SCIENCE AND ART OF DETERMINING THE ASSOCIATION AND CAUSATION OF ADVERSE EVENTS IN PHARMACOVIGILANCE: TECHNIQUES AND DIFFICULTIES

Abstract

Numerous medications are available in the healthcare sector, and the number is growing daily. Since life style changes have significantly increased medicine use, safer pharmaceuticals are urgently needed. To keep things under control, regulators and other authorities have put in place strict regulations and a pharmacovigilance system. The most difficult pharmacovigilance task is establishing causality between adverse occurrences and suspicious medications. Adverse medication reactions can range from minor to life-threatening, causing discomfort or significant morbidity and mortality. It necessitates careful assessment of the patient's underlying medical issues, co-suspect medications, patient-related factors, and adverse events. While reporting of adverse drug reactions (ADRs) have increased over the past few years. The determination of the likelihood of a medicine being responsible for an adverse event, and this is arguably the crucial role in running each nation's national pharmacovigilance programme. It seeks to establish a link between the incidence of an adverse event and the administration of a medicine. Accurate causal assessment is critical for a variety of stakeholders, including healthcare practitioners, regulatory bodies, and pharmaceutical corporations, because it guides drug safety decision-making processes. In pharmacovigilance, determining causality is a routine process. Despite the enormous number of approaches that have been proposed, determining a drug's causal contribution to the development of an

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adverse event continues to be one of the most disputed issues. All of these techniques were divided into three major groups: algorithms, probabilistic techniques (Bayesian approaches), and expert judgement/global introspection. Due to issues with validity and reproducibility, no one method is regarded as the best. Each technique uses a distinct set of causality categories, and each method uses a different set of evaluation criteria to evaluate the categories. When determining new signals, measuring the weight of the evidence, and assessing the benefit-risk profile of pharmaceutical medicines, causality is the crucial aspect.

Keywords: Adverse event, Pharmacovigilance, causality assessment

I. INTRODUCTION

In 1960s Thalidomide disaster and numerous other recent drug market withdrawals have resulted in recognizing adverse drug reactions (ADR) as one of the primary factors that results in morbidity and mortality by healthcare professionals and the general public [1]. After this catastrophe, the US FDA changed its legislation to include stricter criteria for pharmaceutical approvals and a spontaneous reporting PV system to track the occurrence of adverse drug reactions in the healthcare industry [2]. ADRs are responsible for hospital admissions, extended hospital stays, and fatalities. ADR-related inpatient hospitalizations have ranged from 4.8% in Germany, 6.5% in the UK, to 7.3% in the United States [3]. Up to 6.5% of all hospital admissions in the United Kingdom were associated with ADRs, while the overall fatality rate was 0.15% [4]. According to studies, between 2.4% and 30% of hospitalized patients could have an ADR during their hospitalization [5]. The prevalence of fatal ADR ranged from 0% to 5.2% in a recent meta-analysis [6-7]. ADRs also have negative effects on quality of life and the loss of economic resources [5], [8]. According to studies done in India, hospitalized patients are believed to experience suspected ADRs at a rate of between 2% and 3% [9]. The median incidence of ADRs that resulted in hospitalizations and those that occurred while in the hospital was assessed to be 2.85% and 6.34%, respectively, by a systematic study [10].

Causality evaluation, which aims to identify the cause-and-effect relationship between a medication or medical practice and an adverse event, is a crucial part of pharmacovigilance. It is essential for assessing the safety profile of medications and guaranteeing patient welfare. However, pharmacovigilance's causation evaluation procedure continues to be difficult and complex [11]. The complex nature of the human body, a lack of knowledge, under-reporting and reporting bias, a variety of evaluation methods, and challenges related to uncommon events and long-term impacts are only a few of the reasons that contribute to this challenge. These problems need to be fixed in order to improve patient safety and the precision and dependability of causality assessment in the area of pharmacovigilance [12].

