

## **Factors influencing the implementation of medicine risk communications by healthcare professionals in clinical practice: a systematic review using the theoretical domains framework**

### **Abstract**

#### **Background:**

Adverse drug reactions (ADRs) are known to cause hospitalisation, longer hospital stays, as well as higher healthcare costs and mortality. Unrecognised ADRs are anticipated throughout the medicine lifecycle as, before the medicine reaches the market, clinical trials are conducted for a short period on a limited number of people, who might underrepresent the actual population. After the medicine reaches the market, emergent information that could affect its benefit-to-risk balance is usually shared by regulatory agencies and pharmaceutical companies through medicine risk communications. Medicines risk communications aim to prevent harm to patients by targeting their behaviour, knowledge, and attitudes, as well as those of health care professionals (HCPs). Despite their important role in translating these communications into their clinical practice, HCPs do not always adhere to the recommendations provided in risk communications. Measurement of medicine risk communications' effectiveness does not necessarily guarantee their implementation, cost-effectiveness, or transferability in real-world situations. To enhance the impact of drug regulatory interventions, implementation science has been encouraged. However, implementation science was not previously used to identify factors affecting HCPs' implementation of medicines risk communications. A recently widely used framework is the Theoretical Domain Framework (TDF). In this systematic review, the TDF was employed to categorise a range of different factors that could affect HCPs' implementation of medicine risk communications within their clinical contexts.

#### **Methods:**

The search strategy involved a set of predefined search terms and fifteen databases, such as EMBASE, PubMed, Web of Science and CINAHL PLUS. Searches were conducted from April to May 2018 and updated in June 2021 using PubMed, Scopus, and CINAHL PLUS. A second reviewer independently conducted the screening process of the initial search. The total number of records screened was 10,475. A study was included if it reported any factors influencing HCPs' uptake of medicine risk communications. Only studies with English or Arabic abstracts were included. Those studies that did not include pharmacovigilance-related medicine risk communications were excluded. Additionally, studies only assessing HCPs' practice or evaluating the effectiveness of risk minimisation measures were excluded. Likewise, studies related to occupational hazards, case reports, interventional studies, and studies not involving HCPs were excluded. In case the published information was insufficient to decide whether to include or exclude a study, the authors were contacted. Furthermore, the authors of seven eligible abstracts were contacted for full-text articles. The mixed method appraisal tool (MMAT) was used to evaluate the quality of the included studies. All included studies were assessed by one reviewer, and a total of 16 studies were assessed by two reviewers independently. Disagreements were resolved through discussion. Using thematic analysis and concept mapping, a narrative synthesis was performed, followed by a critical reflection on the

synthesis process. This review presents the results of the concept mapping, which involved matching the identified factors to the TDF.

## **Results:**

A total of 28 studies were included. Eleven domains influenced HCPs' implementation of medicine risk communications. A large number of studies included factors related to the "Knowledge" domain (n=23), followed by "Beliefs about Consequences" (n=13), "Memory, Attention and Decision Processes" (n=12) and "Environmental Context and Resources" domains (n=12). Seven studies reported "social influences" and six studies included factors relating to "Goals", followed by four studies involving factors related to "Social/Professional Role and Identity". Underrepresented domains included "Emotion" (n=2), "Beliefs about Capabilities" (n=2), "Behavioural Regulation" (n=1), and "Reinforcement" (n=1). On the other hand, none of the identified factors were related to the "Skills", "Optimism", or "Intentions" domains.

Except for "Beliefs about Consequences", most studies contributing to the other three most commonly reported domains ("Knowledge"; "Environmental Context and Resources"; and "Memory, Attention and Decision Processes") scored low (1 or 2 out of 5) on the MMAT quality assessment. Moreover, the same number of studies (n=5) contributing to the "beliefs about consequences" domain had low (1 or 2 out of 5), and intermediate (3 out of 5) scores on the MMAT.

## **Conclusion:**

Medicines risk communications are important tools for disseminating information that may influence the benefit-to-risk balance of medicines. Even though HCPs are required to implement the recommendations of these communications, they do not always adhere to them. Using the TDF enabled the categorization of the range of factors that affect whether or not HCPs implement the recommendations provided in a medicine risk communication. However, most of these factors relate to four domains only ("Knowledge"; "Beliefs about Consequences"; "Memory, Attention and Decision Processes"; and "Environmental Context and Resources"). Additionally, most of the studies contributing to three of these four domains were of low quality. Future research should focus on using implementation science to identify target behaviours for actionable medicine risk communications. Regulators should use such science to develop cost-effective strategies for improving the implementation of medicines risk communication by HCPs.

## 1. Introduction

Risk communication, an established terminology has historically been applied in the context of sharing information related to risks<sup>1</sup>. Risk communication was conceptualised in different fields including environmental, public health and medical areas<sup>1</sup>. Risk communication has also been used to share information related to medicine's safety. An early documented example of medicine risk communication was published in 1893 when The Lancet medical journal published physicians' reports of deaths attributed to anaesthesia<sup>2</sup>. Despite its controversial aetiology, this was believed to be triggered by the death of Hannah Greener, a 15-year-old girl, in 1848 after she received chloroform as a general anaesthetic for her toenail removal surgery<sup>2-4</sup>. However, it was only after the thalidomide disaster that risk communications related to medicines became an important element of pharmacovigilance activities in terms of sharing information related to adverse drug reactions (ADRs)<sup>5</sup>. In pharmacovigilance, medicine risk communication is usually overseen by regulatory agencies (RAs) such as the United States (US) Food and Drug Administration (FDA) and the European Medicine Agency (EMA)<sup>5,6</sup>. Medicine risk communications are not to be confused with transparency, which aims to share information related to authoritative activities with the public and enable democratic decisions<sup>7,8</sup>. However, medicine risk communications include emergent information about medicines' benefit-to-risk balance and decisions on whether to withdraw medicines from the market, recommend changes to practice or provide the information to healthcare professionals (HCPs) without specifying practice changes<sup>6,9</sup>. This form of communication is one of the pharmacovigilance activities that follows risk identification, assessment and mitigation<sup>10</sup>. Risk communications related to the post-market use of medicines are usually issued by regulatory agencies or pharmaceutical companies<sup>11</sup>. The forms of medicine risk communications and the channels by which they are disseminated, including bulletins or letters to HCPs, might differ according to each regulatory agency<sup>6</sup>. There have been 86 label updates and 17 direct healthcare professional communications between the years 2014 and 2017 in the European Union alone<sup>12</sup>. This review focuses on regulatory-related medicine risk communications that are disseminated to HCPs.

Medicine risk communication is dynamic and complex. An intervention is considered complex based on its characteristics, such as the behaviour it attempts to change or the number of groups or settings involved<sup>13</sup>. Medicine risk communications are dynamic in the sense that they can be sent from different sources to a variety of audiences. These audiences include HCPs at different settings and levels, patients with diverse backgrounds and demographics, and the public. While it is complex in its expected outcomes. Although the ultimate goal is to ensure the safe use of medicine, the expected outcome might range from informing the targeted audiences about the risk, changing their attitudes or changing their behaviour<sup>14,15</sup>.

Medicine risk communications aim to prevent patient harm by targeting both patient and HCP behaviour, knowledge and attitudes<sup>15</sup>. HCPs have an important role in translating these communications into their clinical practice. However, they do not always adhere to the recommendations provided in such communications<sup>16-18</sup>. This was shown by previous systematic reviews that assessed the impact of regulatory-related actions. Previous systematic reviews have also shown that such communications might result in unintended effects<sup>18</sup> or spillover effects, which involve implementing the intended or unintended effects on a population that was not targeted by the medicine risk communication<sup>16</sup>.

RAs recognise the importance of evaluating the impact of medicine risk communications and the need to understand the enablers and barriers to implementing risk messages in clinical practice<sup>19,20</sup>. Such evaluations have been commonly conducted using medical claims or databases<sup>17,21</sup>. Studies focusing on databases without involving human participants might miss the opportunity to understand the reasons behind different behaviours<sup>22</sup>. For example, a prescription analysis might show reduced prescribing post-risk communications but then only provide little information on whether this reduction was caused by HCPs' judgments or other influences, such as patient refusal<sup>17</sup>. As other complex interventions, focusing on measuring the effectiveness of a medicine risk communication might not guarantee implementation, cost-effectiveness or transferability in real-life situations<sup>13</sup>. According to the latest update to the framework for developing and evaluating complex interventions (jointly developed by the Medical Research Council and the National Institute for Health Research in the United Kingdom to maximise the value of complex intervention research to decision-makers), it is important to study both the complexity inherent in the intervention's components and their interaction with the context in which they are implemented<sup>13</sup>.

