., 1982	1	30	0	34	3.39 [0.14 , 80.15]		? + − + ?
Rubin et al., 1980	8	53	2	95	7.17 [1.58 , 32.54]		? ? − + ?
Sabbaj et al., 1985	4	180	0	190	9.50 [0.51 , 175.15]		? − ? ? +
Skjerven et al., 1979	3	63	1	64	3.05 [0.33 , 28.52]		+ + + + ?
Stamm et al., 1987	3	23	1	18	2.35 [0.27 , 20.72]		+ + − + ?
Stein et al., 1988	4	73	2	91	2.49 [0.47 , 13.23]		+ + + − +
Tungsanga et al., 1988	1	45	0	43	2.87 [0.12 , 68.58]		+ + + + ?
Total (95% CI)		**2166**		**2292**	**2.56 [1.69 , 3.89]**		
Total events:	79		28				

Heterogeneity: Tau² = 0.00; Chi² = 12.89, df = 23 (P = 0.95); I² = 0%
Test for overall effect: Z = 4.44 (P < 0.00001)
Test for subgroup differences: Not applicable

0.01 0.1 1 10 100
Favours [SMX-TMP]   Favours [Other Antibiotics]

Risk of bias legend
(A) Random sequence generation (selection bias)
(B) Allocation concealment (selection bias)
(C) Blinding of participants and personnel (performance bias)
(D) Incomplete outcome data (attrition bias)
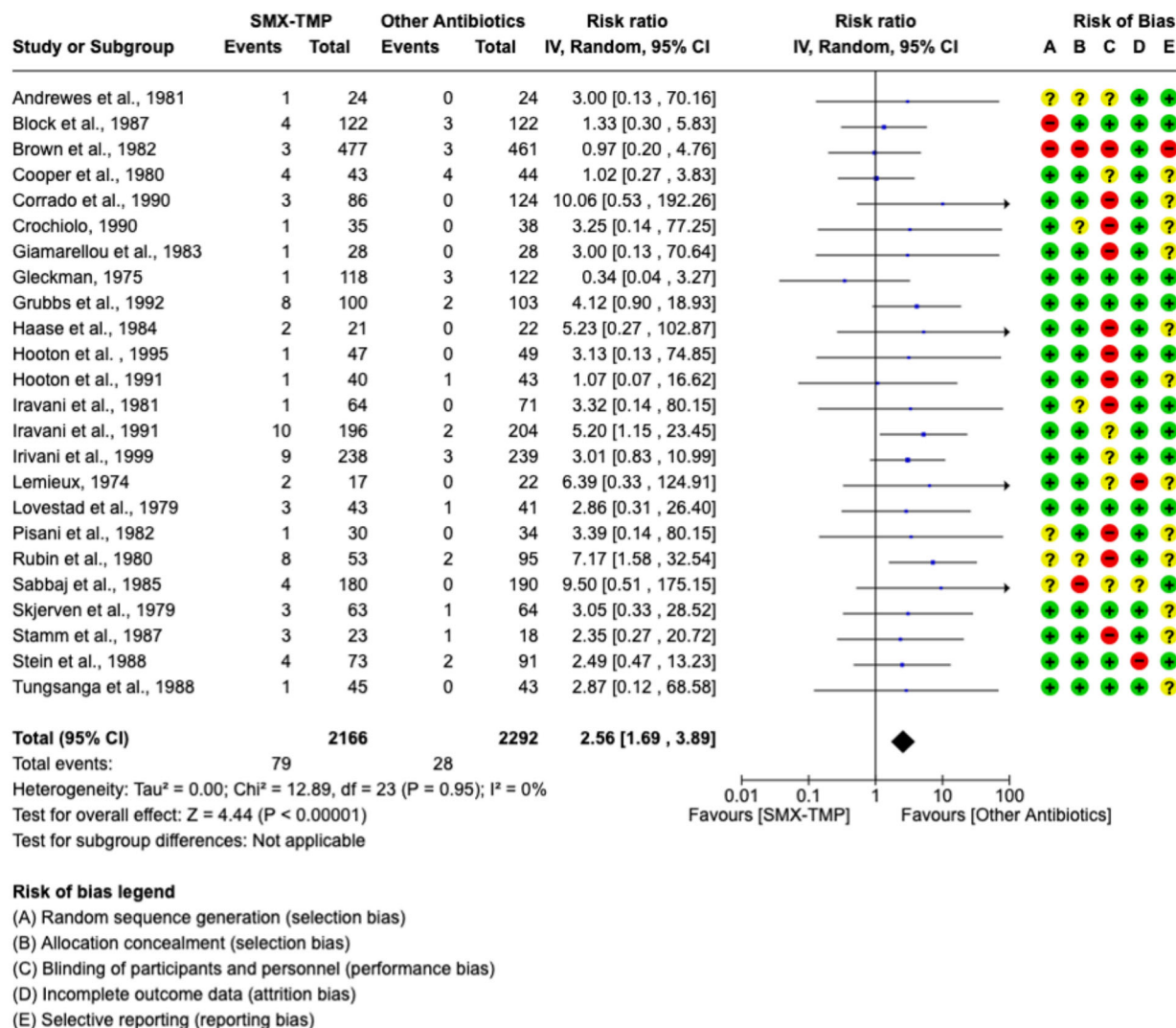(E) Selective reporting (reporting bias)

FIGURE 2 Forest plot, pooled measure of risk of rash and risk of bias assessment in 24 randomized control trials comparing SMX-TMP to antibiotics with a similar indication. Meta-analysis included adult outpatients with an indication of urinary tract infection (UTI) treated with SMX-TMP (n = 2166) or a different antibiotic (n = 2292). Inverse variance was used to determine risk ratio (RR) and a random-effects model was used to assess pooled treatment effects across studies included in each analysis. Red (−) icons indicate high risk of bias, yellow (?) icons indicate unclear risk of bias and green (+) icons indicate low risk of bias.

SMX-TMP users had a higher risk of leucopenia (pooled RR 3.98, 95% CI [0.83, 18.96], $I^2 = 0\%$, n = 530 participants, 2 RCTs; Figure S2). However, the results did not reach statistical significance. A summary of these studies can be found in Table S8.

3.5 | Metabolism disorders

Three studies reported metabolism disorders.[67–69] Hyperkalaemia was the outcome most commonly reported in studies investigating metabolism disorders.[68,69] Table S9 summarizes studies reporting metabolism and nutrition disorders as an outcome following SMX-TMP use.

3.6 | Immune system disorders

Two RCTs and 1 cross-sectional study reported immune system disorders as an outcome following SMX-TMP use.[59,67,70] Immune-related outcomes reported included allergy, anaphylaxis and angioedema. A summary of these studies can be found in Table S10.

3.7 | Other disorders

Two studies reported renal disorders,[59,69] while hepatic and musculo-skeletal disorders were each reported in 1 study.[71,72] Table S11 summarizes these studies.

TABLE 1 Summary of 24 randomized control trials included in meta-analysis of risk of rash associated with sulfamethoxazole–trimethoprim (SMX-TMP) use in comparison to other antibiotics.