The Causality assessment techniques were divided into three major groups: algorithms, probabilistic techniques (Bayesian approaches), and expert judgement/global introspection (Figure 1). The majority of reported instances are classified as suspected ADRs in pharmacovigilance. Drug rechallenges (i.e., when the suspected drug was reintroduced into the patient's medication or the patient had previously taken the same suspected drug) are rare because, in most cases, ADRs are not distinct to each drug. It is requested that consumers and healthcare professionals report any incidents they believe to be connected to drug use. To address this issue, health authorities have developed systematic and uniform methods for causality assessment, categorizing ADR reports in accordance with one of the causality gradations recommended by the WHO-UMC causality evaluation system [13]. Apart from ADR identification, where novel approaches have been put forth [14], causality assessment an essential component of signal detection, which is done by health authorities and is defined as "reported information on a possible causal relationship between an adverse event and a drug, the relationship being unknown or inadequately documented previously," is causality assessment, which helps with the risk-benefit analysis of commercially available medications [13].

1. **Why measure causality in Pharmacovigilance?:** The majority of case reports in pharmacovigilance involve alleged adverse medication responses, which is a problem in and of itself. Drug-specific adverse effects are uncommon, diagnostic testing is typically deficient, and re-challenge is infrequently ethically acceptable. The majority of adverse responses are either "possible" or "probable" in nature; very few are "certain" or "unlikely" in actuality. Many approaches for an organized and unified assessment of causation have been created in an effort to address this issue **[15].** However, it hasn't been demonstrated that any of these algorithms can generate an accurate and trustworthy quantitative evaluation of relationship likelihood. However, causality evaluation has developed into a typical, standard approach in pharmacovigilance. **In Table 1,** the developments and restrictions of causality assessment are discussed **[16].**

Table 1: Standardized Case Causality Assessment Developments And Restrictions

| What causality assessment can do	What causality assessment cannot do
Decrease disagreement between assessors	Give accurate quantitative measurement of relationship likelihood
Classify relationship likelihood	Distinguish valid from invalid cases
Mark individual case reports	Prove the connection between drug and event
Improvement of scientific evaluation; educational	Quantify the contribution of a drug to the development of an adverse event
	Change uncertainty into certainty
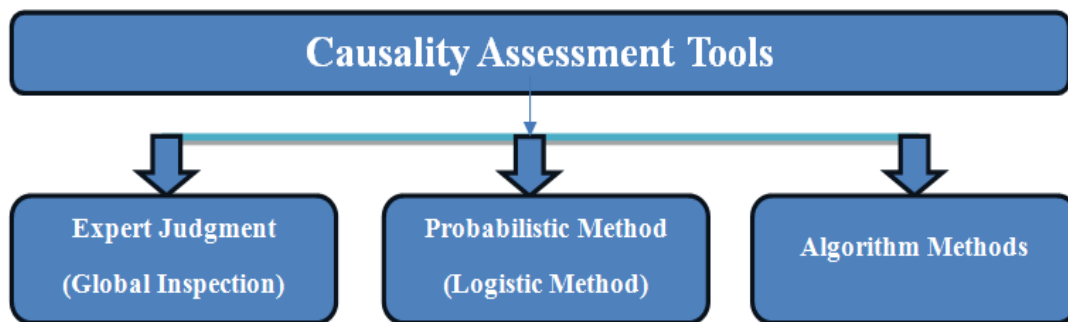
Figure 1: Types of Causality Assessment Tools.

2. **Need for Relatedness/causality Evaluation:** Evaluation of causality is crucial in all facets of medical practice. Finding the offending medication or substances may save a life or help to limit further harm the drug causes to our biological systems. Since the underlying ailment might present in the same way as the drug when a patient is taking multiple medications, it can be challenging to pinpoint which medication is responsible for a drug reaction. Unfortunately, there are no specific diagnostic procedures. Although histology can help in the identification of drug reactions, it is not enough to point to a specific substance. However, identifying the precise medicine is critical since it directly influences a clinician's decision to continue or discontinue drugs. This can be important in some circumstances, hence proving causality with almost perfect accuracy is preferred.

