

INTEGRATED ANTIBIOTIC SAFETY ASSESSMENT MODEL: CAUSALITY, SEVERITY, PREVENTABILITY AND SIGNAL DETECTION

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ABSTRACT

Antibiotics are essential for the management of bacterial infections; however, their widespread and often inappropriate use is associated with adverse drug reactions (ADRs), medication errors, drug interactions, and other preventable harms. Conventional antibiotic safety assessment commonly evaluates causality, severity, preventability, and pharmacovigilance signals as separate domains, potentially limiting comprehensive interpretation and translation of safety findings into clinical action. This review proposes the Integrated Antibiotic Safety Assessment Model (IASAM), a multidimensional framework that combines these complementary domains within a unified and iterative assessment pathway. Causality assessment evaluates the likelihood that an antibiotic is responsible for an adverse event, severity assessment determines its clinical consequences, preventability assessment identifies potentially avoidable factors across the medication-use process, and signal detection examines patterns that may indicate emerging or disproportionate safety concerns at the population level. By integrating individual case assessment with population-level pharmacovigilance, IASAM aims to improve the identification, prioritization, and management of clinically significant and preventable antibiotic-related harm. The model provides a structured feedback loop linking safety assessment with risk mitigation, antimicrobial stewardship, quality improvement, and regulatory decision-making. Its potential applications extend across hospitals, pharmacovigilance centres, formulary committees, and public health programmes, including settings such as the Pharmacovigilance Programme of India. Emerging real-world data and artificial intelligence may further strengthen safety surveillance, although expert clinical judgment remains essential. IASAM represents a conceptual approach to bridge pharmacovigilance and antimicrobial stewardship; however, prospective validation is required to establish its reliability, reproducibility, clinical utility, and applicability across diverse healthcare settings and antibiotic classes.

KEYWORDS: Antibiotic safety; adverse drug reactions; causality assessment; severity assessment; preventability; signal detection; pharmacovigilance; antimicrobial stewardship, etc.

INTRODUCTION

Antibiotics remain indispensable to modern medicine, underpinning the management of bacterial infections and enabling the safe delivery of complex interventions such as surgery, transplantation, cancer therapy, and intensive care. However, their benefits are increasingly challenged by inappropriate prescribing, excessive exposure, antimicrobial resistance (AMR), and medication-related harm. The global burden of bacterial AMR is substantial, with the World Health Organization (WHO) estimating that bacterial AMR was associated with more than 4.7 million deaths globally in 2021. Moreover, approximately one in six laboratory-confirmed bacterial infections worldwide was resistant to antibiotic treatment in 2023. These trends have reinforced the need to view antibiotic use not only through the lens of antimicrobial effectiveness and resistance, but also as a critical component of patient safety.^[1]

Antimicrobial stewardship (AMS) has consequently emerged as a central strategy for optimizing antibiotic use. Contemporary stewardship approaches seek to ensure that antibiotics are prescribed only when indicated, and that the most appropriate agent, dose, route, and duration are selected while minimizing unnecessary exposure and collateral harm. WHO guidance emphasizes an integrated approach to AMS, incorporating prescribing practices, surveillance, education, infection prevention, and monitoring of antibiotic use.^[2] The WHO AWaRe framework further supports stewardship by categorizing antibiotics according to their therapeutic utility and potential contribution to resistance, thereby facilitating monitoring and targeted interventions. Importantly, antibiotic stewardship and antibiotic safety are closely interconnected: inappropriate antibiotic exposure can increase not only resistance but also the probability of adverse drug reactions (ADRs), drug interactions, medication errors, *Clostridioides difficile* infection, secondary infections, and other forms of preventable patient harm.^[3]

The clinical burden of antibiotic-associated adverse events is considerable. Antibiotics are among the most frequently implicated medication classes in emergency department presentations for adverse drug events. In a nationally representative US surveillance study, antibiotics accounted for an estimated 145,490 emergency department visits annually among adults during 2011–2015, representing 13.7% of all adult emergency department visits for adverse drug events. Allergic reactions constituted approximately three quarters of these antibiotic-related visits.^[4] The burden is particularly evident in children, among whom antibiotics accounted for approximately 69,464 emergency department visits annually for adverse drug events during the same period. Beyond hypersensitivity reactions, antibiotic therapy may result in gastrointestinal toxicity, organ-specific adverse effects, microbiome disruption, secondary infections, and clinically important drug-drug

interactions. The risk may be amplified in patients with polypharmacy, renal or hepatic dysfunction, advanced age, multiple comorbidities, or complex treatment regimens.^[5]

Medication errors represent an additional and potentially preventable dimension of antibiotic-related harm. Errors may occur at multiple stages of the medication-use process, including selection of the antibiotic, prescribing, dose calculation, frequency, route, duration, administration, dispensing, and transitions of care. Drug-drug and drug-disease interactions can further modify the safety profile of an otherwise appropriate antibiotic regimen. Consequently, an antibiotic-related adverse outcome may arise from the intrinsic pharmacological properties of the drug, inappropriate selection or dosing, an interaction, an administration error, or a combination of these factors. WHO patient-safety and antimicrobial-resistance guidance therefore emphasizes recognition of adverse effects, clinically relevant interactions, appropriate documentation, and pharmacovigilance as integral components of safe antibiotic use.^[6]