Citation	Sample size and indication	Intervention/ exposure group	Comparator group	Cases of rash	Effect estimates
Andrewes et al. 1981[35]	n = 48 Indication: UTI	SMX-TMP (800/160 mg), BID, 7 days	TMP tablet (300 mg) qd, 7 days	SMX-TMP: 1/24TMP: 0/24	N/A
Block et al. 1987[36]	n = 244 Indication: UTI	SMX-TMP (800/160 mg), BID, 3 days	Ofloxacin (100 mg), BID, 3 days	SMX-TMP: 4/122Ofloxacin: 3/122	Crude risk ratio (95% CI)*:1.75 [0.43, 7.2]
Brown et al. 1982[37]	n = 938 Indication: UTI	SMX-TMP (800/160 mg), BID, 7 days	Tetracycline (1.5 g, followed by 500 mg, QID, 4 days)	SMX-TMP: 3/477 Tetracycline: 3/461	Crude risk ratio (95%CI)*: 0.97 [0.20, 4.8]
Cooper et al. 1980[38]	n = 87 Indication: UTI	SMX-TMP (2 ablets), BID, 7 days	Cephradine (500 mg), qd, 7 days	SMX-TMP: 4/43 Cephradine: 4/44	Crude risk ratio (95%CI)*: 1.02 [0.27, 3.8]
Corrado et al. 1990[39]	n = 210 Indication: UTI	SMX-TMP	Norfloxacin	SMX-TMP: 3/86 Norfloxacin: 0/124	N/A
Crochiolo 1990[40]	n = 73 Indication: UTI	SMX-TMP (800 mg/160 mg), qd, 3 days	Fosfomycin trometamol (3 g), single dose	SMX-TMP: 1/35 Fosfomycin: 0/38	N/A
Giamarellou et al. 1983[41]	n = 56 Indication: UTI	SMX-TMP (400 ug/50 ug), BID, 10 days	Norfloxacin tablet (200 mg), BID, 10 days	SMX-TMP: 1/28 Norfloxacin: 0/28	N/A
Gleckman 1975[42]	n = 240 Indication: UTI	SMX-TMP (1.6 g/320 mg), divided doses, 10 days	Ampicillin (2 g), divided doses, 10 days	SMX-TMP: 1/118 Ampicillin: 3/122	Crude risk ratio (95%CI)*: Rash: 0.34 [0.04, 3.3]
Grubbs et al. 1992[43]	n = 203 Indication: UTI	SMX-TMP (800/160 mg), BID, 10 days	Ciprofloxacin (250 mg), BID, 10 days (n = 103)	SMX-TMP:8/100 Ciprofloxacin: 2/103	Crude risk ratio (95%CI)*: 4.12 [0.90, 18.9]
Haase et al. 1984[44]	n = 43 Indication: UTI	SMX-TMP (800/160 mg), BID, 10 days	Norfloxacin (400 mg), BID, 10 days	SMX-TMP: 2/21 Norfloxacin: 0/22	N/A
Hooton et al. 1991[45]	n = 144Indication: UTI	SMX-TMP (800 mg/160 mg), BID, 7 days	1-Ofloxacin (400 mg), single dose (n = 48) 2-Ofloxacin (200 mg), qd, 3 days	SMX-TMP: 1/47 1-Ofloxacin: 0/48 2-Ofloxacin: 0/49	N/A
Hooton et al. 1995[46]	n = 158 Indication: UTI	SMX-TMP (800/160 mg), BID,3 days	1-Nitrofurantoin (100 mg), QID, 3 days 2-Cefadroxil (500 mg), BID, 3 days 3-Amoxicillin (500 mg), TID, 3 days	SMX-TMP: 1/40 Nitrofurantoin: 0/38 Cefadroxil: 0/37 Amoxicillin: 1/43	Crude risk ratio (95%CI)* (reference: amoxicillin): 1.08 [0.070, 16.6]
Iravani et al. 1981[47]	n = 135 Indication: UTI	SMX-TMP (800/160 mg), BID, 10 days	Nalidixic Acid (1.0 g) QID, 7 days	SMX-TMP: 1/64 Nalidixic Acid: 0/71	N/A
Iravani et al. 1991[48]	n = 400 Indication: UTI	SMX-TMP (800/160 mg), BID, 10 days	Temafloxacin HCl (400 mg), qd, 7 days	SMX-TMP: 10/196Temafloxacin: 2/204	Crude risk ratio (95%CI)*: 5.20 [1.2, 23]
Iravani et al. 1999[49]	n = 713 Indication: UTI	SMX-TMP (800/160 mg), BID, 7 days	1-Nitrofurantoin (100 mg), BID, 7 days (n = 236) 2-Ciprofloxacin (100 mg), BID, 3 days (n = 239)	SMX-TMP: 9/238 Nitrofurantoin: 1/236 Ciprofloxacin: 3/239	Crude risk ratio (95%CI)*: Nitrofurantoin: 8.9 [1.1, 70] Ciprofloxacin: 3.01[0.83, 11]
Lemieux 1974[50]	n = 39 Indication: UTI	1-SMX-TMP (800/160 mg), BID, 4 weeks	2-SMX (1 g), BID, 4 weeks	1-SMX-TMP: 2/17 2-SMX: 0/22	N/A
Lovestad et al. 1979[51]	n = 105 Indication: UTI	SMX-TMP (600 mg/320 mg/ day), 14 days	1-Cotrimazine (180 mg TMP/day + 820 mg sulphadiazine/day), 14 days 2-Sulphalene (200 mg BID (day 1), 100 mg daily, 14 days	SMX-TMP: 3/43 Cotrimazine: 1/41 Sulphalene: 0/21	Crude risk ratio (95%CI)*: 2.86 [0.31–26.4]

TABLE 1 (Continued)

