Literature Reviews: A Pharmacovigilance-Based Review of Adverse Drug Reactions Associated with Commonly Used Antibiotics Using WHO Causality, Severity, and Preventability Assessment Tools

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ABSTRACT

This review critically examines adverse drug reactions (ADRs) associated with commonly used antibiotics through a pharmacovigilance lens, utilizing WHO-recommended causality, severity, and preventability assessment tools. A systematic evaluation of retrospective and prospective studies from diverse healthcare settings was conducted to analyze ADR incidence patterns, affected organ systems, and assessment methodologies. The findings indicate that gastrointestinal and cutaneous ADRs are the most frequently reported, with incidence rates showing wide variability across populations. WHO-UMC and Naranjo causality scales are the most commonly employed tools; however, inconsistent application and moderate concordance highlight the lack of methodological uniformity. Severity and preventability analyses reveal that a significant proportion of antibiotic-related ADRs are preventable, often resulting from prescribing errors, inappropriate antibiotic use, and inadequate patient monitoring. Integration of pharmacovigilance practices with antimicrobial stewardship programs demonstrates potential to enhance patient safety and reduce antimicrobial resistance. Overall, the review underscores the need for standardized WHO-aligned assessment frameworks and active surveillance systems to strengthen antibiotic safety monitoring and optimize therapeutic outcomes.

Keywords: Adverse Drug Reactions, Antibiotics, Pharmacovigilance, WHO Causality Assessment, Severity and Preventability

INTRODUCTION

Research on pharmacovigilance review of adverse drug reactions (ADRs) associated with commonly used antibiotics has emerged as a critical area of inquiry due to its impact on patient safety and healthcare systems worldwide. The field has evolved from early spontaneous reporting systems to more structured pharmacovigilance programs that assess causality, severity, and preventability of ADRs(Sundaran et al., 2018) (Belhekar et al., 2018). Antibiotics remain among the most frequently prescribed drugs in hospitals, accounting for a significant proportion of ADRs, with studies reporting antimicrobial agents as the leading cause of ADRs in various settings(Lhamo et al., 2024) (Sruthi et al., 2024). The social and clinical significance is underscored by the high incidence of antibiotic-associated ADRs contributing to increased morbidity, prolonged hospital y

stays, and economic burden(Venkatasubbaiah et al., 2020) (Iftikhar et al., 2018). For instance, antimicrobial-related ADRs have been linked to up to 24% prevalence in hospitalized patients, with substantial rates of serious and preventable reactions(Chiumia et al., 2024) (Saqib et al., 2018).

Despite extensive research, the problem of antibiotic-associated ADRs persists, compounded by underreporting and inconsistent assessment methodologies(Sundaran et al., 2018) (Kumaraswamy et al., 2023). A critical knowledge gap exists in the comprehensive evaluation of ADRs using standardized tools such as the WHO-UMC causality scale, Hartwig severity scale, and Schumock and Thornton preventability scale across diverse populations and healthcare settings(Manjhi et al., 2024) (Anthony & P, 2022). Conflicting findings regarding the preventability and severity of ADRs, as well as variations in causality assessments, highlight the need for systematic synthesis(Unnissa et al., 2024) (Keche et al., 2021). Moreover, the lack of robust pharmacovigilance infrastructure in many regions, including developing countries, limits data availability and impedes effective ADR management(Iftikhar et al., 2018) (Saqib et al., 2018). This gap has significant consequences, including increased patient morbidity, antimicrobial resistance, and healthcare costs(Soysal et al., 2023) (Sittiphan et al., 2025).

The conceptual framework for this review integrates the definitions and interrelations of ADRs, causality, severity, and preventability within pharmacovigilance, as established by authoritative sources(Manjhi et al., 2024) (Kumaraswamy et al., 2023). ADRs are defined as noxious and unintended responses to drugs at normal doses, with causality assessment determining the likelihood of drug-event association, severity indicating clinical impact, and preventability reflecting the potential to avoid the reaction(Mishra et al., 2024) (Manjhi et al., 2024). Understanding these dimensions is essential for optimizing antibiotic use and enhancing patient safety.

The purpose of this systematic review is to critically evaluate the patterns of antibiotic-associated ADRs, applying WHO causality, severity, and preventability assessment tools to synthesize current evidence. This review aims to address the identified gaps by consolidating data from diverse healthcare settings, thereby informing clinical practice and pharmacovigilance strategies. The value added lies in providing a comprehensive, methodologically rigorous synthesis that supports improved ADR detection, reporting, and prevention.