Earlier systematic reviews attempted to explain the reasons for different behaviours among the HCPs following a medicine risk communication. According to Møllebæk<sup>22</sup>, there are communication factors that could influence the effectiveness of Dear Healthcare Professional Letters, such as the clarity of the content and mode of delivery, as well as HCPs' preferences towards the sources of medicine risk communications. In addition, this review reported that HCPs preferred safety information from RAs to that of pharmaceutical companies<sup>22</sup>. According to a second systematic review, reasons for the unintended effects of safety communications include patients' or their guardians' refusal to take the medicine of concern, concerns related to liability and perceptions that there is no risk or that the risk is minimal<sup>17</sup>. In the third review, Dusetzina<sup>16</sup> found that healthcare providers were well aware of general safety communication and less aware of specific recommendations, such as antidepressant follow-up requirements<sup>16</sup>. The same review found that healthcare providers had different levels of agreement with the communications, with high levels of agreement in communications regarding the use of over-the-counter cough medications in children, but lower levels in others, such as monitoring patients taking antiepileptic medications<sup>16</sup>. Despite the insights these reviews presented on factors underlying HCPs' implementation of medicine risk communications, implementation and behaviour change frameworks were not reported as being utilised in these reviews. The action of communication per se does not necessarily result in the intended implementation. This was evident with the different forms of implementation resulting from a medicine risk communication. Thus, implementation science should be applied to understand the different forms of implementation. The utilisation of implementation science was previously encouraged to improve the impact of drug regulatory interventions<sup>23</sup>. One framework that has been recently extensively used is the Theoretical Domain Framework (TDF), which integrates 128 theoretical constructs from 33 theories<sup>24</sup>. The TDF's first version was refined and validated in 2012, resulting in a second version<sup>25</sup> that was used in this review. This version includes the following 14 domains: "Knowledge"; "Skills"; "Social/Professional Role and Identity"; "Beliefs about Capabilities"; "Beliefs about Consequences"; "Optimism"; "Reinforcement"; "Intentions"; "Goals"; "Memory, Attention, and Decision Processes"; "Environmental Context and Resources"; "Social Influences"; "Emotion"; and "Behavioural Regulation"<sup>25</sup>. The TDF has been utilised in different healthcare settings, including examining healthcare workers' explanations for non-compliance to hand hygiene guidance<sup>26</sup>. It was also used in investigating clinical determinants of antimicrobial prescribing behaviour using the TDF in a quantitative cross-sectional survey involving doctors and pharmacists<sup>27</sup>, as well as in the synthesis of qualitative systematic reviews. An example of this includes identifying barriers and enablers

for monitoring and deprescribing opioid analgesics for chronic noncancer pain<sup>28</sup>. Another example of employing the TDF in synthesising factors in systematic reviews includes classifying factors affecting patients' use of complementary and alternative medicine in diabetes mellitus from the perspective of patients and HCPs<sup>29</sup>. The TDF was also employed to identify barriers to interdisciplinary chronic obstructive pulmonary disease guidance adherence, which were matched to the Behaviour Change Wheel (BCW) to provide future solutions to these barriers<sup>30</sup>.

In our first systematic review, we identified different factors that could affect medicine risk communication implementation in clinical practices. These factors were related to the source of information, the message itself, the communication process, healthcare institutions, the HCPs and the patients<sup>31</sup>. In this systematic review, the TDF was used to classify a range of different factors that could affect HCPs' implementation of medicine risk communications within their clinical contexts, with an attempt to map it to the BCW to aid in identifying targets for intervention.

## 2. Methodology

### 2.1 Systematic Review Registration

A systematic review according to PRISMA Guideline (Supplement 1 & 2 PRISMA checklists)<sup>32</sup> was conducted. The protocol of this review was registered with PROSPERO (CRD42018116468).

### 2.2 Literature Search and Study Selection

In this review, the terms of the search were developed using concepts related to the population, interventions, and outcomes, where the comparator element was deemed irrelevant<sup>33</sup>. The population included HCPs, whose types and ranks were not predefined. Interventions involved regulatory communication about medicines risk. The outcomes included factors that might affect HCPs' implementation of risk-related communications relating to medicines.

Another researcher and an information manager independently reviewed the search terms. According to the database requirements, the final search terms (Supplements 3-8) were adjusted. For PubMed and CINAHL PLUS, mesh terms and alternative terms were used, respectively.

Between April and May 2018, the following databases were searched: AMED; EMBASE; Embase Classic; Global Health; HMIC; International Pharmaceutical Abstracts; Health and Psychosocial Instruments; PsycEXTRA; PsycINFO; MIDIRS; OpenGrey; Web of Science; PubMed; Scopus and CINAHL PLUS. AB and IB independently screened the titles and abstracts of all retrieved articles against the inclusion and exclusion criteria. Any discrepancies between the authors were discussed until a consensus was reached. References of the included studies, as well as references of relevant reviews (i.e., reviews focused on the impact of post-market drug safety communications), were also manually searched by AB.

To ensure that the articles included in the search were up to date, two updates on the search were conducted using the same search strategy. The first update was conducted by AB between May and August 2019 using the same search strategy and the following databases: Web of Science, PubMed, Scopus, and CINAHL PLUS. No new studies meeting the inclusion criteria were identified at this time. AB conducted the second update on the search in June 2021 using the same search strategy and using the following databases: PubMed; Scopus; and CINAHL PLUS. IB reviewed the included study against the inclusion criteria and confirmed its inclusion.

## **2.3 Inclusion & exclusion criteria**

The inclusion and exclusion criteria mentioned in 2.3.1 and 2.3.2 were utilised to screen the identified records for their eligibility. When published information was insufficient to decide inclusion or exclusion, AB contacted the authors of primary studies. AB also reached out to authors of seven eligible abstracts, including an abstract of a Spanish-language article, two conference abstracts, two meetings' abstracts, and two research letters, but none replied with the full-text English version of the article. These abstracts were thus excluded.

### **2.3.1. Inclusion criteria**

A study was included if it involved HCPs as participants and if it included a factor that could affect HCPs' implementation of medicine risk communications issued by pharmacovigilance regulatory agencies.

### **2.3.2 Exclusion criteria**

To avoid translation biases, studies that were not written in either English or Arabic were excluded, as the research team is fluent in both languages. However, none of the identified studies were written in Arabic. Studies not involving pharmacovigilance or patient safety RAs were excluded. Furthermore, studies that measured only HCPs' practice after medicine risk communications or evaluating the effectiveness of risk minimization measures were excluded. Studies involving occupational hazards, case reports, interventional studies, and studies not involving HCPs were also excluded.

## **2.4 Data extraction**

To extract information, a data extraction form was developed to collect information on the paper's first author, publication date, country where the study was conducted, name of the regulatory agency involved, medicine mentioned in the communication, the type of regulatory action, the population targeted by the medicine risk communication, study participants, study settings, method of data collection, method of data analysis, factors and processes identified as affecting implementation. The data extracted were utilised to inform the table of characteristics.

The data extraction was carried out by AB, while seven studies were independently extracted by NS. Comparing the two sets of extracted information, the differences were mainly related to the level of detail to include. In addition, one heading of the data to be extracted was unclear. To reflect the purpose of this heading, it was changed from "targeted patient population" to "targeted population from the alert".

## 2.4 Quality assessment

To assess the quality of the included studies, the Mixed Method Appraisal Tool (MMAT) version 2018 was used<sup>34</sup>. AB assessed the quality of all included studies. Using the MMAT, independent quality assessments were conducted by IB (9 studies) and NU (7 studies). Disagreements were initially resolved through discussions and by agreeing on the criteria for evaluating the MMAT items. The details of this process are outlined in Supplement 9. There was no exclusion of full-text articles due to their quality assessment.