Clinical trial participants, employees of the pharmaceutical sector, academics, and regulatory bodies can all undertake causality analyses in a number of circumstances **[17].**

3. **Principles for Determining Causality:** All approaches or tools for evaluating causality comply to the following four essential ADR diagnosis principles: (i) the temporal relationship between the drug and the drug reaction; (ii) biological plausibility; (iii) dechallenge; and (iv) rechallenge. Positive or negative prechallenge is the term used when dechallenge or rechallenge has previously taken place **[18].**

    Ihtisham K et al. 2019 found that various HLA alleles in North Indians had significant connections to CBZ and PHT that required testing prior to the start of an AED; simply screening for HLA-B*15:02 may not be effective in this community **[19].**

    A 12-year-old child who complained of having erythematous, macular rashes all over his body, including his face, neck, chest, both upper and lower limbs, and abdomen, was admitted to the hospital in 2018. According to the patient's history, the patient had experienced vomiting, nausea, and fever three days ago. He developed conjunctivitis and angioedema the next day, and he was admitted to the hospital as a result of erythematous lesions all over his body, oral ulcers, and crustations on the angle of his mouth. The patient was identified as a newly diagnosed epileptic who was receiving 100 mg of carbamazepine for seizures based on his prescription history. On the eighth day of carbamazepine therapy, the child had erythematous lesions and macular rashes all over their body, which gradually increased to cover 60% of their body surface area. The use of carbamazepine has decreased. The final diagnosis was Stevens-Johnson syndrome brought on by carbamazepine **[20].**

    Dexamethasone and cefotaxime were given intravenously, Betamethasone was applied topically, Clotrimazole mouthwash was used to treat oral ulcers, Tobramycin eye drops were used to treat ocular lesions, IV fluids were given, and additional supportive measures were used. After 7 days in the hospital, the patient improved and was discharged. Case-control research found that short-term carbamazepine use increases the incidence of SJS for fewer than 8 weeks. In this scenario, the offending medicine should be discontinued **[21].**

    Using Naranjo's approach **[22]** and the WHO-UMC Scale, a causality analysis was conducted, and the current ADR was found to be 'PROBABLE' with carbamazepine. The reaction was SEVERE (Level 6) on the modified Hartwig and Siegel severity scale, but "PROBABLY PREVENTABLE" on the modified Schumock and Thornton scale **[23].**

    In previous studies dermatologists diagnosed SJS, SJS-TEN overlap, and TEN using diagnostic criteria developed by **Roujeau et al.[24]** and the severe cutaneous adverse reactions (SCAR) study classification developed by **Batsuji-Garin et al.[25]** Cases having SJS, SJS-TEN overlap, or TEN were categorized as SJS/TEN. The causal relationship between CBZ and SJS/TEN was established using the ALDEN score of 6 or higher **[26].**

4. **Methods of Causality Assessment:** The timing between the administration of the drug and the occurrence of the adverse drug reaction (ADR), the search for non-drug related causes, the confirmation of the reaction through in vivo or in vitro tests, and prior knowledge of similar events connected to the suspected drug or its therapeutic class, among other criteria, are just a few of the criteria that numerous researchers developed numerous techniques for determining the cause of adverse drug reactions (ADRs) **[27].** However, due to the lack of established diagnostic criteria or categories, there may be significant inter- and intra-rater variability **[28].** There is currently no procedure for determining the cause of ADRs that is recognized worldwide **[29].**

Clinical judgement, probabilistic approaches and algorithms are the broad categories of causality evaluation methodologies. Each area contains tools and approaches for determining the likelihood of a drug-adverse event relationship. Expert opinions are distinctive judgements' made without the aid of a standardized technique to establish causality, based on prior knowledge and experience in the field. Algorithms, which are collections of particular questions with related scores, can be used to assess the likelihood of a cause-and-effect relationship. Bayesian approaches take advantage of specific outcomes in a case to transform a prior probability estimate into a posterior probability estimate of drug causation. The data in each specific example is combined with this previous knowledge in the posterior probability to derive an estimate of causality. The epidemiology data are used to calculate the prior probability. Due to issues with validity and reproducibility, no one method is regarded as the best. Several causality assessment methods are available. Different tools and methods used for causality assessment and their key features described in **Table 2.**

Table 2: Different Tools and Methods Used for Causality Assessment and their Key Features.