Citation	Sample size and indication	Intervention/exposure group	Comparator group	Cases of rash	Effect estimates
Pisani et al. 1982[52]	n = 64 Indication: UTI	SMX-TMP (4 × 80 mg TMP + 400 mg SMX), QD, 10 days	Kelfiprim (TMP 350 mg + SMP 200 mg), initial double dose, followed by single dose, 10 days	SMX-TMP: 1/30 Kelfiprim: 0/34	N/A
Rubin et al. 1980[53]	n = 134 Indication: UTI	SMX-TMP (800/160 mg), BID, 10 days	1-Amoxicllin trihydrate (3 g), once 2-Ampicillin sodium (500 mg), QID, 10 days	SMX-TMP: 8/53 Amoxicillin tri: 0/53 Ampicillin Na: 2/42	Crude risk ratio (95%CI)*: 3.17 [0.71,14.1]
Sabbaj et al. 1985[54]	n = 370 Indication: UTI	SMX-TMP (800/160 mg), BID	Norfloxacin (400 mg), BID	SMX-TMP: 4/180 Norfloxacin: 0/190	N/A
Skjerven et al. 1979[55]	n = 127 Indication: UTI	SMX-TMP (800/160 mg), BID, 14 days	Sulphadiazine–trimethoprim (410/90 mg), BID, 14 days	SMX-TMP: 3/63 SD-TMP: 1/64	Crude risk ratio (95%CI)*: 3.05 [0.33, 28.5]
Stamm et al. 1987[56]	n = 65 Indication: UTI	1-SMX-TMP (800/160 mg), BID, 14 days 2-SMX-TMP (800/160 mg), BID, 6 weeks	1-Ampicillin (500 mg), QID, 14 days 2-Ampicillin (500 mg), QID, 6 weeks	1-SMX-TMP: 3/23 2-SMX-TMP: 1/13 1-Ampicillin: 1/18 2-Ampicillin: 0/11	Crude risk ratio (95%CI)*: 1-SMX-TMP + 1-Ampicillin: 2.35 [0.27, 20.7]
Stein et al. 1988[57]	n = 164 Indication: UTI	SMX-TMP (800/160 mg) BID, 10 days	RIF-TMP 300/100 mg AM and 600/200 mg PM	RIF-TMP: 2/91 SMX-TMP: 4/73	Crude risk ratio (95%CI)*: 2.49 [0.47, 13.2] 6 weeks SMX-TMP differed from both treatment groups (P = 0.05)
Tungsanga et al. 1988[58]	n = 88 Indication: UTI	SMX-TMP (800/160 mg), BID, 7 days	Norfloxacin (400 mg), BID, 7 days	SMX-TMP: 1/45 Norfloxacin: 0/43	N/A

Abbreviations: BID, twice daily; CI, confidence interval; qd, once daily; QID, 4 times daily; RIF-TMP, rifampicin–trimethoprim; SD-TMP, sulfadiazine–trimethoprim; SMX-TMP, sulfamethoxazole–trimethoprim; UTI, urinary tract infection.
*The reported effect estimate was calculated by the current reviewers.

3.8 | Analysis of pharmacovigilance FAERS data

There was a total of 10 069 cases reporting SMX-TMP as the primary suspect drug following duplicate removal. The baseline characteristics associated with SMX-TMP ADEs are described in Table 2.

3.8.1 | Skin disorders

Skin disorders investigated included rash, SJS, TEN and DRESS. Compared to azithromycin, SMX-TMP showed a 2.9-fold increase in rash reports (1594 of 10 069 [15.8%] vs. 1307 of 21 435 [6.1%]; ROR, 2.89 [95%CI 2.68–3.13]), a 5-fold increase in SJS reports (458 of 10 069 [4.6%] vs. 200 of 21 435 [0.93%]; ROR, 5.06 [95% CI 4.28–5.98]), a 3-fold increase in TEN reports (202 of 10 069 [2.0%] vs. 127 of 21 435 [0.59%]; ROR, 3.44 [95%CI 2.75–4.29] and a 10-fold increase in DRESS reports (411 cases of 10 069 [4.08%] vs. 89 cases of 21 435 [0.42%]; ROR, 10.21 [95% CI, 8.11–12.85]; Figure 4A). Similarly, signals were detected for each of these outcomes when a comparator group of amoxicillin/clavulanate (Figure 4B) or nitrofurantoin (Figure 4C) was used. In comparison to amoxicillin/clavulanate, SMX-TMP exhibited a nearly 7-fold increase in SJS reports (458 of 10 069 [4.6%] vs. 77 of 11 087 [0.39%]; ROR, 6.82 [95%CI 5.35–8.69]) and 2-fold increase in TEN reports (202 of 10 069 [2.0%] vs. 127 of 11 087 [0.83%]; ROR, 2.45 [95%CI 1.91–3.14]; Figure 4B). When nitrofurantoin was used as the comparator group, SMX-TMP showed a nearly 21-fold increase in SJS reports (458 of 10 069 [4.6%] vs. 9 of 4079 [0.22%]; ROR, 21.56 [95%CI 11.13–41.73]) and a 21-fold increase in TEN reports (202 of 10 069 [2.0%] vs. 4 of 4079 [0.10%]; ROR, 20.86 [95%CI 7.75–56.16]; Figure 4C).

3.8.2 | Blood disorders

The blood disorders examined in this active-comparator disproportionality analysis included aplastic anaemia, thrombocytopenia, neutropenia and pancytopenia. Compared to azithromycin, SMX-TMP exhibited a 10-fold increase in the reports of pancytopenia (199 of 10 069 [2.0%] vs. 43 of 21 435 [0.20%]; ROR, 10.03 [95% CI 7.21–13.96]; Figure 5A). This was a higher increase than the ROR observed with amoxicillin/clavulanate (Figure 5B) or nitrofurantoin (Figure 5C)
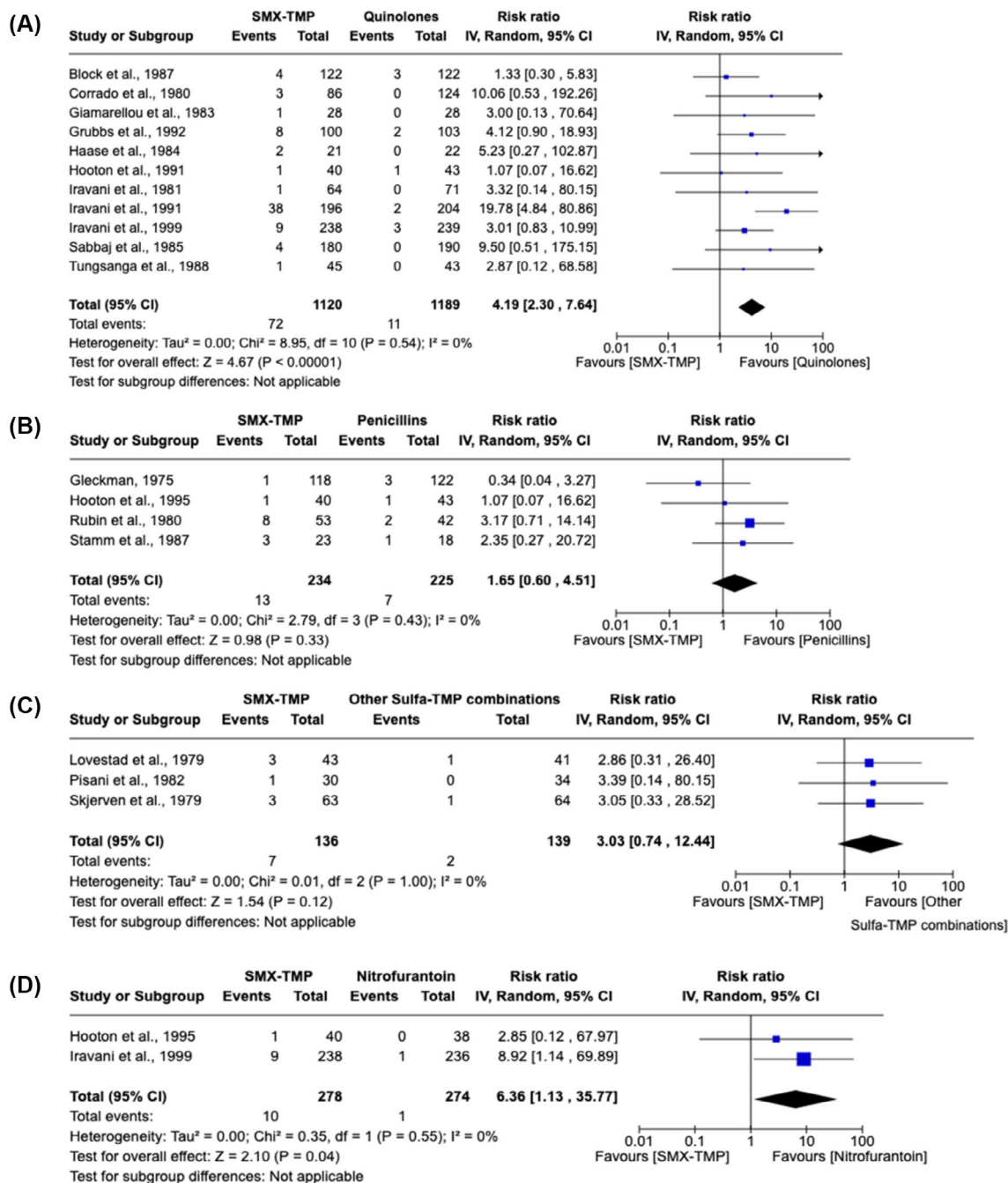
FIGURE 3 Forest plots and pooled risk ratios for rash according to comparator group antibiotic class. For all analyses, inverse variance was used to determine risk ratio (RR) and a random-effects model was used to assess pooled treatment effects across studies. (A) Meta-analysis included adult outpatients with an indication of urinary tract infection (UTI) treated with sulfamethoxazole (SMX)–trimethoprim (TMP; $n = 1120$) or an antibiotic from the quinolone family (i.e. ciprofloxacin, ofloxacin, norfloxacin, temafloxacin, ornalidixic acid; $n = 1189$). (B) Meta-analysis includes adult outpatients with an indication of UTI treated with SMX-TMP ($n = 234$) or an antibiotic from the penicillin family (i.e. ampicillin or amoxicillin; $n = 225$). (C) Meta-analysis includes adult outpatients with an indication of UTI treated with SMX-TMP ($n = 136$) or a different sulfa–trimethoprim combination (i.e. sulfamethopyrazine-TMP or sulfadiazine-TMP; $n = 139$). (D) Meta-analysis includes adult outpatients with an indication of UTI treated with SMX-TMP ($n = 278$) or an antibiotic from the nitrofuran family (i.e. nitrofurantoin) ($n = 274$).