## 2.5 Data analysis

In this study, narrative synthesis was applied, which involves four steps based on the Economic and Social Research Council<sup>35,36</sup>. In narrative synthesis, various types of studies are systematically synthesized when meta-analyses are deemed inappropriate<sup>35,36</sup>. In contrast to summarizing the included studies, this type of synthesis gives new insights and supports decision-making<sup>35</sup>. The steps of this synthesis process were previously explained in a previous systematic review<sup>31</sup>. Figure 1 provides details of the steps of this synthesis differentiating results reported in the previous review from results that are reported in this review.

The current review presents the results of step four, which explores relationships within and across studies. In systematic reviews, it could be difficult to explore the relationships between empirical studies<sup>37</sup>. In heterogeneous data sets, it can be even more challenging<sup>37</sup>. Thus, an analytical framework is required to link the pieces of evidence<sup>37</sup>. Therefore, concept mapping was used. Through a visual exploration of the extracted data, this tool pinpoints concepts related to the review's questions<sup>36</sup>. From step two (preliminary synthesis) the results sections (and open-ended questions in one study's discussion section) were read line by line inductively coded by AB facilitated by MAXQDA, a data analysis software. This process allowed the identification of possible factors, which were then mapped to the TDF constructs<sup>25</sup>, which were presented in a table along the BCW, where we identified the sources of behaviour based on the Capability, Opportunity, and Motivation-Behaviour (COM-B) analysis, and the targets for intervention.<sup>25,38-40</sup> The products of the analysis process were reviewed and approved by the co-authors.

A critical reflection on the synthesis process concludes this narrative approach, which can be seen in the limitations section<sup>36</sup>. The examples in Supplement 10 illustrate the analysis process.

### 3. Results

#### 3.1 Studies' characteristics

In total, twenty-eight full-text articles were included in this review<sup>11,41-67</sup> (Figure 2 PRISMA<sup>32</sup>). A total of 24 studies were quantitative<sup>11,41-44,46-59,62-67</sup> and four qualitative<sup>45,59-61</sup>. Nineteen of these studies (n=19) were conducted in the United States<sup>41-43,45-48,51,52,55-57,59,61,63-67</sup>. Two studies were conducted in nine European countries as part of the Strengthening Collaboration for Operating Pharmacovigilance in Europe (SCOPE) initiative<sup>11,58</sup>. The included studies reported a range of 10 to 3625 participants, although one cohort study reported the number of patients for whom medicines were reviewed but not the number of HCPs<sup>55</sup>. Most frequently, studies focused on the FDA's antidepressant communication related to suicidality in children and adolescents (n=4)<sup>41,52,61,62</sup>. Table 1 lists the characteristics of the included studies. The table of characteristics has been updated following a correction of de Vries<sup>58 68</sup>. The contribution of each study to the TDF domains is presented with their total quality assessment in Table 2.

#### 3.2 Quality assessment

All studies fulfilled the two screening questions of the MMAT. Qualitative studies had fulfilled four or all the five items of the MMAT<sup>45,59-61</sup>. However, quantitative studies differed in their quality scores ranging from meeting one item to meeting four of the five MMAT items<sup>11,41-44,46-59,62-67</sup>. The main reason quantitative studies failed to satisfy MMAT items was a lack of reporting<sup>41,43,44,46-52,56,62-65,67</sup>. The results of the study quality assessment are listed in Table 3.

#### 3.3 Matching the identified factors to the Theoretical Domains Framework

##### 3.3.1 Knowledge

Knowledge has been investigated in most of the studies<sup>11,41,43,45-50,52-54,56,61-63,65-67</sup>. This included measuring HCPs' awareness that a medicine risk communication has been issued<sup>11,41,43,45-50,52-54,56,61-63,65-67</sup> for medicine and their knowledge about the specific content of a medicine risk communication<sup>45,53,56,61,67</sup>. One reason cited for physicians not implementing medicine safety communications was the lack of knowledge<sup>55</sup>. However, no clarification was provided as to what type of information was lacking. HCPs' familiarity with the regulatory agency responsible for regulating medicines safety communications, its website or email service<sup>54,58,59</sup>, and their familiarity with the tools used to communicate emerging medicines' safety information were also possible factors that have been reported in different studies<sup>11,54,56,58</sup>.

Procedural knowledge was reported to a lesser extent and less directly as a potential factor than knowledge. This has been illustrated by reporting the provision of guidance to implement the recommendations<sup>51</sup>, the time devoted by healthcare facilities to interpreting a medicine risk communication<sup>43</sup>, the active efforts taken by HCPs to understand the medicine risk



communication<sup>41</sup>, as well as their knowledge about the lead person responsible for implementing the recommendations within their healthcare facility<sup>49</sup>. Another factor related to procedural knowledge was HCPs' understanding of the implications of the risk on their clinical practices<sup>59</sup>. On the other hand, a lack of guidance and a need for guidelines to address the medicine risk communication were reported<sup>46</sup>. Additionally, it was reported that the lack of guidance hindered the implementation of FDA recommendations<sup>46</sup>.

### **3.3.2 Memory, Attention and Decision Processes**

Possible factors that potentially influenced decision-making were the establishment of the risk<sup>67</sup>, the trustworthiness of the information and the credibility of the source of information<sup>45</sup>, as well as the trust that the information has been rigorously peer reviewed<sup>45</sup>. One study revealed that HCPs were concerned about how the US FDA analysed and presented data<sup>42</sup>. Poor data quality and a lack of evidence were reported as barriers to implementation<sup>46</sup>. When pharmaceutical companies provided information, HCPs reported difficulty differentiating evidence-based information from promotional information<sup>59</sup>. Some physicians felt that knowing about the medicine risk communication before their patients would not allow them to formulate their opinions on it before being asked by patients<sup>59</sup>.

HCPs weighed the risks and benefits of the medicine of concern<sup>55</sup>. In some cases, HCPs believed there was no risk<sup>61</sup>, that the risk was low<sup>61,42</sup> or that the risk was related to a comorbid condition rather than the medicine of concern<sup>42</sup>. Moreover, medicines having an acceptable risk-to-benefit ratio were mentioned by physicians as one reason for nonadherence to medicine risk communications recommendations<sup>55</sup>. Balancing the information received from pharmaceutical companies' representatives with clinical experience was also a potential factor related to decision-making<sup>59</sup>.

Another possible factor that was related to HCPs' decision-making process was the availability of an alternative agent. Healthcare facilities introducing an alternative agent for the medicine of concern to its formulary were reported<sup>43,49</sup>. However, alternative agent unavailability was also reported<sup>44,46</sup>. When available, HCPs compare the effectiveness of the medicine of concern to its alternatives, determining whether the alternative is more effective, equally effective or worse than the medicine of concern<sup>63,64</sup>. On the one hand, not using the medicine of concern was attributed to the availability of more effective alternatives<sup>64</sup>. On the other hand, a lack of alternative agents was cited as a barrier to implementing medicine risk communications recommendations<sup>46</sup>.

HCPs were reportedly presented with medicine risk communications while on the job, which were considered as possible factors to memory and attention. This involved pharmacists' reviews to identify potential nonadherence to the medicine risk communication<sup>43</sup>. In addition, healthcare facilities added the medicine risk communication to the computerised medicine order entry system<sup>43</sup>, the label on medicine bags before dispensing<sup>43</sup>, and the pharmacists' computer system<sup>44</sup>. However, HCPs expressed concerns about screening out information due to becoming immune to electronic medical record flags or alerts, as much of the information appearing on these records is already known to them<sup>59</sup>. Moreover, a physician expressed concerns about pharmacy alert systems that pharmacists do not know the whole clinical picture; thus, they ultimately override the pharmacists<sup>59</sup>.

### 3.3.3 Behavioural Regulation

Physicians demonstrated action planning by creating electronic patient records to identify which patients were receiving which medicines, check for interactions between medicines, and contact patients if necessary<sup>59</sup>.

### 3.3.4 Environmental context and Resources

Two different aspects of organisational culture or climate were possible factors related to the environmental context. The first involved whether healthcare facilities had their interpretation of the medicine risk communication<sup>43,44</sup> or let HCPs interpret the information themselves<sup>43</sup>. Decision-makers in policy changes at the healthcare facility<sup>43</sup> and their interpretation of the medicine risk communication<sup>44</sup> might influence how the healthcare facility responds to the medicine risk communication. The second aspect of organisational culture was staff education, as the education of office staff was reported as one barrier to implementing medicine risk communication recommendation<sup>65</sup>.