Methods of causality assessment tools	Advantages	Limitations
Naranjo et al. (1981)	● A method based on structured questionnaires ● A numerical rating indicating likelihood widely acknowledged	● Relies on proper information reporting and is only applicable in certain circumstances ● Some inquiries could be unclear.
Koh et al. (2008)	● Uses a methodical, objective procedure ● Incorporates a number of aspects	● Requires precise and thorough clinical data ● Complex cases might not be handled well-defined to particular situations
Karch and Lasagna (1977)	● Established standards-based methodology ● Offers category evaluation	● Individual interpretation ● precise quantitative recommendations ● Complex cases might not be handled well.
Kramer et al. (1979)	● An algorithm to	● Restricted to particular

	evaluate the relationship between drugs and events	situations ● Complex cases might not be handled well. ● For a final determination, additional evidence might be needed.
Begaud (1984)	● A methodical technique to evaluating causality ● Analyses a variety of aspects	● Implementation could be challenging ● Interpretation that is subjective ● Limited quantitative guidance
WHO – Uppsala monitoring center- causality assessment 1994	● Widespread, easy to use and considers a variety of aspects	● Interpretation that is subjective and little quantitative evidence ● Complex cases might not be handled well.

II. EXPERT JUDGEMENT/GLOBAL INTROSPECTION

According to Hoskins et al. (1992), either a physician or a clinical investigator suspects or recognizes about 80% of adverse occurrences. Clinical pharmacologists or treating physicians are the ones who suspect or identify ADRs the **most [30].** This expert judgement, also known as global introspection, is the process by which an expert expresses their opinion regarding potential drug causation by taking into account all information pertinent to a suspected ADR **[31]** estimating their relative importance, and allocating weights to determine the likelihood that the drug played a part in the unfavorable event **[30].** ADR in this area is evaluated by either one expert assessor or a team of experts. There is disagreement and significant inter-rater variability since these experts' appraisal and assessment of ADR are solely based on their individual expertise and experience of the topic of concern. Here, we outline two techniques based on professional judgement.

1. **Swedish Causality Assessment Method (Wilholm et al. 1984):** The Swedish regulatory body bases its causation assessment methodology on the opinions of an expert committee. The clinician considers seven important factors when determining whether a relationship is causal: (i) temporal relationship (ii) previous drug knowledge, (iii) dosage connection, (iv) drug response pattern, (v) readministration, (vi) alternative etiological possibilities, and (vii) concurrent medications. If causality has been proven, adverse medication responses are classified as "probable" or "possible" and "non-assessable" or "unlikely" **(Wiholm et al., 1984).** The method's limitation in the categories that causation can be subdivided could lead to overlap and inappropriate evaluation of ADRs **[32]**.

2. **Causality Assessment Criteria of WHO-UMC:** The most frequently used criteria for determining the causation of adverse events in pharmacovigilance are those developed by the WHO-UMC. These scales offer an appropriate and useful method for determining the likelihood that a specific reaction can be a drug's input **[33]**. **Rehan et al. (2009)** claim that the WHO-UMC method is used as a helpful tool for assessing safety case reports. By contrasting the patient history and the calibre of the case safety report, the clinical-pharmacological characteristics of the medication can be evaluated **[34]**. **Table 3** lists the

several causality categories. The four factors listed below are part of the WHO-UMC causality evaluation technique **[34]:**

- The time period between taking a drug and experiencing a side effect.
- The absence of other elements, such as medications or illnesses that are present simultaneously.
- Dechallenge, an adverse drug withdrawal or dosage lowering reaction.
- The response to medication administration after dechallenges. (rechallenge)

Six categories that depend on several of the aforementioned requirements being met are used to classify the level of causal relationship. When all four requirements are satisfied, the causal category is considered "certain." When conditions a, b, and c are satisfied, it is "probable." The occurrence is classified as "possible" when just requirement a is satisfied, and as "unlikely" when both criterion a and b are not met **(Table 4).** In addition to these four categories, ADR can also be characterized in the WHO-UMC causality assessment as "Unclassified/Conditional" or "Unassessable/Unclassifiable." When further information is required and such information is either being sought out or is already being examined, the phrase "Unclassified/Conditional" is used. The judgement is "Unclassifiable" when a report contains inconsistent or incomplete material that cannot be validated or supplemented. The WHO-UMC approach can be used to identify drug-drug interactions by analyzing the interacting drug in the medical context of the patient, which changes the pharmacokinetic or pharmacodynamics of the non-interacting drug.