as comparator groups. Similarly, SMX-TMP showed a higher ROR for neutropenia compared to azithromycin (159 of 10 069 [1.6%] *vs.* 55 of 21 435 [0.26%]; ROR, 6.24 [95% CI 4.59–8.48]), amoxicillin/clavulanate (159 of 10 069 [1.6%] *vs.* 64 of 21 435 [0.30%]; ROR, 2.76 [95% CI 2.07–3.70]) and nitrofurantoin (159 of 10 069 [1.6%] *vs.*

12 of 4079 [0.29%]; ROR, 5.44 [95% CI 3.02–9.79]; Figure 5). The ROR for thrombocytopenia and aplastic anaemia was similar across the comparator groups. However, the ROR for aplastic anaemia was not calculated for the nitrofurantoin group due to fewer than 3 reported cases (Figure 5).

TABLE 2 Clinical characteristics of SMX-TMP associated study ADE reports from the FAERS database (January 2004 to December 2023).

	All SMX-TMP case reports (n = 10 069)	Rash (n = 1594)	Thrombocytopenia (n = 279)	Hyperkalaemia (n = 552)	Acute kidney injury (n = 491)
Age (years)					
Median age (IQR)	56 (36–38)	53 (33–66)	59.5 (40–68)	69 (62–78)	68 (56–75)
Age, n (%)					
<18	698 (6.9)	109 (6.8)	23 (8.2)	2 (0.36)	27 (5.5)
18–<45	2004 (19.9)	397 (24.9)	54 (19.4)	25 (4.5)	45 (9.2)
45–<65	2559 (25.4)	417 (26.2)	85 (30.5)	149 (27.0)	129 (26.3)
>65	2563 (25.5)	354 (22.2)	88 (31.5)	345 (62.5)	262 (53.4)
Unknown	2245 (22.3)	317 (19.9)	29 (10.4)	31(5.62)	28 (5.7)
Sex					
Male	4549 (45.2)	743 (46.6)	169 (60.6)	417 (75.5)	331 (67.4)
Female	4580 (45.5)	734 (46.1)	95 (34.1)	122 (22.1)	134 (27.3)
Unknown	940 (9.3)	117 (7.3)	15 (5.4)	13 (2.4)	26 (5.3)
Weight (kg)					
Median weight (IQR)	77 (63–92)	78 (64–93)	76 (66–89)	84 (72–98)	84 (73–100)
<43	169 (1.7)	42 (2.6)	4 (1.4)	5 (0.91)	1 (0.20)
43–<76	1515 (15.1)	326 (20.5)	49 (17.6)	87 (15.8)	70 (14.3)
76–<92	895 (8.9)	223 (14.0)	29 (10.4)	89 (16.1)	60 (12.2)
>92	876 (8.7)	208 (13.1)	22 (7.9)	104 (18.8)	83 (16.9)
Unknown	6614 (65.7)	795 (50.0)	175 (62.7)	267 (48.4)	277 (56.4)
Indication of use					
Urinary tract infection	1450 (14.4)	281 (17.6)	36 (12.9)	96 (17.4)	73 (14.9)
Respiratory tract infection	274 (2.7)	81 (5.1)	8 (2.9)	15 (2.7)	7 (1.4)
Skin infection	530 (5.6)	124 (7.8)	21 (7.5)	48 (8.7)	50 (10.2)
Serious outcomes					
Death	297 (3.0)	16 (1.0)	11 (3.9)	5 (0.91)	9 (1.8)
Hospitalization	2477 (24.6)	521 (32.7)	105 (37.6)	298 (54.0)	216 (44.0)
Life threatening	608 (6.0)	89 (5.6)	33 (11.8)	61 (11.1)	23 (4.7)
Disability	108 (1.1)	22 (1.4)	0 (0)	3 (0.54)	1 (0.20)
Time to reaction onset					
Median time to reaction onset (IQR), days	7 (3–10)	7 (3–72)	10 (6–79)	10 (6–77)	10 (6–79)
<3	758 (7.5)	184 (11.5)	6 (2.15)	22 (4.0)	17 (3.5)
3- < 7	727 (7.2)	172 (10.8)	23 (8.2)	65 (11.8)	49 (10.0)
7- < 14	755 (7.5)	221 (13.06)	38 (13.6)	102 (18.5)	58 (11.8)
14- < 30	141 (1.4)	32 (2.0)	7 (2.5)	23 (4.2)	10 (2.0)
≥30	887 (8.8)	211 (13.2)	32 (11.5)	101 (18.3)	70 (14.3)
Unknown	6801 (67.5)	774 (48.6)	173 (62.0)	239 (43.3)	287 (58.5)

Abbreviation: IQR, interquartile range.