The second aspect of the environmental context domain was the material resources. One possible factor contributing to this aspect was related to the medicine of concern that was mentioned in the medicine risk communication. This involved the medicine of concern being no longer available in the healthcare facility<sup>63,64</sup>. Healthcare facilities also imposed policy changes in response to the medicine risk communication, including changing stocks of the medicine of concern<sup>64</sup>, applying restrictions on the medicine of concern use<sup>64</sup>, prohibiting the use of the medicine of concern in certain situations<sup>43</sup>, and adjusting restriction policies or auto-substitution of the medicine of concern in favour of its alternative<sup>44</sup>. Formulary discontinuation of the medicine of concern was also reported<sup>43,44</sup>. Some physicians reported that now (at the time of the study), they never use the medicine of concern due to its unavailability, yet it was not revealed whether this was due to the medicine risk communication or not<sup>64</sup>. Changes in the treatment protocols of disease management were also reported in healthcare facilities after the release of the medicine risk communication<sup>51</sup>.

Lack of time<sup>60</sup>, workload<sup>60</sup> and lack of space during high infectious diseases seasons (however, space was not specified in the study) were all resource-related barriers to implementing medicine risk communications recommendations<sup>61</sup>. The final form of resources-related barriers was related to the message and information received. The possible factors within this aspect of the environmental context domain included the understandability of the language used in the letters<sup>53</sup>, the relevance of the content to HCPs practice<sup>53</sup>, clarity of the medicine risk communications<sup>42</sup>, and the use of special formatting in the letter<sup>57</sup>. Receiving a large amount of information that is irrelevant to the HCP-specific practice<sup>60</sup>, dissatisfaction with the quality of information received<sup>45</sup>, and receiving letters that lacked clarity<sup>57</sup> and readability<sup>57</sup> were all reported by HCPs. Moreover, HCPs reported that relevant information was not always apparent in the letters, and important information was overshadowed by less important information<sup>57</sup>. Message formatting was associated with perceptions about the criticality of the information and intent to change practice<sup>57</sup>.

### **3.3.5 Social Influences**

Social influences that were identified were related to group conformity and social pressure. Group conformity was illustrated by HCPs obtaining consensus among their practice partners, in this factor was reported as an implementation barrier<sup>65</sup>. Social pressure, however, was mainly related to the service-receivers, including patients, their families or their carers. The willingness and refusal of service receivers to take medicine of concern after becoming aware of a medicine risk communication were reported<sup>41,52,62</sup>. In addition, service receivers who are already not attending appointments as required might reject additional visits to adhere to the medicine risk communication was also voiced by the HCPs<sup>61</sup>. Patients' willingness to take the risk of a side effect<sup>45</sup> and patients initiating the discussion about the medicine risk communication with their HCPs were all reported<sup>47</sup>. Lack of educational materials for parents and parents demanding treatments were both cited as barriers to medicine risk communications' implementation<sup>65</sup>.

### **3.3.6 Reinforcement**

A study revealed a possible need for incentives, as HCPs questioned reimbursement because they could see more patients with acute illness in the same amount of time it takes them to implement recommendations for just one patient<sup>61</sup>.

### **3.3.7 Emotion**

This domain was identified in two studies, and it was related to the concerns or past experiences of HCPs. HCPs reported being concerned about the medicine risk communication in one of these studies; however, the specific area of concern was not reported<sup>44</sup>. In the other study, the number of physicians stopping the medicine following the medicine risk communication was significantly higher among those who had patients who experienced aggressive behaviour, agitation, or any side effects listed in the medicine risk communication compared to those who did not experience this with their patients<sup>62</sup>.

### **3.3.8 Social/Professional Role and Identity**

Professional identity is the first aspect of professional roles and identity domain-related barriers. This included clinicians' comfort level in prescribing the medicine of concern (the medicines specified in the medicine risk communication) to their patients<sup>52</sup>. In addition, physicians who were hesitant to treat welcomed the medicine risk communication because it supported their reluctance<sup>45</sup>. Furthermore, HCPs' motivation to treat the disease coupled with the availability of disease-related resources (specifically, access to mental health resources) and their views about the efficacy of medicines compared to counselling could influence the way they respond to the medicine risk communications<sup>61</sup>.

The second aspect of this domain was the professional role, which was identified in two situations. First, some paediatric primary care providers indicated that they might provide additional follow-ups as recommended in coordination with a psychologist<sup>61</sup>. Second, some of the in-patient physicians who were identified as having cases of nonadherence to medicine risk communications reported deferring interventions until communication with primary care providers was established<sup>55</sup>.

### 3.3.9 Beliefs about Consequences

The first aspect of the beliefs about consequences domain was beliefs. Beliefs towards the sources of the medicine risk communication were about knowledgeability<sup>54</sup>, credibility<sup>59</sup>, the trustworthiness of the sources<sup>59</sup> or the information they provide<sup>54</sup>, and reliability<sup>45,59</sup>. Beliefs about the sources also included HCPs' trusting that the sources are not affected by potential biases or financial interests<sup>45</sup>. Some of the reported beliefs included that the regulatory agencies' findings and recommendations are controversial<sup>67</sup>, regulatory agencies' information is more trustworthy than those of pharmaceutical companies<sup>54</sup>, the regulatory agency is biased toward the pharmaceutical industry<sup>59</sup>, and pharmaceutical companies are biased<sup>59</sup>. An example of one physician not trusting the regulatory agency believed that they were bought and sold; the same physician reported no longer listening to the regulatory agency<sup>59</sup>. Beliefs about the appropriateness of the placement of the medicine risk communication<sup>63</sup> related to whether they agreed or disagreed with the placement of the medicine risk communication<sup>47,65,66</sup>, and whether the placement of the medicine risk communication was unjustified<sup>63,64</sup>. Lack of agreement with the recommendation was one barrier to implementing it<sup>65</sup>.

Consequents-related factors were the second aspect of the beliefs about the consequences domain. Possible factors related to this aspect included concerns about media attention<sup>61</sup>, liability issues<sup>61</sup>, malpractice<sup>41</sup> and lawsuit<sup>41</sup>. Concerns that medicine risk communications could trigger legal litigation were reported<sup>42</sup>—One reason for not using the medicine of concern after the medicine risk communication was due to medicolegal concerns<sup>64</sup>. The use of a medicine that was licenced for use in the targeted population was reported to avoid the off-label use characterising the rest of medicines within the medicines group of concern<sup>61</sup>.

The last aspect of this domain is the outcome expectancies. Possible factors related to this aspect included concerns about risks to patients<sup>41</sup>, concerns that patients would receive inadequate therapy<sup>49</sup>, and concerns that the medicine risk communication would reduce patient compliance and lead to negative impact<sup>42</sup>. In addition, not knowing the added value of adhering to the recommendation to patients made HCPs uncomfortable with following the recommendation<sup>61</sup>.

### 3.3.10 Goals

Possible factors related to the goals domain were either related to goals priority or implementation intention. Considering medicines safety information in general<sup>54</sup> and medicine risk communications' specific information<sup>57</sup> as important by the HCPs are related to the goal priority aspect. On the other hand, examples of possible factors related to the implementation intention included considering or not considering medicine risk communications when prescribing<sup>56</sup> and an HCP's agreement on how strictly a medicine risk communication recommendation must be followed<sup>44</sup>. In addition, two studies reported that HCPs counselled<sup>61,67</sup> or prescribed the medicine of concern<sup>61</sup> to patients with certain conditions or comorbidities. Likewise, HCPs in a third study reported different choices of which patients to counsel about the medicine risk communications: whether all patients, patients with a particular diagnosis, patients with certain comorbidity, patients starting a certain medicine or drug within a medicine group, patients experiencing certain symptoms, or patients who initiated the discussion<sup>42</sup>. Moreover, some HCPs refused to prescribe the medicine of concern unless there was an initial prescription from a specialist, or unless the patient had a certain comorbidity<sup>61</sup>.

Some HCPs also indicated that they would adhere to the medicine risk communication only if collaboration with a specialist was possible<sup>61</sup>.

### 3.3.11 Beliefs about Capabilities

Beliefs about the capabilities domain were represented by the perceived behaviour control in two studies. In one study, physicians felt the medicine risk communication had affected their ability to treat patients<sup>63</sup>; whereas in another study, physicians feeling the need to prescribe something was reported as a barrier to implementing the recommendation<sup>65</sup>.