Antibiotic safety assessments are frequently undertaken as separate analytical exercises. Causality assessment determines the likelihood that an antibiotic was responsible for a suspected ADR, whereas severity assessment characterizes the clinical consequences of the event. Preventability assessment addresses whether the event could have been avoided through appropriate prescribing, monitoring, administration, or patient management. Signal detection, in contrast, seeks to identify disproportionate or emerging patterns of suspected antibiotic-related safety problems within pharmacovigilance data.^[7] Each approach addresses a legitimate and important question, but evaluating these dimensions independently can fragment the clinical interpretation of an event. A severe event may be highly likely to be antibiotic-related but unavoidable; a moderate event may be only possibly related yet clearly preventable because of an incorrect dose or drug interaction. Similarly, a recurrent safety signal may remain difficult to prioritize unless the associated events are characterized according to their clinical severity, causality, and preventability.^[8]

This fragmented approach may also limit the translation of pharmacovigilance findings into actionable stewardship interventions. Traditional signal detection can identify statistical disproportionality without adequately distinguishing clinically meaningful, preventable harm from expected or unavoidable reactions. Conversely, individual causality or preventability assessments can provide detailed patient-level information but may fail to reveal broader population-level patterns. An integrated framework is therefore needed to connect what happened, how serious it was, whether the antibiotic caused it, whether it could have been prevented, and whether similar events constitute a broader safety signal. Such integration is

particularly relevant to antibiotic therapy because prescribing decisions simultaneously influence individual patient safety and population-level antimicrobial effectiveness.^[9]

Against this background, the **Integrated Antibiotic Safety Assessment Model (IASAM)** is proposed as a multidimensional framework for systematic evaluation of antibiotic-related safety events. IASAM aims to integrate causality, severity, preventability, and signal detection within a unified assessment pathway rather than treating these domains as independent endpoints. By linking patient-level clinical assessment with population-level pharmacovigilance, the model is intended to facilitate more consistent classification of antibiotic-related harm, identify events that are both clinically important and potentially preventable, and strengthen the feedback loop

between pharmacovigilance and antimicrobial stewardship.^[10]

The objective of developing IASAM is therefore to provide a structured and clinically meaningful approach for evaluating antibiotic safety across the continuum of individual adverse events and emerging safety patterns. Such a model may support earlier recognition of important safety signals, improve identification of preventable medication-related harm, guide targeted risk-minimization strategies, and complement existing stewardship frameworks. Ultimately, integrating these dimensions has the potential to move antibiotic safety assessment from isolated event classification toward a more comprehensive system in which causality, severity, preventability, and signal strength collectively inform clinical decision-making, pharmacovigilance, and antimicrobial stewardship.^[11]

