

Post marketing surveillance of suspected adverse drug reactions through spontaneous reporting: current status, challenges and the future

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Abstract

Background: To highlight the importance of spontaneous reporting programs in post marketing surveillance of medicines. Authors also aimed at providing various dimensions of spontaneous programs, including the strengths and weakness, and providing an insight on the future prospects of pharmacovigilance systems.

Methods: Various literature related to post marketing surveillance and spontaneous reporting programs were reviewed and the relevant ones highlighting the strengths and weaknesses are summarized. A balance of information on strengths and weaknesses is listed. The health professionals' awareness regarding existing spontaneous reporting programs is highlighted. Future prospects of pharmacovigilance are discussed.

Results: Though beneficial, spontaneous reporting programs encounter several limitations and difficulties in diagnosing adverse drug reaction. Under-reporting and bias are major challenges. Online signal detection tools and innovative methods are needed to strengthen the spontaneous reporting programs. We provide the various issues to be considered while depending on spontaneous reporting programs as a method of post marketing surveillance.

Conclusion: To strengthen the spontaneous reporting programs as an effective post marketing surveillance method, more awareness among health professionals and innovative strategies is needed. Integrating pharmacogenetic data can be a potential aspect of future pharmacovigilance.

Keywords: challenges, pharmacovigilance, post marketing surveillance, spontaneous reporting programs, under-reporting

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Plain language summary

Monitoring adverse effects of marketed medicines through reporting by healthcare professionals and its challenges and way forward

Introduction: This article highlights the importance of safety monitoring of medicines after they are launched in the market, mainly through reporting by healthcare professionals. We also highlight the strengths and weaknesses, and provide an insight on the future prospects of pharmacovigilance systems.

Methods: Various literature related to the topic were reviewed and the relevant ones highlighting the strengths and weaknesses are summarized. A balance of information on strengths and weaknesses is listed. Health professionals' awareness regarding existing programs on reporting safety of medicines is highlighted.

Results: Though beneficial, reporting of adverse effects by healthcare professionals who deal with patient lacks clarity in diagnosing the adverse effects. Under-reporting and bias are the major challenges. Online software is needed to strengthen reporting by healthcare professionals. We list the various issues to be considered while depending on healthcare professionals' reporting of adverse effects as a method of post marketing surveillance.

Conclusion: To strengthen medicine safety monitoring and reporting by healthcare professionals, more awareness among health professionals and innovative strategies are needed. Integrating the genetic data of patients can be beneficial in predicting adverse effects, therefore avoiding them and enhancing safe prescribing and dispensing by healthcare professionals.

Introduction

Post marketing surveillance (PMS) of medications is the process by which marketed medicines are monitored for adverse drug reactions (ADRs) post clinical trials.¹ Since most drugs may not reach the market without passing phase III clinical trials,² PMS studies are considered to be phase IV studies.³ The safety and efficacy evaluations of any new medicinal product *via* clinical trials will provide only limited information on rare ADRs.⁴ In addition, discovering 'rare' (1 in 1000) and 'very rare' (1 in 10,000) ADRs usually occurs only in the post marketing phase.³ This is mainly due to the limited variety of conditions, described as the 'five toos: too few, too simple, too narrow, too median-aged and too brief', referring to the narrow patient selection criteria and sample size along with the short duration of clinical studies. This makes it challenging to attain all the required safety data when relying exclusively on such studies.⁵ PMS gives more realistic results as they occur in a more natural setting and afford evidence to safeguard or enhance the safety of approved drugs.⁶ As a result of PMS, almost 20% of new medications obtained a black box warning post marketing, and 4% were removed from the market due to safety concerns.⁶

An ADR is defined by the World Health Organization (WHO) as: 'a response to a drug which is noxious and unintended, and which occurs at doses normally used in man for the prophylaxis, diagnosis, or therapy of disease, or for the modification of physiological function'.⁷ Each year, millions of patients experience ADRs, especially with the increased use of medicinal drugs.⁸ From 2009 to 2012, approximately 47% of people in the United States reported using no less than one prescription medication in the past