## 4. Discussion

To the best of our knowledge, this is the first systematic review that categorises the factors affecting HCPs' response or lack of response to medicine risk communications based on the TDF. Factors possibly affecting HCPs' implementation of medicine risk communications were related to eleven domains of the TDF. Most commonly, the included studies reported factors related to the "Knowledge" domain (n=23). This was followed by "Beliefs about Consequences" (n=13), "Memory, Attention and decision processes" (n=12) and "Environmental Context and Resources" (n=12). A total of seven studies reported factors related to "Social Influences", six studies reported factors related to "Goals", and four studies reported factors related to "Social/Professional Role and Identity". Four domains were underrepresented, which included "Emotion", "Beliefs about Capabilities", "Behavioural Regulation", and "Reinforcement". In addition, none of the identified factors were related to "Skills", "Optimism" or "Intentions".

It is not surprising that "Knowledge" was the most identified domain. This is because changing behaviour would be challenging without at least being warned about the medicine risk communication and having a proper understanding of its recommendations<sup>14</sup>. Two previous studies utilised interventions to increase the awareness of the dissemination of medicines-related safety information to HCPs. One utilised an additional email from an RA to HCPs informing them about the information<sup>69</sup>, and the second was a continuing medical education (CME)-related intervention<sup>70</sup>. Both resulted in improved knowledge about the medicine safety information. However, no evidence about the sustainability of the interventions on HCPs' knowledge and or implementation was investigated using these interventions. Nonetheless, "Knowledge" was not the only domain that was identified in this review. Thus, specific intervention functions could be targeted to modify factors relating to HCP implementation. Eight out of the nine intervention functions were linked to the four most identified TDF domains. These intervention functions were training, enablement, education, restriction, environmental restructuring, persuasion, incentivisation, and coercion<sup>71</sup>. Three BCW policy categories target all intervention functions linked to the four most reported domains. These include guidelines, regulations, and legislation<sup>71</sup>. The content of these policy categories could be derived from the findings of the first review<sup>31</sup>. This includes targeting the barriers that could affect HCPs' awareness of the resales of a medicine risk communication, knowledge of its content, accurate perception of the risk, accurate interpretation of the recommendations, and positive attitudes toward implementing the recommendations. However, no evidence is

currently available regarding the degree of influence that each intervention function would have on HCP behaviour following medicine risk communications. Moreover, further evidence is required in terms of utilising the TDF in identifying barriers and facilitators within the context of medicine risk communication implementation, as well as the suitability of these interventions for improving enablers and eliminating barriers. Further research is also required to identify whether a single implementation strategy that targets different domains would be more efficient than using multiple intervention techniques. Multiple stages of intervention had shown contradictory evidence regarding its usefulness compared to single strategies interventions in improving guidelines' implementation by HCPs<sup>72</sup>. A strategy for developing interventions to improve the uptake of medicine risk communications in clinical practices should be developed. When developing such a strategy, policymakers should prioritise the intervention functions to be targeted. This should be based on the knowledge of the degree of influence that a factor has on the desired behaviour change to avoid any waste of resources resulting from targeting un-influential factors.

Compared to thematic analysis, the use of the TDF helped to identify how external influences affected HCPs' implementation of medicine risk communications. This is due to the use of specific TDF domains, which classify influences that could affect implementation. As an example, the thematic analysis process revealed that healthcare facilities made changes (e.g. adding alternative medicines) to their formulary when they received the medicine risk communication; while the TDF revealed that these changes might affect HCPs' decision-making process regarding the implementation. However, challenges occurred while using the TDF. One challenge was not being able to differentiate between memory and knowledge of the content. Nonetheless, both are within the psychological capability of the COM-B system<sup>39</sup>. Another challenge was not accounting for the mediators that could affect the TDF domains. For example, we identified from the included studies that possible factors could affect HCPs' knowledge of medicine risk communications, such as, HCPs' not reading the information or the communication not being received thus eventually influencing the implementation of the medicine risk communications' recommendations. Targeting such mediators might enhance the effectiveness of the intervention as the intervention would be tailored to the root cause of the reason leading to a lack of knowledge.

A further challenge was classifying factors related to trust, as none of the TDF domains included trust. This led to the possibility of trust being an overlapping factor in different domains. The trustworthiness of the information and the sources of information were either considered as factors affecting the decision process or as factors relating to beliefs about consequences. HCPs' trust in the information and the credibility of its sources were considered as factors that could affect HCPs' decisional balance, thus they were categorised into the memory, attention and decision process domains. However, this could also be related to the environmental context. In this case, it would be relating to the role of the sources of the information, the message itself and the channels by which it was disseminated. Similarly, beliefs towards the sources of the medicine risk communication, which included sources' knowledgeability<sup>54</sup>, credibility<sup>59</sup>, the trustworthiness of the sources<sup>59</sup> or the information they provide<sup>54</sup>, and reliability<sup>45,59</sup>, were all categorised into Beliefs about the consequences domain. In addition, beliefs about the sources included HCPs' trusting that the sources are not affected by potential biases or financial interests<sup>45</sup>, which were considered to be part of the beliefs about consequences domain. Nevertheless, these factors may also be influenced by environmental factors, such as if previous events have led to HCPs' distrust of RAs.

#### **4.1 Limitation of the Systematic Review**

The included studies were heterogeneous in terms of the included medicine risk communications, the HCPs involved, the practice setting and location, which affected the ability of the authors of the current systematic review to pool the data mathematically. In addition, the predominant use of cross-sectional surveys also limited this synthesis as causations between the presence or the lack of a behaviour change and a factor could not be claimed<sup>73</sup>. Moreover, the included studies were predominately produced in the US, which could have affected the generalisability of the results.

Our synthesis is also limited by only including studies involving communications issued by RAs. Studies involving only pharmaceutical companies and studies evaluating the effectiveness of risk minimisation measures were excluded. These studies might have provided further insight into industry related factors. Moreover, not including papers that did not have an Arabic or English abstract could limit the result of this review due to language biases. Another limitation in the synthesis process included the subjectivity of interpreting the codes and mapping them to domains, especially with codes, such as trust, that can overlap between domains. Furthermore, the accuracy of matching the BCW to the TDF depends on their validity<sup>74</sup>.

#### **4.2 Methodological limitation of the included studies**

The risk of non-response bias was medium or high in all surveys that were included in this systematic review. As such, the possibility that responses from non-respondents might have produced different factors could not be ruled out. None of the included studies had reported using the TDF in data collection and/ or analysis. This could explain the underrepresentation of some of the domains identified in this review. The most represented domains were “knowledge”, “beliefs about consequences”, “memory, attention and decision process”, and “environmental contexts”. Except for “beliefs about consequences”, most of the studies contributing to the other three domains (knowledge; environmental context; and memory, attention, decision process) had low scores (1 or 2 out of 5) on the MMAT quality assessment. While an equal number of studies contributing to the “beliefs about consequences” domain had low (1 or 2 out of 5), and intermediate (3 out of 5) scores on the MMAT.

### **5. Conclusion**

Medicines risk communications are important for disseminating information that could affect the benefit-to-risk balance of medicines. Although the role of HCPs in implementing the recommendations of these communications is undeniable, HCPs do not always adhere to these recommendations. The utilisation of the TDF aided in categorising the range of different factors affecting whether HCPs implement these recommendation from within their context. Although these factors were related to eleven domains, most reported factors were related to four domains only (“knowledge”, “beliefs about consequences”, “memory, attention, and decision process”

and “environmental context domains”). Moreover, most of the studies contributing to three of these four domains were of low quality. Future research should focus on utilising implementation science to identify targets for behaviour change when it comes to actionable medicines risk communications. The employment of such science should be considered by regulators in order to create cost-effective strategies for improving the implementation of medicines risk communications by HCPs.