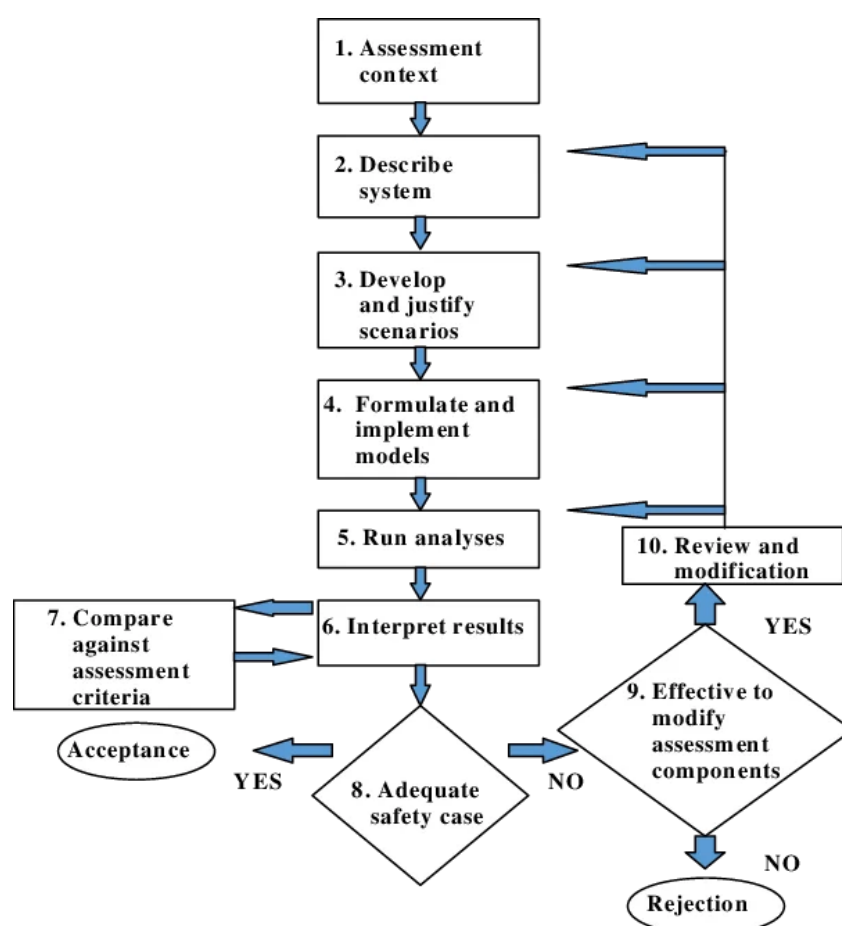


Figure 1: The ISAM Safety Assessment Methodology.

Conceptual Framework of the Integrated Model

The Integrated Antibiotic Safety Assessment Model (IASAM) is proposed as a structured pharmacovigilance framework that integrates causality, severity, preventability, and signal detection into a unified approach for evaluating antibiotic-associated adverse drug reactions (ADRs). Unlike conventional assessments that consider these domains independently, IASAM conceptualizes antibiotic safety as a continuum in which

evidence generated at the individual case level informs population-level risk assessment and subsequent risk mitigation. The model is applicable across clinical, regulatory, and pharmacovigilance settings and is particularly relevant to antibiotics because of their widespread use, diverse patient populations, variable exposure patterns, and the potential for serious or preventable adverse outcomes.^[12]

Interrelationship of Assessment Domains

The conceptual pathway begins with causality assessment, which determines the likelihood that an observed event is attributable to an antibiotic rather than to underlying disease, concomitant therapy, or other competing explanations. Once a causal relationship is considered plausible, severity assessment characterizes the clinical impact, ranging from mild and self-limiting reactions to serious, life-threatening, or fatal outcomes. Preventability assessment then evaluates whether the event could reasonably have been avoided through appropriate prescribing, dosing, monitoring, contraindication screening, drug-interaction management, or patient counselling.^[12]

These individual-level assessments contribute to signal detection, where patterns across multiple cases are examined to identify disproportionate reporting, unusual clinical features, emerging risks, or recurring preventable circumstances. Confirmed or strengthened signals subsequently support **risk mitigation**, including changes in prescribing recommendations, monitoring requirements, clinical guidance, antimicrobial stewardship interventions, educational measures, or regulatory action.^[13] Thus, the pathway can be conceptualized as:

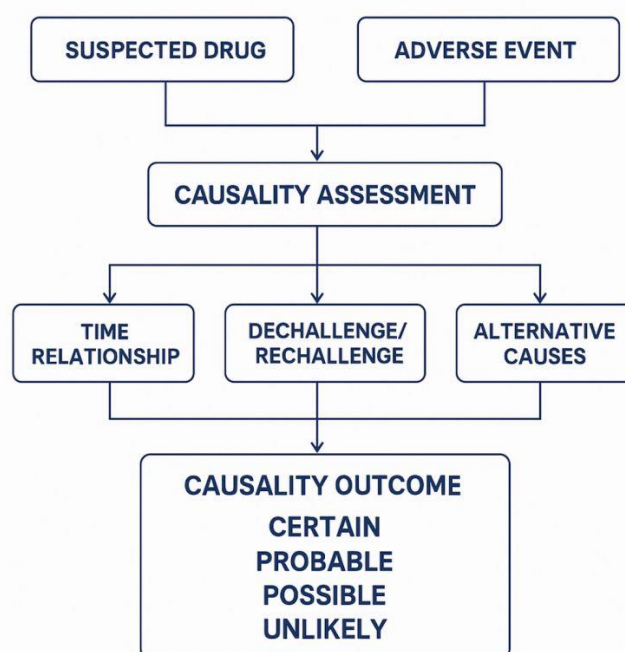


Figure 2: Causality assessment of domain.

Importantly, this sequence is iterative rather than strictly linear. Newly identified population-level signals may trigger re-evaluation of causality, severity, or preventability in individual cases.

Individual Case Versus Population-Level Safety Assessment

IASAM distinguishes, while integrating, two complementary levels of pharmacovigilance. **Individual case assessment** focuses on whether a particular antibiotic caused a specific adverse event, how clinically consequential it was, and whether it was avoidable. In contrast, **population-level assessment** examines the frequency, consistency, clinical characteristics, and preventability of similar events across patients and settings. A single severe and unexpected case may warrant attention despite limited evidence, whereas recurrent moderate events may acquire greater significance when a consistent pattern emerges. IASAM therefore avoids treating case-level certainty as synonymous with population-level risk.^[14]