3.8.3 | Metabolism disorders

SMX-TMP exhibited a 56-fold (552 of 10 069 [5.5%] vs. 22 of 21 435 [0.10%]; ROR, 56.45 [95%CI 36.84–86.51]) and 64-fold (552 of 10 069 [5.5%] vs. 10 of 11 087 [0.19%]; ROR, 64.26 [95%CI 34.36–120.17]) increase in hyperkalaemia reports in comparison to azithromycin and amoxicillin/clavulanate, respectively (Figure 6). There was also an increased risk of hyponatraemia following SMX-TMP use in comparison to all 3 comparator groups.

4 | DISCUSSION

The present study used both a systematic review/meta-analysis and an active comparator disproportionality analysis of the FAERS database to examine the safety profile of SMX-TMP. Forty-three studies were included in the review, covering a wide range of ADEs, including skin disorders, blood disorders, immune system disorders, hepatic disorders, renal disorders and musculoskeletal disorders reported in comparative studies.
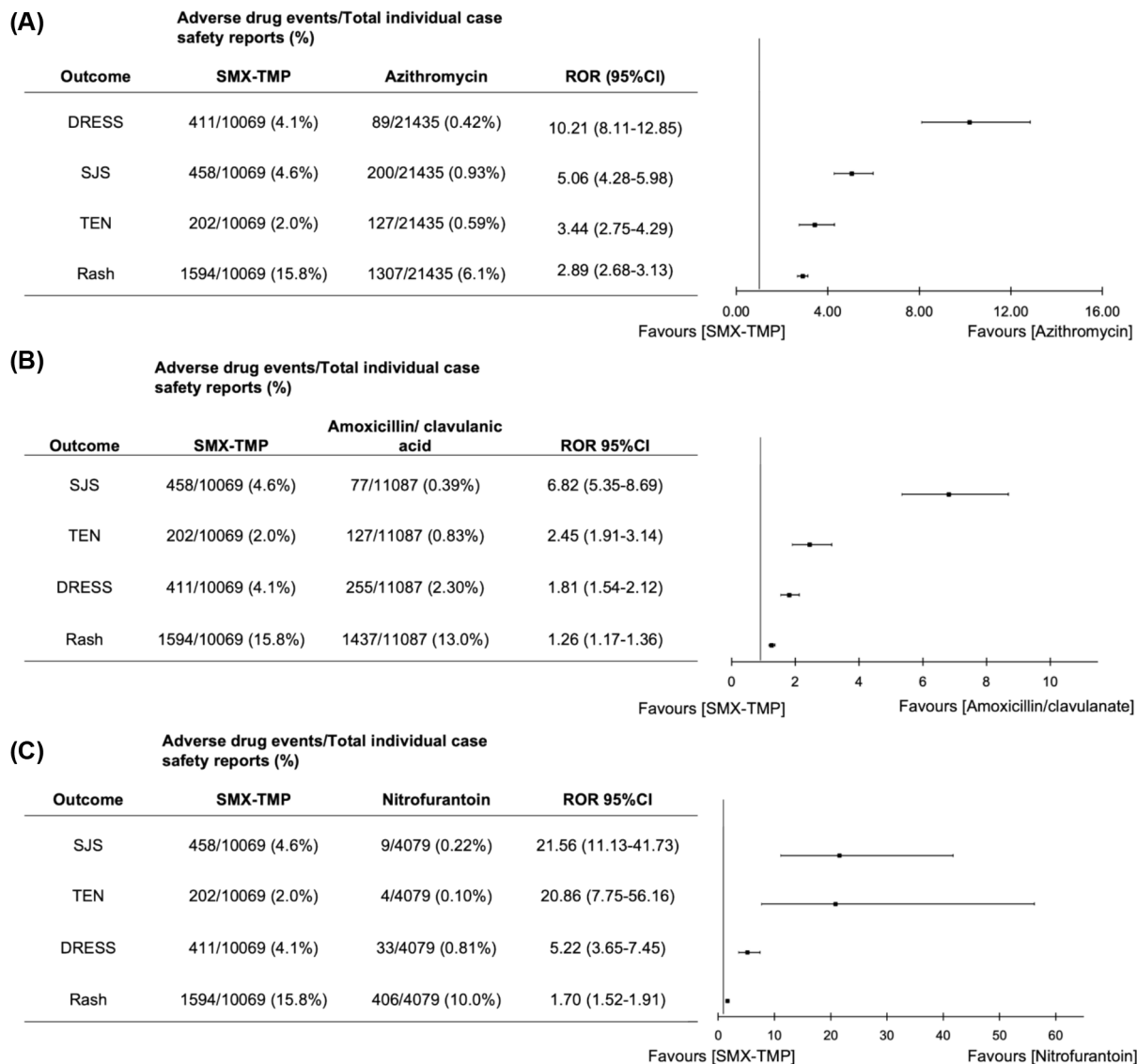
(A)

Outcome	SMX-TMP	Azithromycin	ROR (95%CI)
DRESS	411/10069 (4.1%)	89/21435 (0.42%)	10.21 (8.11-12.85)
SJS	458/10069 (4.6%)	200/21435 (0.93%)	5.06 (4.28-5.98)
TEN	202/10069 (2.0%)	127/21435 (0.59%)	3.44 (2.75-4.29)
Rash	1594/10069 (15.8%)	1307/21435 (6.1%)	2.89 (2.68-3.13)

(B)

Outcome	SMX-TMP	Amoxicillin/ clavulanic acid	ROR 95%CI
SJS	458/10069 (4.6%)	77/11087 (0.39%)	6.82 (5.35-8.69)
TEN	202/10069 (2.0%)	127/11087 (0.83%)	2.45 (1.91-3.14)
DRESS	411/10069 (4.1%)	255/11087 (2.30%)	1.81 (1.54-2.12)
Rash	1594/10069 (15.8%)	1437/11087 (13.0%)	1.26 (1.17-1.36)

(C)

Outcome	SMX-TMP	Nitrofurantoin	ROR 95%CI
SJS	458/10069 (4.6%)	9/4079 (0.22%)	21.56 (11.13-41.73)
TEN	202/10069 (2.0%)	4/4079 (0.10%)	20.86 (7.75-56.16)
DRESS	411/10069 (4.1%)	33/4079 (0.81%)	5.22 (3.65-7.45)
Rash	1594/10069 (15.8%)	406/4079 (10.0%)	1.70 (1.52-1.91)

FIGURE 4 Reporting odds ratio (ROR) and confidence interval (95%CI) for the skin disorders rash, Stevens–Johnson syndrome (SJS), toxic epidermal necrolysis (TEN), and drug reaction with eosinophilia and systemic symptoms (DRESS) using 3 different comparator drugs. Comparator drugs included (A) azithromycin, (B) amoxicillin/clavulanate and (C) nitrofurantoin. ROR > 1 and lower confidence limit >1 indicates signal detection.