month and approximately 11% reported using no less than five prescription medications concomitantly.⁹ As a result, the amount spent on prescription drugs was estimated to be US\$270 billion in 2013 according to the National Center for Health Statistics report in 2014.⁹ Lazarou and his colleagues estimated, in a landmark meta-analysis in 1998, that ADRs were associated with over 2,216,000 hospitalization cases annually in USA (admitted because of ADR or suffered ADR while in hospital), leading to more than 106,000 deaths each year. Therefore, ADRs take the place as the fourth to sixth major cause of death, eclipsing pulmonary disease, diabetes, acquired immunodeficiency syndrome and pneumonia.¹⁰ According to the Centers for Disease Control and Prevention, ADRs are responsible for almost 1,300,000 emergency department visits annually.¹¹ In 1995, the burden of ADRs in financial terms was estimated to be up to US\$136 billion dollars annually.¹² More recently, Poudel *et al.* estimated the cost of ADR related hospitalizations in 2011 to be US\$38.9 billion dollars.¹³

Article selection and search criteria

A literature search was conducted by searching *Medline/PubMed*, as well as *Google Scholar*, using relevant keywords (post marketing surveillance, pharmacovigilance, spontaneous reporting, adverse drug reactions, *VigiBase*, drug safety). Articles older than 20 years were filtered out, unless they were still highly relevant, no updated information can be removed, or for historical perspective. Non-relevant results were excluded as well. After initiating the review, and in order to get more details on a specific point or topic, a Google search was conducted and the reference fulfilling the sought information was included.

Post marketing surveillance of suspected ADRs

Post marketing drug monitoring actions deal with two pharmacology fields: pharmacovigilance and pharmacoepidemiology.¹⁴ Pharmacovigilance, also known as drug safety surveillance, is mainly concerned with the ‘timely detection’ of ‘novel’ ADRs that are unique in their ‘clinical nature, severity and/or frequency’.¹⁵ Pharmacoepidemiology represents the ‘population-based study of drug uses and the risks associated with these uses’.¹⁴ The significance of using pharmacovigilance should be encouraged by highlighting that the life of a drug truly starts post marketing.¹⁶

Nowadays, PMS can be conducted actively, due to technological progress, with the help of computer systems and electronic medical records. This can be achieved when the regulatory authorities, as well as the pharmaceutical companies, have access to electronic medical records database and seek drug-associated ADRs.¹⁷

Three of the main limitations of pharmacovigilance are: under-reporting, difficulty in identifying low risks, and the difficulty or impracticality of quantifying risks. Moreover, ADR reporting is determined by numerous factors, for example how serious or severe an ADR is, how long the drug has been on the market, the experience of the health care professional, and the qualifications of the reporting physician (specialists report more often than general practitioners do).¹⁴

Nevertheless, spontaneous reporting is still the basis of post marketing drug safety surveillance.¹⁸ The fact remains that the main source of data collection for post marketing pharmacovigilance since the 1960s is spontaneous reporting systems (SRSs). They are considered to be a passive approach and are composed of reports of suspected ADRs gathered spontaneously from healthcare professionals, consumers and pharmaceutical companies that are maintained for the most part by ‘regulatory health agencies’.¹⁵ As such, PMS is applied in passive national reporting schemes, for example, ‘Yellow Card Scheme’ in the United Kingdom and ‘MedWatch’ in the United States. It is also applied as active surveillance, by ‘Medicines and Healthcare products Regulatory Agency’ (in the UK) and the U.S. Food and Drug Administration (US FDA), which carries out post marketing surveys.¹⁹

In order to regulate PMS, the US FDA established the US FDA Adverse Event Reporting System (FAERS) to collect ADR reports from healthcare professionals, patients and pharmaceutical companies.⁹ The purpose of FAERS is to support the post marketing safety surveillance program for all approved drugs and other ‘therapeutic biologic products’. They receive between 300,000 and 500,000 new safety reports annually.¹⁵ Similarly, at an international level, the WHO maintains a large database of ADR reports known as ‘VigiBase’ at Uppsala Monitoring Centre (UMC).^{9,20} The startup of the WHO Programme for International Drug Monitoring was in 1968 as a pilot project, with 10 countries already having established national systems for reporting of ADRs. The project then expanded to include more countries all over the world. New member countries developed Pharmacovigilance (PV) centers to report the ADRs and coordinate with the WHO center in Uppsala, in which the global database for the reported ADRs is established, which is VigiBase. VigiBase contains, as of June 2019, more than 20 million ADR reports, from which 12.5% were from low- and middle-income countries.²¹ Currently, there are 139 countries with full membership of the WHO Programme for International Drug Monitoring, as well as 32 associate members.²²