Causality Assessment of Antibiotic Associated ADRs

Causality assessment is a central component of antibiotic safety evaluation because the occurrence of an adverse drug reaction (ADR) during antimicrobial therapy does not, by itself, establish that the antibiotic caused the event. A clinically meaningful assessment integrates pharmacological knowledge, patient-specific factors, and the chronology of drug exposure and adverse events. The principal objective is to estimate the likelihood that an observed clinical event is attributable to an antibiotic rather than to the underlying infection, concomitant therapy, or another disease process.^[15]

Clinical and Pharmacological Principles

The **temporal relationship** between antibiotic exposure and onset of the suspected ADR is a fundamental determinant. The timing should be biologically compatible with the known pharmacokinetics, pharmacodynamics, and mechanism of the suspected reaction. **Dechallenge**, defined as improvement after withdrawal or reduction of the suspected antibiotic,

provides supportive evidence, although spontaneous recovery or treatment of the underlying condition may confound interpretation. **Rechallenge**, in which the reaction recurs following re-exposure, provides stronger evidence but is rarely appropriate when the initial reaction was serious or potentially life-threatening.^[12]

Other important determinants include the presence of **alternative causes**, biological plausibility, and a compatible **dose-response relationship**. Pharmacological mechanisms, known class effects, organ-specific toxicity, drug concentrations, and patient susceptibility should be considered. Laboratory abnormalities and objective clinical findings can further strengthen causal inference when they correspond to established antibiotic toxicity patterns.^[13]

Major Approaches to Causality Assessment

The **WHO-UMC system** categorizes suspected ADRs as certain, probable/likely, possible, unlikely, conditional/unclassified, or unassessable/unclassifiable. It emphasizes clinical judgment, temporal compatibility, alternative explanations, and dechallenge/rechallenge information. Its principal advantage is flexibility and applicability to spontaneous-reporting systems.^[14]

The **Naranjo algorithm** uses a structured questionnaire and numerical scoring system to classify reactions from doubtful to definite. Its standardized format improves reproducibility and facilitates comparisons across studies. However, several questions may be difficult to answer in routine clinical practice, particularly where rechallenge is unethical or where objective drug-level information is unavailable.^[15]

Clinical expert judgment remains essential, particularly for complex patients. Experts can integrate disease trajectory, pharmacological mechanisms, competing diagnoses, laboratory findings, and the complete medication history. This approach may be subjective and vulnerable to differences in clinical experience.^[16]

Antibiotic-Specific Challenges

Antibiotic-associated ADR assessment is complicated by **polypharmacy**, frequent exposure to multiple antimicrobials, and rapidly changing treatment regimens. Symptoms such as fever, diarrhea, rash, nausea, altered liver enzymes, or renal dysfunction may also arise from the underlying infection itself, making attribution particularly difficult. Concomitant diseases, including hepatic or renal impairment, can both mimic ADRs and modify antibiotic exposure and toxicity. Drug-drug interactions and cumulative toxicity further complicate attribution when several agents share similar adverse-effect profiles.^[17]

Strengths, Limitations, and Inter-Rater Variability

No single causality instrument provides definitive proof of drug causation. WHO-UMC offers clinical flexibility, Naranjo provides structured standardization, and expert

judgment permits nuanced interpretation. However, all approaches are limited by incomplete information, uncertain alternative causes, lack of rechallenge data, and dependence on clinical documentation. **Inter-rater variability** is therefore substantial, particularly for reactions classified as possible or probable. An integrated model should consequently combine structured causality tools with expert review and pharmacological evidence, while documenting the rationale for attribution. This approach provides a more transparent and clinically credible foundation for subsequent assessment of ADR severity, preventability, and safety signals.^[18]

Severity Assessment

Clinical Importance of Grading ADR Severity

Severity assessment is a fundamental component of antibiotic safety evaluation because adverse drug reactions (ADRs) differ substantially in their clinical consequences, required interventions, and impact on healthcare resources. While causality assessment establishes the likelihood that an antibiotic is responsible for an adverse event, severity grading determines the magnitude of harm experienced by the patient. A standardized assessment of severity supports clinical decision-making, prioritizes urgent safety concerns, and facilitates meaningful comparisons across patients, antibiotics, and healthcare settings. Importantly, severity should reflect not only the biological seriousness of the reaction but also its effect on treatment, hospitalization, and long-term patient outcomes.^[19]

Common Approaches to Severity Grading

Several structured approaches have been developed to classify ADR severity. The Hartwig and Siegel Severity Assessment Scale is among the most widely used methods in clinical pharmacovigilance. This approach categorizes reactions into increasing levels of severity according to the interventions required and their consequences, ranging from reactions requiring no change in therapy to those causing permanent harm or death. Its practical strength lies in linking severity to clinical management and healthcare utilization.^[20]

Other approaches classify ADRs broadly as mild, moderate, severe, life-threatening, or fatal. Although simpler, these categories provide an intuitive framework for communicating clinical risk. Mild reactions generally cause minimal discomfort and require little or no therapeutic intervention. Moderate reactions may require treatment modification, additional medication, or closer monitoring. Severe reactions are associated with substantial morbidity, prolonged recovery, or hospitalization, whereas life-threatening reactions require immediate intensive intervention. Fatal reactions result directly or indirectly in death.^[21]