Skin disorders, particularly rash, were the most commonly reported ADEs following SMX-TMP use across the included studies. Compared to other antibiotics, SMX-TMP was associated with a 2.6-fold increased risk of rash. Results were consistent across subgroup analyses when antibiotic classes served as comparator groups. Findings from this meta-analysis of RCTs were consistent across other study designs. Two observational studies reporting SCARs showed that the risk of SJS/TEN was higher among SMX-TMP users compared to other antibiotic users.[59,60] However, these results should be interpreted with caution. Although the risk of SJS was higher for SMX-TMP users in the first study, the hazard ratio could not be quantified due to low case counts, and the results were not adjusted for potential confounders.[59] In the second study, the SJS/TEN risk magnitude was higher for SMX-TMP users. A similar increase was also observed for penicillin users, which might suggest a confounding

indication. However, it is also possible that penicillin users are at a higher risk of developing SJS/TEN. Although only 2 studies included in the review reported on SJS/TEN following SMX-TMP treatment, our active comparator-restricted disproportionality analysis showed a 5-fold increase in the risk of SJS, a 3-fold increase for TEN and a 10-fold increase for DRESS with SMX-TMP compared to azithromycin. Similar results were observed when using amoxicillin/clavulanate and nitrofurantoin as comparator groups. These results align with a previously conducted disproportionality analysis of the Vietnamese spontaneous reporting database, reporting an adjusted ROR of 3.1 (95%CI 1.16–6.9) for SMX-TMP compared to reports of other medications.[73]

Immunoglobulin E (IgE)-mediated hypersensitivity cutaneous reactions are hypothesized to be mediated by the 5-methyl group or the N1-substitute group in SMX-TMP, which are both important for
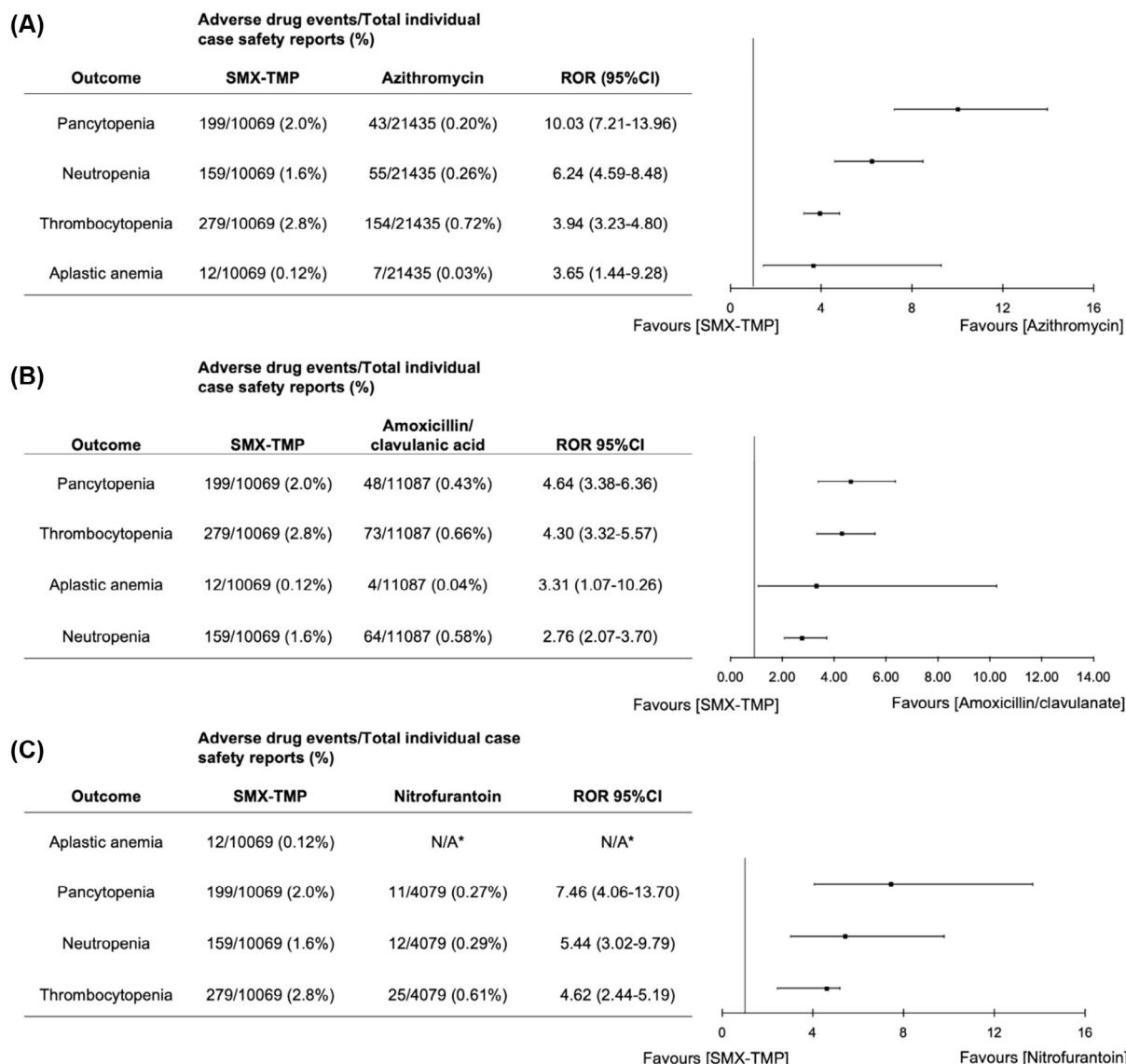
(A)

Adverse drug events/Total individual case safety reports (%)

Outcome	SMX-TMP	Azithromycin	ROR (95%CI)
Pancytopenia	199/10069 (2.0%)	43/21435 (0.20%)	10.03 (7.21-13.96)
Neutropenia	159/10069 (1.6%)	55/21435 (0.26%)	6.24 (4.59-8.48)
Thrombocytopenia	279/10069 (2.8%)	154/21435 (0.72%)	3.94 (3.23-4.80)
Aplastic anemia	12/10069 (0.12%)	7/21435 (0.03%)	3.65 (1.44-9.28)

Favours [SMX-TMP] 0 4 8 12 16 Favours [Azithromycin]

(B)

Adverse drug events/Total individual case safety reports (%)

Outcome	SMX-TMP	Amoxicillin/ clavulanic acid	ROR 95%CI
Pancytopenia	199/10069 (2.0%)	48/11087 (0.43%)	4.64 (3.38-6.36)
Thrombocytopenia	279/10069 (2.8%)	73/11087 (0.66%)	4.30 (3.32-5.57)
Aplastic anemia	12/10069 (0.12%)	4/11087 (0.04%)	3.31 (1.07-10.26)
Neutropenia	159/10069 (1.6%)	64/11087 (0.58%)	2.76 (2.07-3.70)

Favours [SMX-TMP] 0.00 2.00 4.00 6.00 8.00 10.00 12.00 14.00 Favours [Amoxicillin/clavulanate]

(C)

Adverse drug events/Total individual case safety reports (%)

Outcome	SMX-TMP	Nitrofurantoin	ROR 95%CI
Aplastic anemia	12/10069 (0.12%)	N/A*	N/A*
Pancytopenia	199/10069 (2.0%)	11/4079 (0.27%)	7.46 (4.06-13.70)
Neutropenia	159/10069 (1.6%)	12/4079 (0.29%)	5.44 (3.02-9.79)
Thrombocytopenia	279/10069 (2.8%)	25/4079 (0.61%)	4.62 (2.44-5.19)

Favours [SMX-TMP] 0 4 8 12 16 Favours [Nitrofurantoin]

FIGURE 5 Reporting odds ratio (ROR) and confidence interval (95%CI) for the blood disorders aplastic anaemia, pancytopenia, neutropenia and thrombocytopenia using 3 different comparator drugs. Comparator drugs included (A) azithromycin, (B) amoxicillin/clavulanate and (C) nitrofurantoin. ROR > 1 and lower confidence limit >1 indicates signal detection.*indicates number of cases < 3, so ROR was not calculated.