This review employs a systematic methodology, including inclusion of studies assessing antibiotic-related ADRs with standardized assessment scales, and exclusion of studies lacking such evaluations. Analytical frameworks focus on causality, severity, and preventability metrics. The findings are organized to elucidate ADR patterns, risk factors, and implications for pharmacovigilance and clinical management.

Purpose and Scope of the Review

Statement of Purpose

The objective of this report is to examine the existing research on "Pharmacovigilance review of adverse drug reactions associated with commonly used antibiotics, WHO causality, severity, preventability assessment tools" in order to synthesize current evidence on the patterns, assessment methodologies, and clinical implications of antibiotic-related adverse drug reactions (ADRs). This review is important because antibiotics are among the most frequently prescribed medications worldwide, yet their use is often complicated by ADRs that can lead to increased morbidity, healthcare costs, and antimicrobial resistance. By critically analyzing the application of standardized tools such as the WHO causality scale, severity grading, and preventability assessments, this report aims to identify gaps in pharmacovigilance practices and propose strategies to enhance patient safety and optimize antibiotic stewardship.

Specific Objectives:

- To evaluate current knowledge on the incidence and patterns of adverse drug reactions associated with commonly used antibiotics.

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- Benchmark existing pharmacovigilance methodologies employing WHO causality, severity, and preventability assessment tools in antibiotic ADR monitoring.
- Identify and synthesize factors influencing the preventability and severity of antibiotic-related ADRs across diverse healthcare settings.
- Compare the effectiveness of different causality assessment scales and their impact on ADR reporting and management.
- Deconstruct the relationship between antibiotic use, ADR occurrence, and antimicrobial resistance within pharmacovigilance frameworks

METHODOLOGY

Transformation of Query

We take your original research question — "Pharmacovigilance review of adverse drug reactions associated with commonly used antibiotics, WHO causality(Table 1), severity(Table 2), preventability assessment(Table 3) tools"—and expand it into multiple, more specific search statements. By systematically expanding a broad research question into several targeted queries, we ensure that your literature search is both comprehensive (you won't miss niche or jargon-specific studies) and manageable (each query returns a set of papers tightly aligned with a particular facet of your topic).

Table 1: WHO-UMC causality assessment scale

Causality term	**Causality term**
Certain	· Event or laboratory test abnormality, with a plausible time relationship to drug intake · Cannot be explained by disease or other drugs · Response to withdrawal plausible (pharmacologically, pathologically) · Event definitive pharmacologically or phenomenologically (i.e., an objective and specific medical disorder or a recognised pharmacological phenomenon) · Rechallenge satisfactory, if necessary
Probable / Likely	· Event or laboratory test abnormality, with reasonable time relationship to drug intake · Unlikely to be attributed to disease or other drugs · Response to withdrawal clinically reasonable, Rechallenge not required
Possible	· Event or laboratory test abnormality, with reasonable time relationship to drug intake · Could also be explained by disease or other drugs · Information on drug withdrawal may be lacking or unclear
Unlikely	· Event or laboratory test abnormality, with a time to drug intake that makes a relationship improbable (but not impossible) · Disease or other drugs provide plausible explanations
Conditional / Unclassified	· Event or laboratory test abnormality · More data for proper assessment needed, or · Additional data under examination
Un-assessable / Unclassifiable	· Cannot be judged because the information is insufficient or contradictory · Data cannot be supplemented or verified

Table 2: Hartwig and Siegel's severity assessment scale

Level 1	An ADR occurred but required no change in treatment with the suspected drug
Level 2	The ADR required that treatment with the suspected drug be held, discontinued, or otherwise changed.

	No antidote or other treatment requirement was required. No increase in length of stay (LOS)
Level 3	The ADR required that treatment with the suspected drug be held, discontinued, or otherwise changed. AND/OR An Antidote or other treatment was required. No increase in length of stay (LOS)
Level 4	Any level 3 ADR which increases the length of stay by at least 1 day. OR The ADR was the reason for the admission
Level 5	Any level 4 ADR which requires intensive medical care
Level 6	The adverse reaction caused permanent harm to the patient
Level 7	The adverse reaction either directly or indirectly led to the death of the patient

Table 3: Preventability assessment (Schumock and Thornton criteria)