Antibiotic-Specific Severe Outcomes

Antibiotics can produce a spectrum of serious and potentially life-threatening adverse outcomes that require

particular attention during severity assessment. Anaphylaxis following exposure to beta-lactams or other antibiotics represents an acute medical emergency requiring prompt recognition and treatment. Drug-induced hepatotoxicity and nephrotoxicity may lead to significant organ dysfunction, prolonged hospitalization, or irreversible injury. Similarly, antibiotic-associated *Clostridioides difficile* infection can range from uncomplicated diarrhea to fulminant colitis, toxic megacolon, and death.^[22]

Serious cutaneous adverse reactions, including Stevens-Johnson syndrome and toxic epidermal necrolysis, are particularly important because of their high morbidity, mortality, and long-term complications. These events illustrate why severity assessment must consider both immediate clinical manifestations and the potential for persistent disability.^[17]

Integrating Clinical Outcomes and Healthcare Utilization

An integrated antibiotic safety assessment model should combine clinical outcome measures with indicators of healthcare utilization. Hospital admission or prolonged hospitalization, intensive care requirement, emergency treatment, additional diagnostic procedures, and the need for specialist consultation provide important evidence of the real-world burden of an ADR. Similarly, permanent treatment discontinuation, organ damage, disability, and death should receive substantial weight in severity classification.^[23]

Therefore, severity assessment should extend beyond symptom intensity alone. By integrating clinical consequences with the resources required to manage an ADR, the proposed model can provide a more comprehensive and patient-centered evaluation of antibiotic safety. Such an approach strengthens pharmacovigilance, improves the identification of clinically important safety signals, and supports safer, more rational antibiotic use.^[24]

Preventability Assessment

Preventability assessment is a critical component of antibiotic safety evaluation because it distinguishes adverse outcomes that could reasonably have been avoided from those occurring despite appropriate clinical care. Preventable antibiotic-related harm generally arises from identifiable deficiencies in medication selection, prescribing, dispensing, administration, monitoring, or patient use. In contrast, non-preventable harm refers to adverse reactions or clinical outcomes that occur despite appropriate antibiotic choice, dosing, surveillance, and adherence to accepted standards of care. This distinction is particularly important in antibiotic therapy, where some adverse drug reactions may be intrinsically unpredictable, whereas many complications, including toxicity, treatment failure, and resistance-related consequences, may be linked to modifiable practices.^[25]

Assessment Across the Medication-Use Process

A comprehensive preventability assessment should examine the entire medication-use pathway. At the prescribing stage, reviewers should assess whether there was a clear indication for antibiotic therapy and whether the selected agent was appropriate for the suspected or confirmed infection. Dispensing-related factors include incorrect drug supply, labeling errors, or failures to identify prescribing discrepancies. Administration errors, such as incorrect timing, route, or infusion rate, may also contribute directly to patient harm.^[26]

Monitoring and adherence are equally important. Failure to monitor renal or hepatic function, therapeutic drug concentrations, microbiological results, or emerging adverse effects can convert a potentially manageable risk into preventable harm. Similarly, poor patient adherence, inadequate counselling, or failure to communicate treatment instructions may result in therapeutic failure or unnecessary prolonged exposure. Medication errors should therefore be evaluated not as isolated events but within the broader clinical and organisational context in which they occur.^[27]

Key Determinants of Preventability

Inappropriate antibiotic selection remains a major source of preventable harm. Use of an unnecessarily broad-spectrum agent, an ineffective drug, or an antibiotic unsuitable for the patient's infection increases the risk of toxicity, resistance, and treatment failure. Incorrect dose or duration may similarly produce subtherapeutic exposure or excessive toxicity. Preventability assessment should also consider clinically significant drug interactions, known contraindications, allergy history, and patient-specific factors such as organ dysfunction. Importantly, failure to reassess therapy after culture results or clinical improvement represents a common missed opportunity for prevention.^[28]

Preventability Scales and Their Limitations

Several structured scales and expert-judgement approaches can be used to classify adverse drug events as definitely, probably, possibly, or not preventable. Such tools promote consistency and transparency, particularly in retrospective reviews. However, preventability remains partly dependent on clinical judgement, available documentation, and evolving standards of care. Inter-rater variability, incomplete records, and differences in guideline interpretation may limit reproducibility. Furthermore, a scale developed for general adverse drug events may not fully capture antibiotic-specific issues such as antimicrobial resistance, delayed de-escalation, or diagnostic uncertainty.^[29]

Implications for Antimicrobial Stewardship and Quality Improvement

Preventability assessment provides actionable information for antimicrobial stewardship and patient-safety programmes. Identifying recurrent preventable

factors can guide interventions such as prescribing audits, clinical decision support, dose optimisation, allergy verification, medication reconciliation, and improved monitoring systems. Integrating preventability with causality, severity, and signal detection enables organisations to move beyond counting adverse events towards understanding why they occur. Ultimately, this approach supports continuous quality improvement by reducing avoidable antibiotic-related harm while promoting appropriate, effective, and responsible antimicrobial use.^[30]