IgE antibody recognition.[74,75] Predisposition to SMX-TMP induced rash has been linked to pharmacogenetic factors, including N-acetyltransferase 2 (NAT2) slow acetylator phenotypes. Previous studies have demonstrated that NAT2 slow acetylators are at increased risk for SCARs including SJS and TEN.[76,77] It has been suggested that the structural features of SMX-TMP metabolites, such as SMX-nitro, contribute to non-IgE-mediated reactions.[75,78] In slow acetylators, the cytochrome P450 isoenzyme 2C9 facilitates the formation of these reactive compounds, which can bind to T cells and induce hypersensitivity reactions. Different ethnic groups exhibit different prevalences of the NAT2 slow acetylator phenotype, with rates of approximately 5–25% in East Asians, 40–60% in Caucasians and 90% in Arab populations.[79]

In our study, the median time to rash onset was 7 days, with most AEs occurring within 30 days. This is consistent with findings from a recent population-based study examining severe cutaneous drug reactions associated with oral antibiotics, including TMP-SMX.[80] However, this onset time is longer than typically expected for an IgE-mediated allergic reaction, which often occurs within minutes to hours after allergen exposure. Our results suggest that T-cell-mediated delayed hypersensitivity mechanisms may be the primary drivers of TMP-SMX-induced cutaneous reactions rather than immediate-type hypersensitivity. As outlined above, some mechanistic studies may support this hypothesis, suggesting that pharmacogenetic factors such as NAT2 slow acetylator phenotypes contribute to SCARs such as SJS and TEN. Additionally, reactive SMX metabolites in individuals with reduced acetylation capacity may play a role in non-IgE-mediated hypersensitivity reactions hypersensitivity reactions. However, further mechanistic studies are required to confirm this hypothesis.
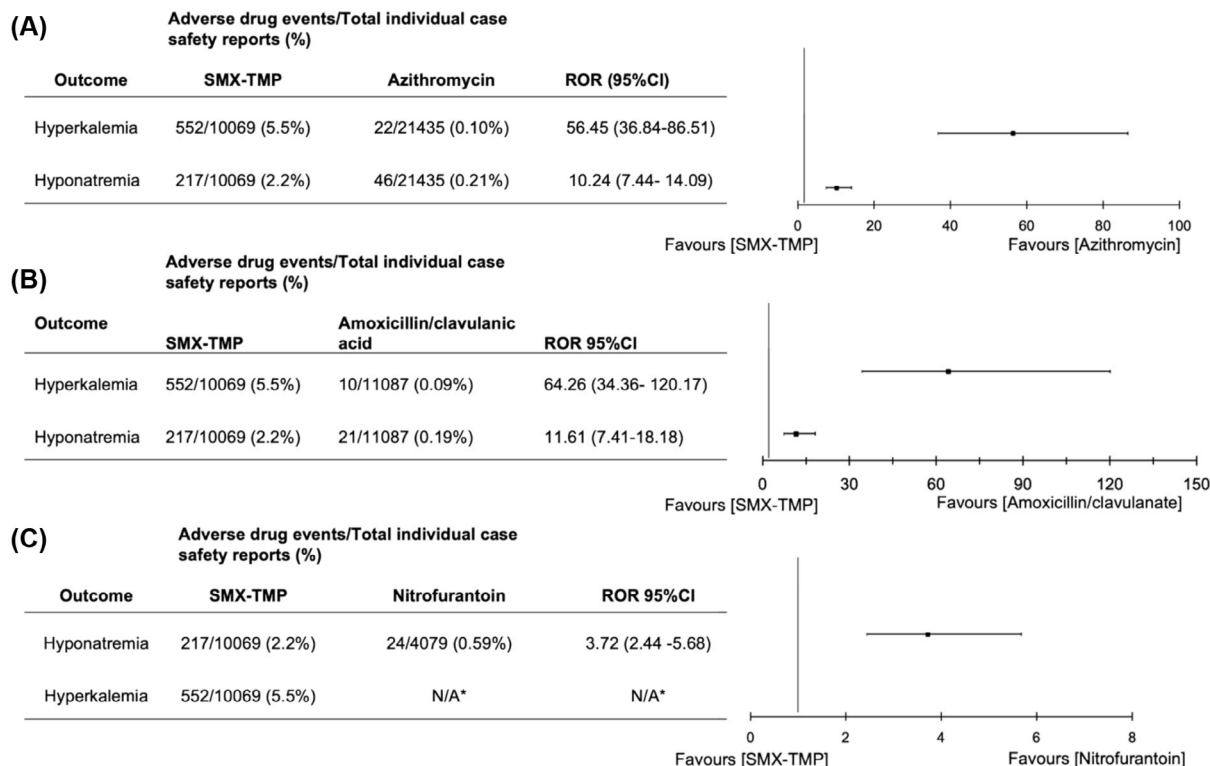
FIGURE 6 Reporting odds ratio (ROR) and confidence interval (95%CI) for the metabolic disorders hyperkalaemia and hyponatraemia using 3 different comparator drugs. Comparator drugs included (A) azithromycin, (B) amoxicillin/clavulanate and (C) nitrofurantoin. ROR > 1 and lower confidence limit >1 indicates signal detection. * Indicates fewer than 3 cases, ROR not calculated.

Clinicians should remain vigilant for any signs of skin adverse reactions in patients who have been prescribed SMX-TMP. It is essential to consider alternative antibiotics for patients with a history of skin reactions to SMX-TMP or those who are at a higher risk of developing skin conditions.

Blood disorders were the second most reported ADEs following SMX-TMP use in the included studies. Compared to quinolone users, SMX-TMP users had an almost 4-fold higher risk of leucopenia, but the results did not reach statistical significance due to a lack of power. Our pharmacovigilance study showed a 10-fold increase in reports of pancytopenia, a 6-fold increase in neutropenia and a 4-fold increase in both thrombocytopenia and aplastic anaemia for SMX-TMP compared to azithromycin. These results were consistent when nitrofurantoin and amoxicillin/clavulanate were used as comparator groups. Prolonged use of SMX-TMP has been associated with myelosuppression, leading to thrombocytopenia, anaemia and pancytopenia.[81] This ADE may result from SMX-TMP's inhibition of dihydrofolic acid in haematopoietic progenitor cells, leading to impaired proliferation and maturation of blood cell lineages.[81,82] Further investigation is required to determine the risk of blood disorders associated with SMX-TMP use in outpatients.