In Europe, the European Medicines Agency (EMA) established the Pharmacovigilance Risk Assessment Committee with the responsibility of medicines safety assessment and monitoring, from all aspects. Adverse events are captured, recorded and analyzed in the EudraVigilance database.²³ EudraVigilance is considered one of the largest databases globally, with over 16.7 million individual case safety reports (ICSRs).²⁴

It is proposed that there is a need to expand the types of PMS activities, including those using ‘large-scale health care information databases’.⁵ One possibility they stated was to exclude expected and non-serious adverse reactions previously identified through new drug application clinical studies, besides the ones that are more likely to be underreported. They also proposed for important potential adverse reactions that post marketing intervention studies ‘should be proactively planned and conducted using a control group to identify the degree of risks’. Performing PMS studies only in certain medical

Table 1. Examples of medicines with serious ADRs identified during the post marketing period.

Drug	Examples of ADRs identified through post-marketing reports
Amisulpride ²⁸	Torsades de pointes
Cyamemazine ²⁸	Torsades de pointes
Olanzapine ²⁸	Torsades de pointes
Benfluorex ³⁰	Valvular heart disease
Pergolide ³¹	Increased incidence of cardiac valvulopathy
Hydromorphone hydrochloride extended-release ³²	Dose dumping with alcohol, which leads to accidental overdosing
Cisapride ³³	Palpitations, tachyarrhythmias, torsades de pointes, ventricular fibrillation, QT prolongation, sudden death
Rosiglitazone ³⁴	Fluid retention and congestive heart failure
ADR, adverse drug reaction	

institutions with quality systems can present another potential solution.⁵ With such efforts, post marketing safety data can be collected in a better and more efficient way to enhance patient safety.⁵

Spontaneous ADR reporting systems

Spontaneous ADR reporting systems are important since they are a cost-effective method that can lead to the detection of new or rare ADRs.²⁵ Spontaneous reports are collected in databases through different channels (pharmaceutical companies, national and international pharmacovigilance centers or regulatory authorities). These databases belong to different institutes, such as US FDA and EMA, through which ADRs are collected and exchanged. Following analysis of the spontaneous reports, signals of unidentified or potential ADRs are generated.²⁶

Contributions of SRSs

National pharmacovigilance systems rely heavily on spontaneous ADR reporting by healthcare professionals in monitoring post marketing drug safety. SRSs are the most effective source of unidentified ADRs²⁵ as they cover a large population (from global sources)²⁶ and they are cost-effective.²⁵ Spontaneous ADR reporting systems are used by healthcare professionals or patients themselves to report an ADR to national coordinating

centers that analyze the ADR, leading to formulating a hypothesis and early detection of signals.²⁷ The importance of spontaneous ADR reporting systems was clarified in many studies such as the report of the arrhythmogenic ADR of drugs that lead to raising three potential signals of torsadogenicity (torsades de pointes) for some antipsychotics. The drug-induced torsades de pointes were identified because 25 cases were reported due to the use of amisulpride, due to cyamemazine and 189 cases with olanzapine.²⁸ After identifying the safety signal, the responsible institute may perform additional investigations to confirm, or raise warnings and mandate the manufacturing companies to include the detected ADR in their leaflets. In the case of serious ADRs, the drug may be withdrawn from the market, as in the case of cerivastatin, where association between the drug and rhabdomyolysis was noticed due to the increased number of ICSRs.²⁷ Wyskowski and Swartz identified 24 drugs withdrawn from the US market between 1969 and 2002, as a result of risks identified through spontaneous or case reports.²⁹ See table 1 for further details.