Antibiotic Safety Signal Detection

Safety signal detection is a fundamental component of antibiotic pharmacovigilance, particularly because antimicrobial agents are widely prescribed across diverse patient populations and may produce rare, delayed, or population-specific adverse effects. Within an integrated antibiotic safety assessment model, signal detection complements causality assessment, severity evaluation, and preventability analysis by identifying potential new risks that warrant systematic investigation.^[25]

Distinguishing an ADR Case from a Safety Signal

An adverse drug reaction (ADR) case refers to an individual patient-level report describing a suspected harmful and unintended response associated with an antibiotic under normal conditions of use. Such a report may arise from clinical observation, spontaneous reporting, or structured healthcare data and does not, by itself, establish a causal relationship. In contrast, a safety signal represents information suggesting a possible causal association, or a new aspect of a known association, between an antibiotic and an adverse event that justifies further assessment. Thus, individual ADR cases constitute the evidence base from which broader safety signals may emerge.^[31]

Sources of Antibiotic Safety Signals

Safety signals can originate from multiple complementary data sources. Spontaneous reporting systems remain essential for detecting rare and unexpected reactions, while electronic health records provide longitudinal clinical information and enable assessment of outcomes in routine practice. Published literature, patient registries, and clinical trials contribute structured evidence, although trials may have limited power to identify uncommon adverse events. Increasingly, real-world data from healthcare databases, insurance claims, and linked datasets support the identification of safety patterns across large and heterogeneous populations. Integrating these sources can improve the timeliness and robustness of antibiotic safety surveillance.^[32]

Qualitative and Quantitative Signal Detection

Qualitative case review remains indispensable for evaluating the clinical plausibility of a suspected association. Reviewers assess temporal relationships, dechallenge and rechallenge information, alternative

explanations, concomitant medicines, and biological mechanisms. Quantitative approaches complement this assessment through disproportionality analysis of large pharmacovigilance databases. Common measures include the reporting odds ratio (ROR) and proportional reporting ratio (PRR), which identify drug-event combinations reported more frequently than expected. Bayesian methods, including the Bayesian Confidence Propagation Neural Network (BCPNN) and Multi-item Gamma Poisson Shrinker (MGPS), can provide more stable estimates, particularly for sparse data. Importantly, disproportionality indicates statistical association rather than causation.^[33]

Signal Validation, Prioritization, and Clinical Assessment

Detected signals require validation through data quality assessment, case verification, literature review, and replication across independent datasets where possible. Prioritization should consider clinical seriousness, frequency, strength and consistency of evidence, biological plausibility, preventability, and public health impact. Clinical assessment must also account for antibiotic-specific factors, including dose, duration, indication, renal or hepatic function, drug interactions, and antimicrobial resistance-related treatment constraints. Signals with substantial potential consequences should progress to focused pharmacoepidemiological studies or regulatory evaluation.^[34]

Emerging Role of Artificial Intelligence

Data mining, machine learning, and artificial intelligence are increasingly enhancing pharmacovigilance by processing large volumes of structured and unstructured data, including clinical narratives and published reports. Natural language processing can facilitate case identification, while machine-learning algorithms may detect complex drug-event patterns that conventional methods overlook. However, algorithmic findings require transparent validation and expert clinical interpretation to minimize bias, confounding, and false-positive signals. Ultimately, artificial intelligence should strengthen, rather than replace, multidisciplinary clinical judgment in antibiotic safety signal detection.^[35]

The Integrated Antibiotic Safety Assessment Model

Antibiotic safety assessment requires a multidimensional approach because adverse events associated with antimicrobial therapy vary substantially in their cause, clinical impact, avoidability, and implications for wider patient safety. An Integrated Antibiotic Safety Assessment Model (IASAM) can provide a structured framework for evaluating individual adverse drug events while simultaneously identifying opportunities for clinical intervention and system-level learning. The proposed model integrates four complementary domains: causality, severity, preventability, and signal detection.^[36]

Integration of the Four Safety Domains

Causality addresses whether the antibiotic is likely responsible for the observed adverse event. Assessment should consider the temporal relationship between exposure and event onset, biological plausibility, alternative explanations, dose-response relationships, dechallenge or rechallenge information, and existing evidence. A standardized causality assessment helps distinguish probable antibiotic-related events from coincidental clinical outcomes.^[37]

Severity evaluates the magnitude of clinical harm. Events may range from mild and self-limiting reactions to serious outcomes requiring hospitalization, prolonged hospital stay, intensive care, permanent disability, or resulting in death. Severity assessment is essential because events with lower certainty of causality may still warrant urgent attention when their potential consequences are substantial.^[36]