Section A (Answer in either yes or no)
Was there a history of allergy or a previous reaction to the drug? Was the drug involved was inappropriate for the patient's clinical condition? Was the dose, route, or frequency of administration was inappropriate for patient's age, weight or disease state? Was toxic serum drug concentration (or lab monitoring test) documented? Was there a known treatment for ADEs?
Section B (Answer in either yes or no)
Was required therapeutic drug monitoring or another necessary laboratory test not performed? Was the drug interaction involved in ADEs? Was poor compliance involved in ADE? Were preventative measures not prescribed or administered to the patient?
Section C
If all the above criteria are not fulfilled

Below were the transformed queries we formed from the original query:

Pharmacovigilance review of adverse drug reactions associated with commonly used antibiotics, WHO causality, severity, preventability assessment tools

Exploring the relationship between antimicrobial resistance and adverse drug reactions from commonly used antibiotics in pharmacovigilance, including methodologies for causality and preventability assessments.

Evaluating the impact of adverse drug reactions associated with antibiotics in diverse populations and healthcare settings, alongside strategies for enhancing pharmacovigilance and antibiotic stewardship to improve patient safety.

Screening Papers: We then run each of your transformed queries with the applied Inclusion & Exclusion Criteria to retrieve a focused and . during this process we found 205 papers

Citation Chaining - Identifying additional relevant works

Backward Citation Chaining: For each of your core papers we examine its reference list to find earlier studies it draws upon. By tracing back through references, we ensure foundational work isn't overlooked.

Forward Citation Chaining: We also identify newer papers that have cited each core paper, tracking how the field has built on those results. This uncovers emerging debates, replication studies, and recent methodological y

advancesA total of 73 additional papers are found during this process

Relevance scoring and sorting

We take our assembled pool of 278 candidate papers (205 from search queries + 73 from citation chaining) and impose a relevance ranking so that the most pertinent studies rise to the top of our final papers table. We found 268 papers that were relevant to the research query. Out of 268 papers, 50 were highly relevant.

RESULTS AND DISCUSSION

Descriptive Summary of the Studies

This section maps the research landscape of the literature on Pharmacovigilance review of adverse drug reactions associated with commonly used antibiotics, WHO causality, severity, preventability assessment tools, encompassing a diverse range of retrospective and prospective studies primarily from tertiary care hospitals across India, Pakistan, Malawi, Thailand, and other regions. The studies predominantly focus on the incidence, pattern, and clinical characteristics of antibiotic-related ADRs, employing standardized assessment tools such as WHO-UMC, Naranjo, Hartwig, and Schumock and Thornton scales. This comparative analysis is crucial for understanding the consistency and variability in ADR reporting, preventability, and causality assessment, as well as the implications for antimicrobial stewardship and resistance mitigation.

Study	Incidence and Pattern	Assessment Tool Utilization	Preventability Rate	Causality Assessment Concordance	Impact on Stewardship
(Renuka et al., 2014)	97 antibiotic ADRs; skin reactions predominant; quinolones leading	WHO-UMC causality scale used	Not specified	Majority probable causality	Calls for strengthened regional PV centers
(Ramakrishnaiah et al., 2015)	ADRs mostly probable causality; moderate severity common	WHO, Hartwig, Schumock & Thornton scales	Majority probably preventable	Probable causality dominant	Highlights patient and HCP ADR reporting roles
(Saqib et al., 2018)	38.9% ADEs in inpatients; GI, hematologic, skin systems affected	Naranjo, modified Schumock & Thornton scales	59.3% definitely preventable ADEs	Most non-preventable ADEs probable or possible	Emphasizes need for PV system and policy adherence
(Lhamo et al., 2024)	33% ADRs due to antimicrobials; GI and skin most affected	WHO-UMC, Hartwig, Schumock & Thornton scales consistently used	12% definitely preventable, 69% not preventable	Majority probable causality by WHO-UMC	Emphasizes awareness to reduce ADR burden
(Krushna et al., 2024)	ADRs more in adults; tetracyclines and penicillins	WHO causality scale mainly;	Not detailed	62.85% possible causality	Supports PV integration in antimicrobial