Quantification of ADRs

Following the identification of an ADR, and verification, it should be quantified.³⁵ An assessment should be conducted to evaluate the incidence, type, causality, preventability and severity of the ADR.³⁶

There are different tools and scales to measure these characteristics. For example, Willis and Brown Classification can be utilized to describe the type of ADR, which classifies ADRs into nine types. Causality can be assessed to be probable, possible, definite or unlikely by using Naranjo's algorithm. Predictability or incidence may be evaluated according to the prescribing information, as well as through a literature review. Severity is assessed by measuring tools such as Modified Hartwig and Siegel scale, which classifies the severity into seven levels. Preventability scales (such as Modified Schumock and Thornton) will conclude whether an event is definitely, probably, or not preventable. Impact of ADR on quality of life (QOL) may also be important to measure. Tools such as WHO Quality of Life BREF scale can be used for this purpose.³⁷ Evaluating costs of ADRs is rather complicated, as it includes direct costs, mainly hospitalization, as well as indirect costs such as loss of productivity, increased load on healthcare providers and social costs. Despite its difficulty, assessing costs of ADR remains of extreme importance, and pharmacoeconomics may be employed for that purpose.³⁸

Potential limitations of the spontaneous ADRs reporting systems

Difficulty in diagnosing the ADR. The first limitation is the difficulty in diagnosing the ADR even though most of the ADRs are included in a differential diagnosis list that is available for doctors.³⁹ Moreover, doctors mostly prefer to find a clear causal relationship before reporting any ADR, which could be difficult to obtain, and be time and effort consuming. As one physician stated: 'When a patient is taking a lot of drugs, how can we determine which drug is causing the adverse reaction?'.³⁹ Moreover, approximately 66% of physicians declared that a diagnosed ADR was not reported due to uncertain causal relationship between the ADR and the suspected drug.⁴⁰

To overcome the diagnosis problems, the causality scales have been introduced to healthcare professionals. The Naranjo ADR Probability Scale is widely used since it is simple and not specific. However, this scale has low capability of diagnosing drug-induced liver impairment. Another scale, known as Council for International Organizations of Medical Sciences/Roussel Uclaf

Causality Assessment Method, is considered valid and reliable in the diagnosis of drug-induced hepatotoxicity. However, this scale is complicated and not easy to use on day-to-day basis.⁴¹

Under-reporting. Under-reporting of ADRs by healthcare professionals (doctors, pharmacists or nurses) is another important aspect that heavily affects the ADR SRS. In Germany, the under-reporting of ADRs weakened the SRS.⁴⁰ A study done on a random sample of physicians showed that about 25% of the participants 'have never diagnosed an adverse drug reaction'.⁴⁰ Similarly, only 10% or less of serious ADRs, and 2–4% of non-serious ones, were reported to the British spontaneous reporting program.²⁵ Another study, that was done in Ghana, indicated that about 59.5% of the studied doctors suspected an ADR at the period of the study, but only 20% of them reported the suspected ADR.⁴²

Several factors may lead to ADR under-reporting, and since it is an important aspect, these factors must be detected first in order to find solutions to avoid the problem of under-reporting. Lack of time and increased administrative work for doctors are important factors that lead to ignoring ADR reporting. As stated in a study, many ADRs were noted, but the lack of time made it difficult for them to report the ADRs, and sometimes they even forgot to report them.³⁹

Under-reporting can be due to lack of knowledge regarding the different aspects of the SRS. Examples of this are: a lack of knowledge about pharmacovigilance, the definition of ADRs, a lack of knowledge of the criteria of adverse events to be reported, and the ADR.⁴⁰ It is also reported that 20% of the participating physicians did not even know that a national SRS exists, and 30% of the studied physicians did not know how to report.⁴⁰ A systematic review on factors leading to under-reporting identified ignorance, insecurity and indifference to be the major reasons.⁴³

To overcome the issue of under-reporting, healthcare providers must be educated and trained in the concept of pharmacovigilance and the ADR reporting systems. Easy channels for reporting ADRs must be established, such as through the phone and through user-friendly computer tools designed for reporting ADRs, hence encouraging doctors to report any ADR they face throughout

their busy working hours. Pharmacovigilance centers may encourage healthcare providers to report by recognizing their effort, giving feedback about the reported case or a pharmacovigilance activity, as well as offering support; a clinical advice, for example. These ways may be tested to positively impact the SRS.⁴⁰

Bias. When a drug is released to the market it is freely judged by doctors, who raise spontaneous ADR reports that are not obtained under controlled conditions, hence the reporter's decision can be affected by different bias factors. One factor is known as the Weber Effect, where the drug will be subjected to a high number of reported ADRs in the first 2 years, then the number of reports decreases.^{25,28} The Weber Effect was noticed in a study regarding the association of pancreatitis with exenatide use, there have been an irregular reporting trend.⁴⁴ The number of ADR reports increased after approval to reach its maximum by the year 2006 with 4411 reports. Then the number of reports dropped rapidly. In this study notoriety bias was also noticed, where the number of pancreatitis reports due to the drug increased by the year 2008 to reach 1470 immediately after the first FDA alert, then it decreased again in the fourth quarter of the year 2009.⁴⁴ Duplication of ADR reports is another form of bias that can lead to over-estimation of the safety signal.⁴⁴