Preventability examines whether the adverse event could reasonably have been avoided. Preventable events may arise from inappropriate antibiotic selection, excessive dose or duration, failure to account for renal or hepatic dysfunction, overlooked drug interactions, inadequate monitoring, or delayed recognition of toxicity. This domain directly connects case assessment with antimicrobial stewardship and quality improvement.^[35]

Signal detection extends the assessment beyond the individual patient. It considers whether an event represents an unusual pattern, an unexpected reaction, an increase in frequency, or a possible emerging safety concern associated with a particular antibiotic, population, dose, or clinical setting. Thus, individual case reports can contribute to broader pharmacovigilance intelligence.^[34]

Development of an Integrated Scoring and Decision Matrix

The IASAM may employ a standardized scoring system in which each domain is assigned a graded score. For example, causality can range from unlikely to definite, severity from mild to life-threatening, preventability from non-preventable to definitely preventable, and signal strength from isolated to strongly suggestive of an emerging pattern. These scores can be incorporated into a decision matrix rather than interpreted in isolation.^[38]

Importantly, the model should allow certain high-risk findings to override a simple cumulative score. A life-threatening event, for instance, should trigger urgent review even when causality remains uncertain. Similarly, a cluster of moderately severe events may warrant investigation because of its signal-detection value.

Priority Levels for Intervention

Based on the integrated assessment, individual cases can be categorized into low, moderate, high, and critical

priority levels. Low-priority cases may require routine documentation and monitoring. Moderate-priority cases should prompt clinical review and reinforcement of safe prescribing practices. High-priority cases require targeted intervention, such as modification of treatment protocols, enhanced monitoring, or specialist consultation. Critical-priority cases, particularly severe, preventable, or signal-generating events, should prompt immediate multidisciplinary investigation and escalation to institutional pharmacovigilance and antimicrobial stewardship systems.^[39]

Closing the Feedback Loop

A central strength of the IASAM is its capacity to create a continuous feedback loop. Signals detected through individual case assessments should inform preventive strategies, including prescribing alerts, revised treatment guidelines, monitoring recommendations, and targeted education. Conversely, changes in antibiotic policy should be evaluated through ongoing safety surveillance to determine whether they reduce harm.

By integrating causality, severity, preventability, and signal detection into a unified framework, the Integrated Antibiotic Safety Assessment Model can transform adverse-event reporting from a passive documentation process into a dynamic system for clinical prevention, antimicrobial stewardship, and evidence-informed antibiotic policy.^[40]

Clinical and Public Health Applications

The proposed Integrated Antibiotic Safety Assessment Model, combining causality assessment, severity grading, preventability evaluation, and signal detection, has important applications across clinical practice, pharmacovigilance, and public health. By providing a structured and multidimensional assessment of antibiotic-related adverse drug reactions (ADRs), the model can support timely identification of safety concerns and facilitate targeted interventions.^[41]

Hospital Antimicrobial Stewardship Programmes

Within hospital antimicrobial stewardship programmes (ASPs), the model can strengthen the safety component of antibiotic optimization. Antibiotic prescribing is traditionally evaluated in terms of appropriateness, spectrum, dose, duration, and resistance patterns; systematic assessment of ADRs adds an equally important patient-safety dimension. Identifying severe or preventable antibiotic-related reactions can help stewardship teams modify prescribing protocols, promote safer alternatives, and prioritize high-risk patient populations. Aggregated safety findings may also support interventions such as dose adjustment, therapeutic monitoring, allergy verification, and early recognition of toxicity.^[42]

Pharmacovigilance Centres and ADR Monitoring Systems

Pharmacovigilance centres can use the integrated framework to improve the consistency and clinical relevance of ADR assessment. Combining causality, severity, and preventability provides a more comprehensive characterization of individual reports than reliance on causality alone. Furthermore, integrating structured clinical assessments with signal detection approaches can facilitate recognition of unusual or emerging patterns of antibiotic toxicity. This may improve the prioritization of reports for further evaluation and enable earlier communication of clinically significant safety signals to healthcare professionals and public health authorities.^[43]

Regulatory Decision-Making and Risk Minimization

For regulatory authorities, systematically generated evidence on the nature, seriousness, and preventability of antibiotic-related harms can inform risk-benefit assessment and post-marketing safety decisions. Recurrent signals involving severe or preventable ADRs may justify strengthened warnings, revisions to product information, restrictions in selected populations, or additional post-marketing studies. The model may therefore support a more proactive approach to risk minimization by distinguishing unavoidable adverse effects from harms potentially attributable to modifiable prescribing or monitoring practices.^[44]

Antibiotic Formulary Decisions

Hospital and institutional formulary committees can incorporate safety data generated through this model alongside efficacy, resistance patterns, availability, and cost. Comparative information on the frequency and severity of ADRs, particularly preventable reactions, may help identify antibiotics requiring prescribing restrictions or enhanced monitoring. Such evidence can promote formulary decisions that reflect real-world safety performance rather than efficacy alone.^[45]