Hyperkalaemia was reported most frequently in studies investigating metabolism disorders. A well-conducted population-based study showed that SMX-TMP vs. amoxicillin was associated with a >3-fold increase in the risk of hyperkalaemia.[69] Our pharmacovigilance study showed a 56-fold increase in reports of hyperkalaemia

and a 10-fold increase in reports of hyponatraemia for SMX-TMP compared to azithromycin. Standard doses of SMX-TMP are linked to metabolic disorders such as hyperkalaemia and hyponatraemia in patients with pre-existing renal function deficiencies.[83,84] SMX-TMP may cause hyperkalaemia primarily through TMP's interference with epithelial sodium channels in the distal nephron, leading to increased potassium retention and decreased sodium reabsorption.[85] Healthcare providers should be aware of the possible association of SMX-TMP with hyperkalaemia, especially in elderly patients who are potentially at high risk of this ADE. While our study results indicate that SMX-TMP is associated with an increased risk of several adverse effects, including severe cutaneous reactions such as SJS, pancytopenia and hyperkalaemia, we acknowledge that TMP-SMX is often the treatment of choice for serious infections, such as Pneumocystis pneumonia, particularly in HIV patients. In these cases, the benefits of using TMP-SMX, which is highly effective for treating these infections, may outweigh the risks of rare and potentially severe ADEs. The risk of ADEs must always be balanced against the much higher risk of morbidity or mortality associated with ineffective treatment in such critical conditions. Physicians should carefully monitor and consider patient-specific factors when prescribing TMP-SMX, especially for patients with underlying comorbidities or in settings where alternative treatments may not be as effective. Additionally, our findings should be confirmed in future pharmacoepidemiological studies to validate these safety signals and better guide clinical practice.

The results of our study are consistent with previous findings and provide further insight into ADEs associated with SMX-TMP use in outpatient treatment of bacterial infections.[86] This systematic review had several limitations. First, most RCTs included in the review (71%; 24/34) were subject to a high or unclear risk of bias. The 2 studies included in the meta-analysis for leucopenia were scored as high and unclear risk of bias, respectively, leading to low evidence. Second, most studies included in the review (84%; 36/43) were published before 2000. The temporal limitation may affect the findings' applicability to current clinical practices, as both antibiotic safety profiles and ADE management practices have evolved over time. However, results for the pharmacovigilance study, which include a contemporary period of time (2004–2023), were consistent with the results observed in this review. Third, 93.8% of individuals included in the meta-analysis were female. This is mainly because the studies focused on UTIs, which predominantly affect women. This sex imbalance may limit the generalizability of our findings to males or individuals using SMX-TMP for other indications. However, results from the pharmacovigilance study showed consistent reporting odds ratios for rash in both males and females, suggesting that the risk of skin reactions associated with SMX-TMP may not be limited to women. Fourth, studies reviewed came from diverse geographic locations, which could result in variability in the reported ADEs due to differences in patient populations, healthcare systems and antibiotic prescribing practices. Due to this variability, our findings may not be generalizable to specific regions or populations. Sixty percent of reports from the FAERS database that were included in our active comparator disproportionality analysis came from the USA, which can limit the generalizability of the results. Fifth, fewer studies were included in the review for many ADEs, such as immune system disorders and metabolic disorders, which precluded further meta-analyses of these outcomes. However, data from our pharmacovigilance study showed potential signals for these outcomes that require further research with a more robust study design. Although the pharmacovigilance study extended and supplemented the findings of the review, it remains limited by the spontaneous reporting nature of the database. The FAERS database is subject to underreporting because it relies on a voluntary reporting system, and healthcare professionals and consumers do not always report ADEs. Further, the reports on the database often lack detailed patient information and information on crucial confounding variables such as medical history. The FAERS database is also subject to confounding by indication and notoriety bias.[32,87] Disproportionality analyses, such as the current study that calculate effects such as ROR, are not indications of the strength of an association between a drug and ADE. This study was intended to generate hypotheses for future studies to investigate ADE association with SMX-TMP use. Sixth, while including the Cochrane Central Register of Controlled Trials (CENTRAL) could increase the coverage of our studies, we conducted a comprehensive search using MEDLINE (Ovid) and Embase (Ovid), both of which are well-regarded for their extensive coverage of medical and pharmacological literature. Searching 2 or more databases provides >95% coverage of relevant references.[21] Additionally, we manually reviewed the reference lists of included studies to ensure completeness. We are confident that our literature search was comprehensive and minimized the risk of missing studies.

Seventh, while we did not include the Baktar brand name for SMX-TMP used in some regions, we are confident that our search strategy captured all relevant studies. We included both the generic terms "sulfamethoxazole–trimethoprim" and "cotrimoxazole," as well as widely recognized commercial brand names such as "Bactrim" and "Septra." This approach ensured that studies using various brand names were incorporated. Baktar is not commonly used or reported in the literature and would probably be captured under the generic terms "sulfamethoxazole–trimethoprim" and "cotrimoxazole." Therefore, its omission is unlikely to compromise the thoroughness of our search. Eighth, we acknowledged that SMX-TMP dosing can vary widely depending on the indication. Unfortunately, dosing information was not consistently available in the studies included in our analysis, preventing us from performing subgroup analyses based on specific dosing regimens. Future research with more detailed dosing data would be valuable in understanding how dosing impacts the risk of AEs. Ninth, pre-existing sulfa allergies were not assessed or reported in individuals who developed a rash. This is a potential limitation, as a known sulfa allergy could increase the likelihood of rash development. Future studies that account for this risk factor could provide clearer insights into the relationship between sulfa allergies and the risk of skin reactions associated with SMX-TMP.

Our findings highlight the need for additional high-quality studies to further explore the safety of SMX-TMP. Future research should address the limitations identified in our review and in our pharmacovigilance study by conducting contemporary, well-designed, population-based studies with rigorous methodologies. Clinical decision-making needs to consider a variety of patient populations when researching ADEs.

5 | CONCLUSION

Our meta-analyses and pharmacovigilance study suggested that SMX-TMP may be associated with an increased risk of rash and SCARs, such as SJS, TEN and DRESS, and other ADEs, such as pancytopenia, neutropenia, thrombocytopenia and hyperkalaemia compared to other commonly used antibiotics. However, potential biases in both the meta-analysis and the pharmacovigilance study may affect the validity of these findings. Further research is needed to accurately quantify the association between SMX-TMP and ADEs to guide clinicians in considering alternative treatments or enhanced monitoring strategies for at-risk patients.

CONFLICT OF INTEREST STATEMENT

All authors reported no conflicts of interest.

DATA AVAILABILITY STATEMENT

The data that supports the findings of this study are available in the supplementary material of this article.

PATIENT CONSENT

This study does not include factors necessitating patient consent.

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SUPPORTING INFORMATION

Additional supporting information can be found online in the Supporting Information section at the end of this article.