Table 3: Causality Categories Developed by the WHO-UMC

Causality term	Criteria for Assessment
Certain	• Event or laboratory test abnormality, with 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 recognized pharmacologic 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 explanation
Conditional/unclassified	● Event or laboratory test abnormality ● More data for proper assessment needed, or ● Additional data under examination
Unassessable/unclassifiable	● Report suggesting an adverse reaction ● Cannot be judged because information is insufficient or contradictory ● Data cannot be supplemented or verified

Table 4: The WHO- UMC Causality Assessment Method Includes 4 Criteria's

Type of causality	Temporal relationship	Other drugs/disease ruled out	Dechallenge	Rechallenge
Certain	Yes	Yes	Yes	Yes
Probable	Yes	Yes	Yes	No
Possible	Yes	No	No	No
Unlikely	No	No	No	No

Dechallenge is the therapeutic choice to stop taking a medication after it may have caused an adverse pharmacological reaction. Dechallenge are classified as "positive" or "suggestive" if the reaction disappears completely or partially once the drug is withdrawn, and "negative" or "against" if the reaction persists. Rechallenge simply means giving a patient who has previously experienced an unpleasant event or an ADR that may have been medication-related another dose (or doses) of the same medication, whether on purpose or mistakenly. Negative rechallenge occurs when the product is reintroduced and fails to produce the same signs and symptoms that were seen when the suspect drug was first introduced, while positive rechallenge occurs when the same signs and symptoms return after the suspect product is reintroduced [35].

III. ALGORITHMS

According to **Lanctot KL et al. (1994),** an algorithm is a flow chart with specific instructions on how to solve a particular problem [36]. When an ADR is suspected, there is a clinical tool in the form of a questionnaire that offers exact operational criteria for determining the likelihood of cause. Algorithms provide structured and standardized methods of assessment in a systematic approach to identifying ADRs based on characteristics including the temporal sequence or time to the commencement of the ADR, previous drug/adverse response history, and dechallenge and rechallenge. Because each situation is treated methodically, there is a high level of uniformity and reproducibility. To reach a judgement, however, clinical discretion is needed at different points [37]. There are numerous computational techniques for determining causality at the moment, but none of

them are recognized as the "gold standard" due to their flaws and differences **[38]**. Here, we've narrowed down a few key algorithmic techniques.

1. **French Imputability Causality Assessment Scale:** Dangoumau et al. first published this approach in 1978, and Begaud et al. refined it in 1985. It is the only technique for determining causality that distinguishes between internal and external accountability. French imputability is indicated by the following scores: extrinsic imputability score (B), intrinsic imputability score (I), chronological imputability score (C), and semiologic imputability score (S). When the provided information's details are considered along with the C and S ratings, the resultant imputability score (I), which stands for intrinsic accountability, is calculated. In order to estimate the extrinsic accountability, the B score is evaluated using the most recent scientific research that is currently available. France uses a single approach of imputability that was selected for maximal sensitivity at the expense of specificity **[39-40]**. The alert system employs this technique, which independently takes into account any recorded information as well as any drug a patient has taken. The data are examined in light of the national data bank when an alert is established. The use of a standard adverse drug reaction assessment system by all parties involved in the pharmacovigilance programme is the key benefit of this novel approach. Because the categories of criteria, such as "compatible," "suggestive," or "inconclusive," have never been properly defined, there is only partial reproducibility. Although imprecisely, the process of expert judgement is founded on the same deciding element that underlies algorithms.