Minimum awareness of spontaneous ADR reporting systems

A study done in Korea on a selected sample from the general population showed that the awareness of an ADR reporting system was quite low, at 8.3%. The main source of information was television/radio (69.9%), then the internet (19.3%), while only 6.1% obtained the information from posters or brochures. These findings indicate that awareness of the importance of ADR spontaneous systems should be boosted by campaigns, to emphasize the importance of this subject.⁴⁵

A cross-sectional study done in Ghana on randomly selected doctors showed that less than 30% of the selected doctors were trained in the spontaneous ADR reporting system. The trained doctors showed a higher percentage of ADR reports than those who did not get the training.⁴² In one meta-analysis from India, authors found a huge gap among health professionals' knowledge

and awareness on pharmacovigilance. Over half of the health professionals studied were unaware of the pharmacovigilance program in the country.⁴⁶ In Saudi Arabia, a health professional had a lack of knowledge, but had a positive attitude.⁴⁷ Similarly, lack of knowledge on the national pharmacovigilance program was considered a reason for under-reporting of ADRs in Turkey.⁴⁸ With no doubt, one could say, based on the available literature evidence, health professionals lack awareness on spontaneous reporting programs and strategies to be implemented to fill the gap.

Future prospects of pharmacovigilance

Pharmacovigilance has clear, well-established goals: to detect ADRs associated with the use of drugs as early as possible, and to avoid risks that may outweigh the benefits of the medication.⁴⁹

The evolution of pharmacovigilance has been a slow and steady one. From individual doctors noticing unusual effects in patients and sharing their findings with colleagues to the methods used today to monitor a drug after its release into the market, including spontaneous reports, risk management plans, prospective safety studies, and registries.⁵⁰

The main focus of pharmacovigilance has been to detect rare ADRs while giving less attention to the common ones. Recently, however, there has been a climate of change and efforts are now being made to focus on patient-centered pharmacovigilance rather than population-based and regulation-based pharmacovigilance.⁵¹

A study was conducted to evaluate the different aspects of pharmacovigilance currently, and in the future. The study claimed that there are developments within the field of pharmacovigilance, including the setting of rules and regulations, as well as the scientific-related issues. Specifically, the study mentioned details regarding those two aspects by stating that: 'On a regulatory level, these include conditional approval and risk management plans; on a scientific level, transparency and enhanced patient involvement are two important elements'. Overall, these new developments will guarantee continuous progress in pharmacovigilance.⁵²

There are three aspects to consider when evaluating ADRs: causality, severity and preventability. There are systems for assessing each of the three

categories, which set scales that are then scored to quantify and hence evaluate them. For instance, there are two systems to assess causality: the first is the WHO–UMC causality assessment system and the second is Naranjo's ADR probability scale. To assess severity, there is the Hartwig and Siegel ADR severity assessment scale, and finally, in order to assess the preventability of an ADR, the Schumock and Thornton ADR preventability assessment scale is used.⁵³

Thus, the goals of pharmacovigilance are the earliest detection as well as evaluation of ADRs. Currently there are new tools and algorithms that are being developed for that purpose, in order to better achieve those goals. The first example of those tools is the Online Signal Management, developed by GlaxoSmithKline and Lincoln Technologies, which is a data-driven framework used in the pharmacovigilance of products in the market. It combines traditional reporting methods with quantitative statistical methods.⁵⁴ The second example is a triage algorithm developed for the early detection of ADRs. The algorithm aims to detect drug interactions which may cause an ADR, so that it will identify signals of ADRs prior to any assessment by healthcare practitioners.⁵⁵ The third example is the Liverpool Adverse Drug Reaction Avoidability Assessment Tool. This tool evaluates the preventability of ADRs in pediatrics. The study stated that a recent systematic review of the incidence of ADRs among hospitalized children showed a very similar rate to that of adults admitted to hospitals. Due to the high rate, they developed this tool specifically for pediatrics.⁵⁶