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Figure 1: The narrative synthesis process<sup>35,36</sup>

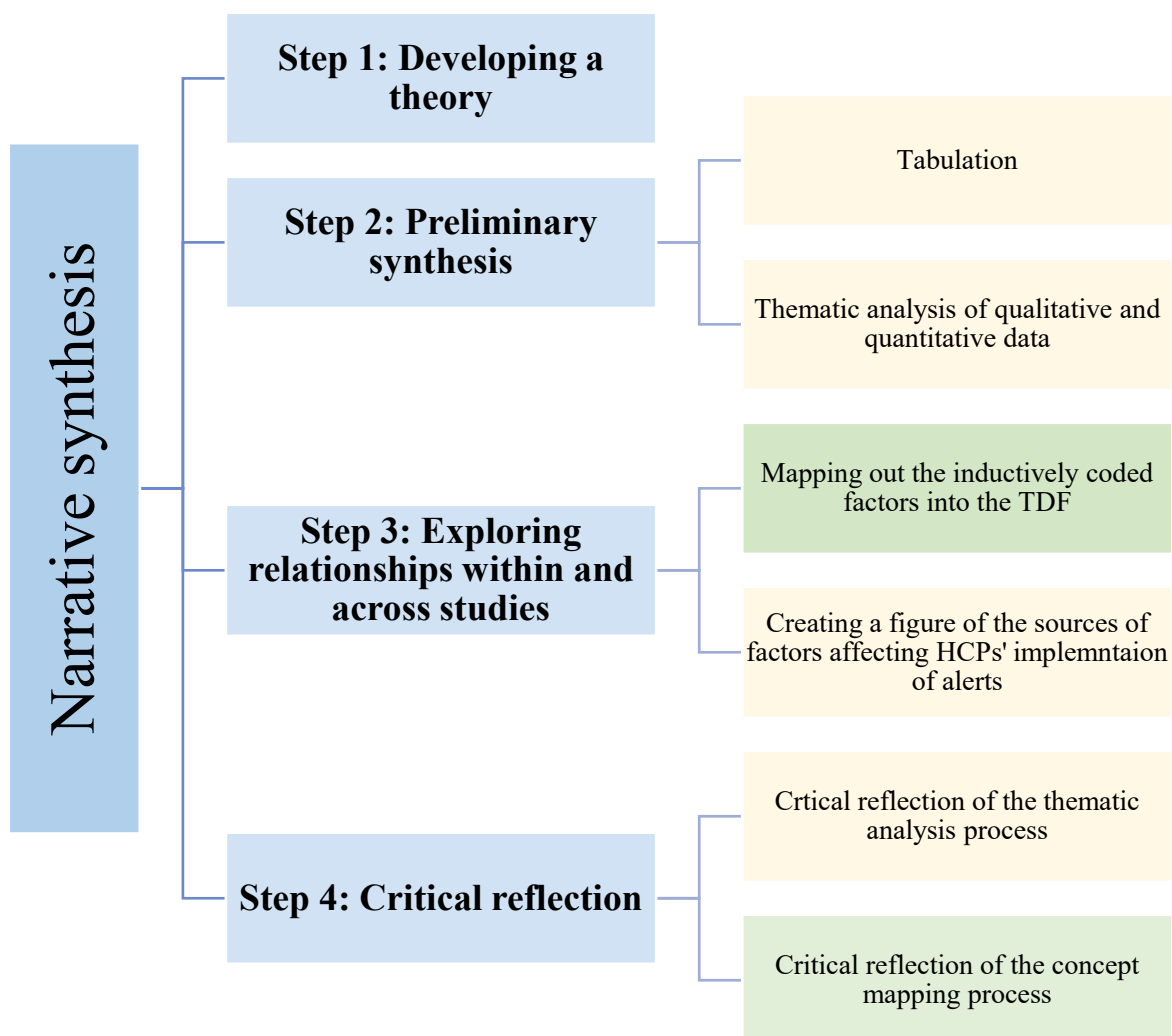
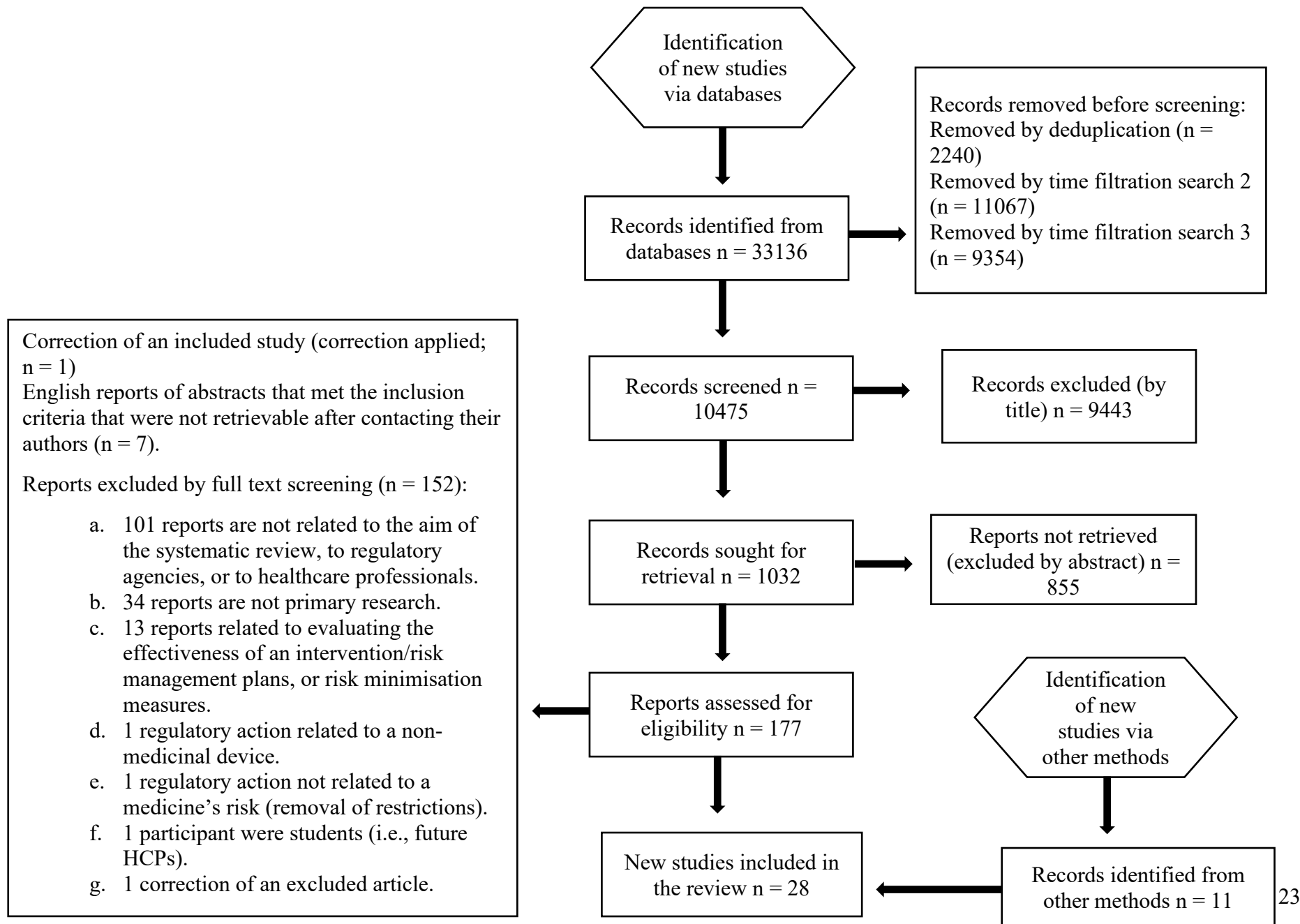


Figure 1 represents the narrative synthesis process. Steps coloured in yellow were presented in a previous systematic review<sup>31</sup>. Steps coloured in green are represented in the current systematic review.