Patient Safety Surveillance and Quality Improvement

The model also offers a practical framework for continuous patient safety surveillance. Analysis of preventable ADRs can reveal system-level weaknesses, including inappropriate prescribing, inadequate renal dose adjustment, drug interactions, delayed recognition of toxicity, or insufficient monitoring. These findings can be translated into targeted quality-improvement initiatives, clinical decision-support tools, staff education, and standardized monitoring protocols. Reassessment over time can further measure the effectiveness of these interventions.^[46]

Potential Application within the Pharmacovigilance Programme of India (PvPI)

The model has particular relevance to the Pharmacovigilance Programme of India (PvPI), where standardized assessment of antibiotic-related ADRs could strengthen national safety surveillance. Integration

within reporting and assessment workflows may enable more systematic evaluation of causality, clinical severity, and preventability while supporting the identification of emerging safety signals across diverse healthcare settings. Aggregated findings could inform national treatment guidance, antimicrobial stewardship initiatives, and risk communication strategies. Importantly, the framework could help bridge pharmacovigilance and antimicrobial resistance programmes by positioning antibiotic safety as a central component of rational antibiotic use and public health protection.^[47]

Challenges and Future Directions

The development of an integrated antibiotic safety assessment model faces several methodological and practical challenges. A major limitation is the incompleteness and underreporting of adverse drug reaction (ADR) data, particularly in spontaneous reporting systems, which may result in substantial uncertainty in estimating antibiotic-related risks. Causality and preventability assessments are also influenced by considerable subjectivity and inter-rater variability, reflecting differences in clinical judgment, available documentation, and the assessment tools applied. Furthermore, distinguishing antibiotic-related harm from outcomes attributable to infection severity, underlying comorbidities, polypharmacy, or concomitant therapies remains challenging and may lead to misclassification of drug-related events. Another important consideration is the difference between individual-case and population-level evidence. Individual case assessments provide clinically detailed information but may be vulnerable to reporting and attribution biases, whereas population-level studies offer estimates of comparative risk but may lack the clinical granularity required to establish causality in specific patients. Future research should therefore focus on standardizing and validating an integrated scoring system that combines causality, severity, preventability, and signal strength while demonstrating acceptable reliability, reproducibility, and clinical interpretability.

The increasing availability of real-world data from electronic health records, claims databases, antimicrobial stewardship programs, and pharmacovigilance systems offers opportunities to strengthen antibiotic safety surveillance. Automated signal detection and artificial intelligence-assisted assessment could facilitate earlier identification of potential safety signals, improve consistency in case evaluation, and reduce the workload associated with manual review. However, such approaches should complement rather than replace expert clinical judgment and must address issues of data quality, transparency, bias, and algorithmic validation. Ultimately, prospective validation across diverse patient populations and multicentre implementation are essential to establish the generalizability and clinical utility of the proposed model. Harmonized methodologies, continuous performance evaluation, and integration with routine pharmacovigilance and antimicrobial stewardship

practices will be critical for translating this framework into a robust and actionable antibiotic safety assessment system.

CONCLUSION

The Integrated Antibiotic Safety Assessment Model (IASAM) offers a structured and multidimensional framework for evaluating antibiotic-associated adverse drug reactions (ADRs) by bringing together causality, severity, preventability, and signal detection within a unified assessment approach. Unlike isolated evaluation of individual pharmacovigilance dimensions, this integrated model has the potential to provide a more comprehensive understanding of the clinical significance and public health relevance of suspected antibiotic-related harms. By systematically combining these domains, IASAM can facilitate more consistent identification and prioritization of ADRs that warrant clinical attention, regulatory consideration, or further investigation. Integration of causality and severity can help distinguish likely antibiotic-related events from coincidental occurrences and identify those with the greatest clinical consequences. Incorporating preventability adds an important dimension by identifying potentially avoidable medication-related harm, while signal detection can facilitate recognition of emerging or previously underappreciated safety concerns at the population level. Collectively, these components may strengthen the prioritization of clinically important ADRs and support more informed pharmacovigilance decision-making. Importantly, IASAM is intended to have relevance beyond individual case assessment. At the patient level, its structured approach may support timely recognition, clinical management, and prevention of recurrent antibiotic-related harm. At the population level, aggregation of multidimensional assessments could contribute to antibiotic risk characterization, surveillance, stewardship, and the early identification of safety signals across healthcare systems. Thus, IASAM may provide a useful bridge between clinical pharmacovigilance and broader antibiotic risk management. Nevertheless, the model requires systematic validation before widespread implementation. Future research should evaluate its reliability, reproducibility, clinical utility, and predictive performance across different antibiotic classes, healthcare settings, patient populations, and pharmacovigilance databases. Comparative studies against established ADR assessment and signal detection approaches would further clarify its added value. Such validation will be essential to refine IASAM and establish its role as a practical, scalable, and evidence-based framework for strengthening antibiotic safety assessment and pharmacovigilance.

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