2. **Naranjo Algorithm Causality Assessment Scale:** In order to assess the causation between a adverse event and a prospective treatment medicine, the Naranjo Algorithm provides likelihood scores to a list of ten simple questions. Using terms and concepts like "definite," "probable," "possible," and "doubtful," it evaluates the causality in various clinical disorders. Based on the ultimate score determined after evaluating 10 questions, the negative reaction is categorized as a likelihood type. The type is "definite" if the total score is less than 9, "probable" if the total score is between 5-8, "possible" if the total score is between 1-4, and "doubtful" if the total score is less than 0 **(Table 5).** Reviews frequently compare the author's conclusions with ADR using the score generated by this algorithm following the assessment **[41].** When standardizing the cause analysis for ADR, the Naranjo scale and the WHO-UMC scale are compared.

Table 5: Naranjo Algorithm Causality Assessment Scale

Questions	Yes	No	Don't know
● Presence of previous conclusive report on adverse reaction.			
● Did adverse event appear subsequent to administration of suspected drug?			
● Did adverse event improve on drug discontinuation or on administration of specific antagonist?			
● Did the adverse event reappear when the drug was re-administered?			

● Are there any alternative causes other than the suspected drug that could have caused the reaction on their own?			
● Did the adverse event reappear when a placebo was administered?			
● Was the incriminated drug detected in toxic concentrations in blood (fluids)?			
● Did the adverse event worsen on increasing the dose or decreased in severity with lower doses?			
● Past history of any similar reaction to the same or similar drugs.			
● Was the adverse event confirmed by objective evidence?			
Total score 0– Doubtful 1–4 Possible, 5–8 Probable, ≥9 Definite			

3. **Method of Kramer et al. [17]:** This algorithm is relevant to a single clinical symptom that develops following the use of a single questionable medication. When numerous medicines are present, each is evaluated separately. The transparency of this algorithm is one of its benefits. However, to apply this strategy successfully, a certain amount of knowledge, experience, and time are needed **[42]**.

4. **Balanced Assessment Method (Lagier et al.) [19]:** It grades case reports using a set of visual analogue scales (VAS) based on the likelihood that each criteria is met. The benefit of this approach is that each aspect is considered as a potential causative option rather than merely as a separate factor. Despite the fact that each case is examined by two different assessors, the assessment still strongly depends on the assessors' expertise. For an evaluation to be accurate, the evaluator must be an authority in the subject matter **[43]**.

5. **Summary Time Plot (Castle et al.) [20]:** ADR pattern recognition was recommended to be carried out in an industrial setting. The graphic provides a timeline between the course of therapy and any probable side effects. When the causality criteria give sufficient information, the length of therapy and any potential adverse reactions are plotted with time on the x-axis and strength of the potential adverse reactions on the y-axis. This method cannot show causation because it just summarizes the time factor along with other variables that are crucial to the drug-event relationship. However, the method is easy to apply, avoids using ambiguous terminology, and is effective even with a limited level of understanding **[44]**.

6. **Ciba Geigy Method (Venulet et al.) [21]:** Numerous expert consensus sessions led to the creation of the "Ciba-Geigy method." Experts evaluated occurrences and determined causality on a VAS using their clinical opinion. This strategy was altered, and it was replaced with a 23-item checklist that was broken down into three sections: (i) keeping an eye on experience of physician (ii) unfavourable effects the patient has experienced in the past, and (iii) History of the current unfavourable reaction. There is a lot of consensus (62%) was found when this modified method was compared to the assessors' assessments. Even though the degree of dependability does not ensure validity **[45]**, this

technique reflects the knowledge and experience of the evaluator as well as the type of ADR that is being examined.

7. **Loupi et al. method [22]:** It was created to evaluate a drug's potential for teratogenicity. The medicine can be disregarded in the algorithm's initial parts (chrono-semiological axis) if it is not thought to be the cause of the aberration. The bibliographical data are weighted in the second part (bibliographical axis). The three inquiries consider the drug's chronology, any potential alternate aetiological options, and other bibliographical data to determine **causation [46].**

8. **Roussel Uclaf Causality Assessment Method (RUCAM)[7] [Danan G et al. 1993]:** The purpose of this therapy is to treat predetermined sickness conditions, like liver and skin damage. A retrospective investigation of the repeatability of this process among four specialists revealed a 37-99% agreement rate. Although it seems rather easy to use, this method is organ-specific. Therefore, the criteria must be established by a consensus of experts in each medical specialty and validated before it may be utilized in ADRs other than hepatic or dermatological damage **[47]**.