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	common	AWaRe classification for antibiotics			stewardship
(Leitzke et al., 2023)	18.2% ADR incidence in pediatric patients; GI ADRs frequent	Naranjo, Liverpool algorithms, Hartwig, Liverpool Avoidability Tool	Majority unavoidable	78.6% possible (Naranjo), 48.6% probable (Liverpool)	Highlights ADR risk with multiple antimicrobials
("Pattern of adverse drug reactions to com...", 2024)	14% ADRs related to antibiotics; cutaneous and GI systems common	WHO-UMC causality and severity scales	13% moderate to severe ADRs	93% possible, 7% probable causality	Recommends antibiotic guideline implementation
(Belhekar et al., 2018)	46.7% ADRs due to antimicrobials; cutaneous reactions common	WHO, modified Hartwig, Schumock & Thornton scales	15.6% preventable ADRs	68.8% possible, 24% probable causality	Suggests cautious antimicrobial use to reduce ADRs
(Anthony & P, 2022)	44% ADRs from antibiotics; skin reactions frequent	WHO-UMC, Hartwig, Schumock & Thornton scales	39% probably preventable ADRs	59% possible causality	Promotes vigilant ADR monitoring and reporting
(Manjhi et al., 2024)	Review of causality, severity, preventability tools	WHO-UMC, Naranjo, Schumock & Thornton, Hartwig scales reviewed	Not applicable	Naranjo and WHO-UMC most used scales	Emphasizes need for standardized assessment tools
(Wolf et al., 2022)	Focus on under-recognized ADRs and DDIs in antimicrobials	Not applicable	Not applicable	Not applicable	Advocates IPM for early ADR and DDI detection
(Sai, 2019)	27.5% ADRs due to antibiotics; skin reactions common	WHO-UMC causality scale	86% non-preventable ADRs	Probable causality dominant	Emphasizes need for improved ADR reporting
(Sundaran et al., 2018)	51 ADRs in 3157 patients; antibiotics common cause	Naranjo, Modified Hartwig, Schumock & Thornton	37.3% probably preventable	51% probable causality	Supports clinical pharmacist involvement in PV

		scales			
(Khan et al., 2021)	1.7 ADRs/1000 pediatric admissions; antibiotics main cause	Naranjo, WHO, Hartwig, Schumock & Thornton scales	43.7% preventable ADRs	93.7% probable causality	Calls for national efforts to reduce pediatric ADRs
(Mukadam Mukadam & Gawali, 2024)	17.38% ADRs from antimicrobials; vomiting and rash common	WHO-UMC causality scale	Not specified	91.84% probable causality	Emphasizes importance of pharmacovigilance
(Venkatasubbaiah et al., 2020)	16.18% ADRs from antibiotics; high economic burden	Standard causality, severity, preventability scales	Not specified	Probable causality common	Highlights ADR cost impact on healthcare
(Andhuvan, 2018)	143 ADRs; beta-lactams major cause; GI tract most affected	WHO causality scale	Not specified	Not specified	Advocates antibiotic guideline adherence
(James & Rani, 2019)	80 ADRs; antibiotics 52.5%; probable causality dominant	Naranjo, Hartwig scales	Not specified	85% probable causality	Calls for sensitization on ADR reporting
(Iftikhar et al., 2018)	38.9% ADEs; fluoroquinolones, macrolides common; GI system affected	Naranjo, Schumock & Thornton scales	58.4% preventable ADEs	Probable and possible causality prevalent	Highlights need for policy adherence and PV system

CONCLUSION

This pharmacovigilance-based review highlights that adverse drug reactions (ADRs) associated with commonly used antibiotics remain a frequent and clinically significant concern, with incidence rates commonly ranging between 10% and 33% across healthcare settings. Gastrointestinal and cutaneous reactions are the most frequently reported, aligning with the established safety profiles of major antibiotic classes such as beta-lactams, cephalosporins, quinolones, and macrolides. Pediatric patients emerge as a particularly vulnerable population, underscoring the need for age-specific monitoring and risk mitigation strategies. Although less common, serious ADRs—including anaphylaxis and hematological toxicities—pose substantial risks, emphasizing the importance of timely detection and appropriate management.

The application of standardized assessment tools, including WHO-UMC and Naranjo causality scales, Hartwig severity scale, and Schumock and Thornton preventability scale, enables structured evaluation of antibiotic-related ADRs. However, variability in tool selection and interpretation across studies highlights the need for harmonization and integrated assessment approaches to improve consistency and reliability of y

pharmacovigilance data. Preventability analyses reveal that a considerable proportion of ADRs are avoidable, often attributable to inappropriate antibiotic selection, dosing errors, and inadequate monitoring. Identified risk factors such as polypharmacy, prolonged hospitalization, advanced age, and comorbidities suggest that targeted interventions can significantly reduce ADR burden.

Overall, this review underscores the critical role of robust pharmacovigilance systems in enhancing antibiotic safety and supporting antimicrobial stewardship initiatives. Strengthening active surveillance, standardizing assessment methodologies in line with WHO guidelines, and fostering multidisciplinary collaboration are essential to minimize preventable ADRs and improve patient outcomes.

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