Figure 2: PRISMA<sup>32</sup> flowchart



List of Tables:

Table 1: Characteristics of the included studies

Table 2: Total quality scores of the included studies mapped to the TDF domains and BCW

Table 3: Quality assessment of the included studies using the MMAT



Table 1: Characteristics of the included studies

First author (Year)	Country, regulatory agencies involved	Research participants and sample size	Setting
Barker (2019)	Canada, Health Canada, among other different sources of quality-related events.	15 community pharmacy managers (12 females). The participants were from different community pharmacies, including nine large corporates, two small banner chains, and four independent pharmacies.	The participants were from different community pharmacies, including nine large corporates, two small banner chains, and four independent pharmacies.
Bell (2013)	US, FDA	505 neurologists	Participants' practice settings were described as the following: 39.8% of participants worked in academic or government-based hospitals or clinics, 31.9% in a group practice, 17.6% in solo practice, 6.7% in community hospitals, 1.2% in research and 2.8% were described as "other" without further demonstration.
Bhatia (2008)	US, FDA	- 605 Family medicine clinicians with the following specialities: family medicine physicians, family medicine nurse practitioners, family medicine physician assistants, family medicine residents, general practice). - 139 Paediatric clinicians with the following specialities: paediatricians, paediatric nurse practitioners, paediatric physician assistants, developmental and behavioural. - 122 Psychiatric clinicians with the following specialities: general psychiatrists, child and adolescent psychiatrists, psychiatric nurse practitioners, psychiatric physician assistants, psychiatric residents. 739 clinicians practised in urban and 127 in rural settings.	85.3% of participants worked in an urban setting.
Cheung (2008)	US, FDA	670 paediatricians	The setting was not specified.
Cordero (2008)	US, FDA	115 primary care providers work in medical centres affiliated with medical schools or primary care clinics.	74% practised in medical centres affiliated with medical schools. The sampling frame included primary care providers in academic medical centres and primary care clinics.
de Vries (2017)	Croatia, Denmark, Ireland, Italy, Spain, Sweden, the Netherlands, Norway and the United Kingdom, National competent authorities.	1766 general practitioners ( 25 from Denmark, 847 from Spain, 85 from Croatia, 144 from Ireland, 183 from Italy, 72 from Netherlands, 105 from Norway, 108 from Sweden, and 197 from the UK). Of 1766, 1551 were community-based, 39 were hospital-based, and 32 practised in other settings	Participants' primary work settings were as the following:  1551(96%) worked in community-based settings. 39 (2%) worked in hospital-based settings. 32 (2%) described their work settings as "other" without further specification.

de Vries (2018)	Croatia, Denmark, Ireland, Italy, Spain, Sweden, the Netherlands, Norway, and United Kingdom, National competent authorities.	3288 participants, of which 54% were GPs, 40% were pharmacists, and 7% were cardiologists, their distribution per country was as follows: (General practitioners: Croatia 85; Denmark 25; Ireland 144; Italy 183; Netherlands 72; Norway 105; Spain 847 Sweden 108; UK 197); (Cardiologists*: Croatia 4; Denmark 7; Ireland 5; Italy 63; Netherlands 17; Norway 40; Spain 56 Sweden 15; UK 15); (Pharmacists*: Croatia 104; Denmark 35; Ireland 281; Italy 104; Netherlands 64; Norway 381; Spain 13 Sweden N/A; UK 318).	The setting was not specified.
Esterly (2011)	US, FDA	Members of the Society of Infectious diseases pharmacists (SIDP) with a hospital practice site affiliation. 94 responses were included in the analysis. From those, 11% described their roles as administration, 78% as clinical and 54% reported their professional role as antibiotic stewardship pharmacists. In addition, 77% of the respondents reported a university affiliation.	Duplicate institutions' responses were removed, i.e. each survey participant represented a single institution that is different from the other responses.  All targeted institutions were hospital-based.  Of 93 respondents to this question, 61 participants (nearly 65% described their workplace as not for a profit), 10% for profit, 17% government, 3% reported as 'other' without further specification, and 4% were not aware of the type of their workplace.  77% of the 94 participants were affiliated with a university, while 23% were not.
Flood (2014)	The United Kingdom, National patient safety agency (NPSA)	100 gastroenterology clinicians	The setting was not specified.
Fogler (2009)	US, FDA	26 infectious disease physicians; 36 obstetrician/gynaecologists; 29 primary care physicians (family/internal medicine); 5 other physicians; 18 nurse practitioners/certified nurse midwives; seven pharmacists.	The setting was not specified.

Garbutt (2010)	US, FDA	105 community paediatricians	The sample involved community paediatricians affiliated with St. Louis Children's Hospital.  The participant's practised at the following locations:  8% inner city, urban. 12% not inner city, urban. 75% suburban. 4% rural.
Habib (2007)	US, FDA	A total of 295 physicians completed the survey. 257 (93%) of 277 respondents were attending anesthesiologists, 9 (3%) were fellows, and 11 (4%) were residents in training.	176 (62%) of the 282 practised in a private hospital and 106 (38%) in an academic institution. 176 (87%) of the 203 respondents practised in a surgery centre, 44 (22%) practised in an office practice and 48 (24%) practised in a procedure facility or other location.
Harder (2009)	Canada, Health Canada	A total of 152 pharmacists from nine provinces and one territory evenly divided between teaching or tertiary care and community or general hospitals, where the participants commented that they represented paediatric hospitals.	The majority of participants (75%) were from individual hospitals that were evenly divided into teaching or tertiary care hospitals and community or general hospitals. Two participants indicated that they worked in paediatric hospitals.
Karpel (2009)	US, FDA	1107 in total, consisted of the following: 429 pulmonologists, 395 allergists, 141 internists, 132 family physicians and 10 paediatricians.	The setting for the entire sample was as the following: 64.4% were in private practice, 24.1% in academic practice, 4.8% in training programmes and 6.6% in other settings (clinic groups, military or hospitals).
Kesselheim (2017)	US, FDA	10 physicians who practised primary care were listed as a prescriber of zolpidem or eszopiclone sometime between 1 July 2012 and 30 June 2013.	Primary care
Kloet (2017)	US, FDA	The study involved reviewing medications of 393 general medicine and ICU patients (18 years and older) who were being cared by physicians at an urban, academic medical centre.	An urban academic medical centre.
Mazor (2005)	US, FDA	10 primary care physicians (internists) were recruited to serve as raters.	Primary care; exact setting not reported
Morrato (2008)	US, not specified	20 physicians (specialty: psychiatry (n = 10) and internal medicine (n = 10)).	The setting was not specified.
Piening (2012)	The Netherlands, Netherlands Pharmacovigilance Center (Lareb)	Total 1141 healthcare professionals, including 233 general practitioners, 410 internists, 223 community pharmacists, 175 hospital pharmacists	The setting was divided into primary care healthcare professionals (GPs and community pharmacists) and secondary care healthcare professionals (internists and hospital pharmacists).

	and Dutch Medicines Evaluation Board (MEB).		
Reed (1999)	US, FDA	94 paramedics	The survey was distributed in three sites (the exact number of participants from each site was not reported): Syracuse, New York; Greenville, North Carolina; and, Minneapolis, Minnesota.
Richards (2003)	US, FDA	506 Emergency physicians	The settings were described in terms of the type of hospitals and areas.  55% worked in private or community hospitals. 37% worked in academic or county hospitals. 8% worked in health maintenance organisation hospitals.  25% worked in inner city, 59% in urban and 16% in rural areas.
Richardson (2007)	US, FDA	Nine practices. The total number of individuals participating were 35, of which 32 were paediatricians and three were paediatric nurse practitioners.	Five rural paediatric primary care practices and four were urban.
Saad (2010)	US, FDA	65 geriatric practitioners pharmacists (94%) physicians (3%) and nurses (3%).	Eight participants practised in nursing home facilities, eight worked in teaching practice settings, seven in veterans affairs, two in private clinical practice, one in a community hospital, one in the university health centre, and eight in other settings that were not further specified.  Note: 20 practised in two or more settings.
Sabblah (2016)	Ghana, FDA	913 health workers; The professional backgrounds of the 913 health workers were 597 (65.39%) pharmacists, 136 (14.90%) doctors, 95 (10.40%) nurses and 85 (9.31%) physician assistants.	Of 908 respondents, 508 (55.95%) worked in government, 270 (29.74%) quasi-government, 96 (10.57%) in Christian Health Association of Ghana and 34 (3.74%) in private health facilities.

Shneker (2009)	US, FDA	175 clinicians who treat patients with epilepsy	Participants' work settings were described in terms of:  1. The type of clinical practices as: 60% academic, 30% private, 1% veterans' affairs and 9% described as 'other' without further specification. 2. The location of practice as: 75% urban, 20% suburban, and 5% rural. 3. Practice being a part of a comprehensive epilepsy programme as 74% of practices were a part of a comprehensive epilepsy programme, while 26% were not.
Smollin (2016)	US, FDA	A total of 81 physicians: 50 were emergency medicine physicians and 31 were paediatricians. Sixteen participants were in their 1 <sup>st</sup> postgraduate (PG) year, 20 in their 2 <sup>nd</sup> year, 16 in their 3 <sup>rd</sup> year, 5 in their 4 <sup>th</sup> PG year and 24 were attending or fellows.	Department of Emergency Medicine and Paediatrics at University of California San Francisco.
Théophile (2011)	France, French Medicines Agency (Agence Française de Sécurité Sanitaire des Produits de Santé: [AFSSAPS])	The included participants were paediatricians (31%, n = 45), GPs (37%, n = 255) and pharmacists (40%, n = 92)	The setting was not specified.
Yaghmai (2010)	US, FDA	33 general paediatricians	The setting was not specified.