Pharmacogenetics and pharmacogenomics are two new evolving sciences in the field of pharmacy related to pharmacovigilance. Pharmacogenetics deals mainly with effect of variability in genes on the effect of drug response,⁵⁷ while pharmacogenomics studies the genetic basis of ADRs.⁵⁸ The fourth example is based on that principle. There is a new method for the early detection and prediction of possible ADRs, which is a network-based method relying on gene expression. This method links between the protein targets network and any potential ADRs based on gene expression.⁵⁹ Integrating pharmacogenomics into clinical practice requires translating the concept to practical tools that are adopted in routine practice. This will lead to more widespread adoption of clinical pharmacogenomics and, therefore, more optimized pharmacotherapeutic approaches with fewer

ADRs.⁵⁸ Various efforts have been devoted to pushing for implementing pharmacogenomics approaches. One of the steps taken toward this direction is the Ubiquitous Pharmacogenomics (U-PGx) project, which involves preemptive testing of various variants of pharmacogenomic markers for patients, and incorporating them into patients' electronic records. A clinical study is being conducted: PREemptive Pharmacogenomic testing for prevention of Adverse drug REactions (PREPARE), as a block-randomized, controlled trial on 8100 patients to assess outcomes of this project. The project is funded by the European Union, and seven countries are involved in it. The study results will provide robust data related to clinical outcomes and cost-effectiveness of U-PGx, and may aid in the implementation of pharmacogenomics-guided prescriptions, leading to safer, more customized pharmacotherapy.^{58,60} Similar projects have been initiated in the USA (Pharmacogenomics Research Network (PGRN) and Asia [the South East Asian Pharmacogenomics Research Network (SEAPharm) program].⁶⁰ The fifth example is similar in terms of having a predictive concept. It is called the Augmented Random-Walk with Restarts (ARWAR). This approach is used for highly related drugs, based on the concept of 'similar drugs have similar ADRs', and follows computational approaches that convert different properties of drugs (chemical structures, protein targets, etc.) to numerical values, which are then systematically translated into desired effects or ADRs of those drugs. Information for this method is extracted from a database (such as DrugBank). A total of 146 drugs are chosen which have a minimum of five target proteins and five ADRs. For each drug, target proteins, protein–protein interaction and functional annotations of proteins are taken as input, and a Human Drug Network (HDN) is constructed, which is considered as output. HDNs of all chosen drugs have by now become a connected network with relationships between drugs. Then, this initial network is augmented by new drugs ('nodes') and relationships between drugs ('edges'). Afterwards, an algorithm for link predictions, Random-Walk with Restarts, is applied, and will lead to predicting novel ADRs.⁶¹

Artificial intelligence and predictive pharmacovigilance: the way ahead

Predictive analytics, a method employing artificial intelligence, is a novel method that uses existing information to make predictions of future outcomes

or future trends in all areas of Medicine and Health Care.⁶² Thus, predictive analytics models help regulatory authorities in better understanding the risks and benefits of the medicines once a new medicine moves from risk–benefit regulatory efficacy to real-world risk-effectiveness. This enables the development of a Real-World Pharmacovigilance Score – a three-dimensional baseline prediction of likely adverse events based on projected volume and specific clinical use.⁶³ In one of the predictive analytics models, authors judge whether safety signals observed on an investigational drug were more likely to have occurred by chance or to have been caused by the drug.⁶⁴ These methods, making use of artificial intelligence, thus can play an important role in future PV. Apart from the predictive analytics modeling, descriptive modeling and prescriptive modeling, disproportionality methods are also employed in PV for early identification of signals.⁶⁵

Conclusion

Spontaneous reporting programs, though considered beneficial in post marketing surveillance of medicinal products, still lack clarity in multiple aspects. It is important to incorporate newer methodologies into these programs to overcome the limitations, and innovative signal detection methods are needed. Integrating pharmacogenetic data can be a potential source in advancing pharmacovigilance processes.

Author contribution

MAO conceptualized the idea, performed the literature review, and wrote the initial draft. AMT, NH, and SP performed the literature review and edited subsequent versions. AMT synthesized information extracted from various articles. SP wrote the abstract and conclusion. All authors read and approved the submission version of the manuscript.

Availability of data and materials

Available upon direct requests to Muaed Alomar; muayad74@yahoo.com

Conflict of interest statement

The authors declare that there is no conflict of interest.

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