9. **Maria and Victorino (M and V) scale [23]:** This scale was created by Maria and Victorino to identify drug-induced liver damage (DILI). Scores between 6 and 20 were used to convey probability, which was then separated into five causation levels (definite, scores of >17; probable, 14–17; plausible,10–13; unlikely, 6–9; excluded medication related hepatotoxicity). The accurate diagnosis of DILI is difficult and demands the assistance of qualified medical professionals. Even though it is well-known, it has certain gaps. The scale must be determined for each drug when there is suspicion of more than one substance. Calculating scores for other hepatic conditions using the M&V scale is difficult since it contains some questions that are exclusively applicable to immunoallergic hepatitis **[48].**

10. **Drug Interaction Probability Scale (DIPS) [24]:** The concept originated with Horn et al. To evaluate drug interaction situations, the Drug Interaction Probability Scale (DIPS) is used. Ten questions with a "yes" or "no" response each are posed by the DIPS to provide a score indicating the possibility of a medication interaction **(Table 6).** The inquiries relate to the drug's pharmacological characteristics, potential interactions with other medications, and information specific to the patient. The approach was created to aid users in evaluating the negative effects caused by drug interactions as well as to function as a roadmap for further research into possible drug interactions. The only prerequisite is having a sufficient understanding of the implicated medications and the fundamental mechanisms of interaction **[49]**.

Table 6: Questions for Drug Interaction Probability Scale

S. No	Question	Yes	No	NA
1.	'Are there previous credible reports of this interaction in humans?'			
2.	'Is the observed interaction consistent with the known interactive properties of the precipitant drug?'			

3.	'Is the observed interaction consistent with the known interactive properties of the object drug?'			
4.	'Is the event consistent with the known or reasonable time course of the interaction (onset and/or offset)?'			
5.	'Did the interaction remit upon de-challenge of the precipitant drug with no change in the object drug?'			
6.	'Did the interaction reappear when the precipitant drug was re-administered in the presence of continued use of the object drug?'			
7.	'Are there reasonable alternative causes for the event?'			
8.	'Was the object drug detected in the blood or other fluids in concentrations consistent with the proposed interaction?'			
9.	'Was the drug interaction confirmed by any objective evidence consistent with the effects on the object drug (other than drug concentrations from question 8)?			
10.	'Was the interaction greater when the precipitant drug dose was increased or less when the precipitant drug dose was decreased?'			
Total Score				
Highly Probable: >8, Probable: 5- 8, Possible: 2- 4, Doubtful: "A NO answer presumes that enough information was presented so that one would expect any alternative causes to be mentioned. When in doubt, use Unknown or NA designation."				

IV. PROBABILISTIC OR BAYESIAN METHODS

The Bayesian technique transforms a prior probability of drug causality into a posterior probability using specific discoveries in a safety instance **[50].** A probability ratio is further divided into many elements (much like report-specific data, such as time sequence or re-challenge/dechallenge that helps to identify between sources of events). A posterior probability of drug causality is obtained by multiplying the numerous components out to get at the final conclusion **[51].** Each component is used to a certain group of case information. Multiple reasons can be evaluated simultaneously using this strategy. There is no restriction on the amount of report details that can be evaluated simultaneously using this method. It can be carried out using a spreadsheet on paper or online. As soon as additional evidence of the suspected ADR is discovered, our technique immediately produces mathematical and practical conclusions **[50].** It is regarded as the method for determining causation that makes the greatest sense **[52].**

1. **Australian Methodology [27] [Mashford ML et al. 1984]:** It was one of the first probabilistic methods to be applied. Conclusions are generated from internal data from case reports, such as time and laboratory data. In the assessment, prior information regarding the suspect-drug profile is purposefully left out. Making likelihood decisions only takes into account the probability of a causal relationship **[53].**

2. **Bayesian Adverse Reactions Diagnostic Instrument (BARDI):** To overcome the numerous limitations imposed on expert judgement and algorithms, the Bayesian Adverse Reactions Diagnostic Instrument (BARDI) was developed **[54].** When comparing a drug's likelihood of producing an adverse event to another cause, the BARDI is employed to determine the likelihood. The posterior odds are what are known as. Six assessment subsets are taken into account when calculating the posterior odds factor; the prior odds subset deals with background epidemiologic or clinical trial data, while the other five likelihood ratio subsets deal with case-specific data.