**FDA:** Food and Drug Administration; **UK:** United Kingdom; **US:** United States; \* based on published correction of de Vries et al. (2018) published in de Vries et al. (2020).

Table 2: Total quality scores of the included studies mapped to the TDF<sup>25</sup> domains and BCW<sup>71</sup>

First Author (Year)	Quality score	TDF domain													
		Knowledge <sup>1</sup>	Memory, attention and decision processes <sup>1</sup>	Behavioural regulation <sup>1</sup>	Skills <sup>2</sup>	Environmental context <sup>3</sup>	Social influences <sup>4</sup>	Reinforcement <sup>5</sup>	Emotion <sup>5</sup>	Social/professional role and identity <sup>6</sup>	Beliefs about consequences <sup>6</sup>	Goals <sup>6</sup>	Beliefs about capabilities <sup>6</sup>	Optimism <sup>6</sup>	Intentions <sup>6</sup>
Barker (2019)	★★★★★	-	-	-	-	√	-	-	-	-	-	-	-	-	-
Bell (2013)	★★★☆☆	√	√	-	-	-	-	-	-	-	√	-	-	-	
Bhatia (2008)	★★★★☆☆	√	-	-	-	-	√	-	-	√	-	-	-	-	
Cheung (2008)	★★★★☆☆	√	-	-	-	-	√	-	√	-	-	-	-	-	
Cordero (2008)	★★★★☆☆	√	-	-	-	-	√	-	-	-	√	-	-	-	
de Vries (2017)	★★★★☆	√	-	-	-	-	-	-	-	-	-	-	-	-	
de Vries (2018)	★★★★☆	√	-	-	-	-	-	-	-	-	-	-	-	-	
Esterly (2011)	★★★☆☆	√	√	-	-	√	-	-	-	-	-	-	-	-	
Flood (2015)	★★★★☆☆	√	√	-	-	-	-	-	-	-	√	-	-	-	
Fogler (2009)	★★★☆☆	√	-	-	-	-	-	-	-	-	-	-	-	-	
Garbutt (2010)	★★★★☆☆	√	-	-	-	√	√	-	-	-	√	-	√	-	

Habib (2008)	★ ★ ☆ ☆ ☆	-	√	-	-	√	-	-	-	-	√	-	-	-	-
Harder (2009)	★ ★ ★ ☆ ☆	-	√	-	-	√	-	-	√	-	-	√	-	-	-
Karpel (2009)	★ ★ ★ ☆ ☆	√	-	-	-	-	√	-	-	-	√	-	-	-	-
Kelsselheim (2017)	★ ★ ★ ★ ☆	√	√	-	-	√	√	-	-	√	√	-	-	-	-
Kloet (2017)	★ ★ ☆ ☆ ☆	√	√	-	-	-	-	-	-	√	-	-	-	-	-
Mazor (2005)	★ ★ ☆ ☆ ☆	-	-	-	-	√	-	-	-	-	-	√	-	-	-
Morrato (2008)	★ ★ ★ ★ ★	√	√	√	-	-	-	-	-	-	√	-	-	-	-
Piening (2012)	★ ★ ★ ☆ ☆	√	-	-	-	-	-	-	-	-	√	√	-	-	-
Reed (1999)	★ ☆ ☆ ☆ ☆	√	-	-	-	√	-	-	-	-	-	-	-	-	-
Richards (2003)	★ ★ ☆ ☆ ☆	√	√	-	-	√	-	-	-	-	√	-	√	-	-
Richardson (2007)	★ ★ ★ ★ ★	√	√	-	-	√	√	√	-	√	√	√	-	-	-
Saad (2010)	★ ★ ☆ ☆ ☆	√	√	-	-	-	-	-	-	-	-	-	-	-	-
Sabblah (2016)	★ ★ ★ ★ ☆	√	-	-	-	√	-	-	-	-	-	-	-	-	-
Shneker (2009)	★ ★ ★ ☆ ☆	-	√	-	-	√	-	-	-	-	√	√	-	-	-
Smollin (2016)	★ ★ ☆ ☆ ☆	√	-	-	-	-	-	-	-	-	-	√	-	-	-
Theophile (2011)	★ ★ ★ ☆ ☆	√	-	-	-	-	-	-	-	-	-	-	-	-	-

Yaghmai (2010)		√	-	-	-	-	-	-	-	√	-	-	-	-
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- <sup>1</sup> **Source of behaviour:** Capability (Psychological capability); **Intervention functions:** Training; Enablement.
- <sup>2</sup> **Source of behaviour:** Capability (Physical capability) **Intervention functions:** Education; Training; Enablement.
- <sup>3</sup> **Source of behaviour:** Opportunity (Physical opportunity) **Intervention functions:** Training; Restriction; Environmental Restructuring; Enablement.
- <sup>4</sup> **Source of behaviour:** Opportunity (Social Opportunity) **Intervention functions:** Restriction; Environmental Restructuring; Modelling; Enablement.
- <sup>5</sup> **Source of behaviour:** Motivation (Automatic motivation); **Intervention functions:** Persuasion; Incentivisation; Coercion; Training; Environmental Restructuring, Modelling; Enablement.
- <sup>6</sup> **Source of behaviour:** Motivation (Reflective motivation); **Intervention functions:** Education, Persuasion; Incentivisation; Coercion.



Table 3: Quality assessment of the included studies using the MMAT<sup>37</sup>

<b>Qualitative studies</b>	Item 1: Qualitative approach appropriate to answer the research question	Item 2: Qualitative data collection method adequate to address the research question	Item 3: Findings adequately derived from data	Item 4: Interpretation of results sufficiently substantiated by data	Item 5: Coherence between qualitative data sources, collection, analysis and interpretation
Barker (2019)	Y	Y	Y	Y	Y
Kelsselheim (2017)	Y	U	Y	Y	Y
Morrato (2008)	Y	Y	Y	Y	Y
Richardson (2007)	Y	Y	Y	Y	Y
<b>Quantitative observational studies</b>	Item 1: Participants representative of the target population	Item 2: Measurements appropriate regarding both outcome and intervention (or exposure)	Item 3: Complete outcome data	Item 4: Confounders accounted for in the design and analysis	Item 5: Intervention administered during the study period (or exposure occurred) as intended
Kloet (2017)	U	Outcome: Y Exposure: Y	N.	N	Y
<b>Quantitative cross-sectional studies</b>	Item 1: Sampling strategy relevant to address the research question	Item 2: Sample representative of the target population	Item 3: Measurements-appropriateness	Item 4: Risk of nonresponse bias is low.	Item 5: Statistical analysis appropriate to answer the research question
Bell (2013)	Y	Y	U	N	U
Bhatia (2008)	Y	Y	U	N	Y
Cheung (2008)	Y	Y	U	N	Y
Cordero (2008)	Y	Y	U	N	Y
de Vries (2017)	Y	Y	Y	U	Y
de Vries (2018)	Y	Y	Y	N	Y

Esterly (2011)	N	U	U	U	Y
Flood (2015)	Y	U	U	U	Y
Fogler (2009)	N	N	U	N	Y
Garbutt (2010)	Y	Y	U	N	Y
Habib (2008)	Y	N	U	N	Y
Harder (2009)	Y	Y	U	U	Y
Karpel (2009)	Y	Y	U	N	Y
Mazor (2005)	U	U	Y	U	Y
Piening (2012)	Y	Y	Y	N	U
Reed (1999)	Y	N	U	N	Y
Richards (2003)	Y	Y	U	N	N
Saad (2010)	Y	N	U	N	Y
Sabblah (2016)	Y	Y	Y	U	Y
Shneker (2009)	Y	Y	N	N	Y
Smollin (2016)	Y	Y	U	U	U
Theophile (2011)	Y	Y	U	N	Y
Yaghmai (2010)	U	U	U	U	Y