The previous odds factor for a patient is calculated by contrasting the anticipated drug-attributable risk with the background risk of a particular adverse event in a population that shares key characteristics with the patient under consideration (such as a medical condition). The five likelihood ratios (LRs) take into account any information with differential diagnostic value in the areas of patient history (Hi), timing of the adverse event in relation to drug administration (Ti), characteristics of the adverse event (Ch), drug dechallenge (De), which refers to any signs, symptoms, or occurrences after drug withdrawal, and drug rechallenge (Re), or readministration of the suspected causal drug(s). The posterior odds are the result of these factors **[55].**

$$PsO = PrO \times LR(Hi) \times LR(Ti) \times LR(Ch) \times LR(De) \times LR(Re)$$

On paper or a computer, a spreadsheet tool can be used to implement the Bayesian technique. It calculates and provides instant numerical and graphical feedback whenever new pieces of information pertaining to the suspected ADR are taken into account **[56].** Case reports are read, and descriptions that match reports from the literature are listed in order to calculate the prior likelihood. Also taken into account and indicated are factors that help distinguish potential causes. The software consists of two worksheets: one for case findings and one for scoring, which are used to impute case parameters. This method can assess more than two potential reasons at once, although it does require some experience to use. The spreadsheet enables quick computations and conversation while working **[57].**

V. EVALUATION OF THE CAUSALITY OF ADVERSE REACTIONS TO VACCINATIONS

Every year, 2-3 million children's lives are thought to be saved worldwide thanks to immunizations. Approximately 1.7 million children still pass away from vaccine-preventable diseases each year, despite tremendous improvements in the field **[58].** In order to guarantee that children received the recommended set of vaccinations, the World Health Organization (WHO) launched the Expanded Programme on Immunization (EPI) in 1974. The EPI served as the inspiration for India's Universal Immunization Programme (UIP) in 1985 **[59].** The UIP now provides immunization services to the 26 million babies who comprise the largest birth cohort in history of the world, with over 100 million doses of vaccines administered annually to infants under 1 year old in the nation **[60-61].**

Vaccines can cause adverse effects, which are most frequently fever and rash with more serious disorders like anaphylaxis happening extremely seldom **[62].** For the UIP-recommended vaccinations, the expected rate of serious AEFIs varies from 1 in 1000 doses

for the Bacillus Calmette-Guérin vaccine to 1 in 2-3 million doses for the oral polio vaccine **[63].** India launched its National AEFI Surveillance Programme in 1986, and the majority of countries use passive AEFI surveillance. In 2005, India became the first nation to legally ratify a collection of operational rules for surveillance. Both in 2010 and again in 2015, the recommendations underwent updates that were modelled after those made to the WHO's international AEFI guidelines **[64].**

VI. CONCLUSION

Both routine monthly reporting for all AEFIs and urgent reporting for serious and severe AEFIs are options in India. The typical facility-based Health Management Information System must receive monthly reports of all AEFIs, including mild, substantial, and severe events. Medical officers must notify the national monitoring programme of serious and severe AEFIs within 48 hours of receiving notification of the incident using the appropriate forms **[65].**

The evaluation of reported serious/severe AEFI's causality is one of the key components of an adverse event surveillance system. The job of completing the evaluation review of all reported AEFI cases has been delegated to the Causality evaluation panel. The formation of the AEFI secretariat and National AEFI Technical Collaborating Centre has allowed for the streamlined, progressive, more frequent, and more effective causality assessment approach.

Serious and severe AEFIs are more likely to attract media attention and have the potential to increase community concerns about vaccination safety. Such worries could trigger calls for a vaccine to be taken off the market if they are not properly evaluated and handled **[66].** To ensure the safety of vaccinations used in the field, thorough investigations of serious and severe AEFIs must be carried out promptly.

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