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# Effectiveness of interventions to improve adverse drug reaction reporting by healthcare professionals over the last decade: a systematic review

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# 1. Introduction

Underreporting of adverse drug reactions (ADRs) is one of the pressing issues affecting medication safety in clinical practice. Over-reliance on spontaneous reporting system coupled with lack of accountability means the majority of ADRs goes unnoticed until such incidents result in patient harm. (1) A recent systematic review found that over 9 out of 10 ADRs identified by healthcare professionals (HCPs) were not reported.(2) Furthermore, the spontaneously reported ADRs usually contain inadequate information to allow for an informed judgement in confirming any causal relationship with the suspect medicine. These deficiencies can delay regulatory actions with a systematic review showing that the median interval from drug launch to drug withdrawal was 10 years for drugs with an unacceptable safety profile.(3) These delays significantly increase the healthcare costs associated with the management of ADRs as they are a major cause of hospital admissions, prolongation of an existing hospitalization, morbidity and mortality.(4) A Canadian study showed that the overall cost for the management of a single ADR related hospital admission was $7528, and this increased to $10,388 if the patient was admitted to the intensive care unit. (5, 6)

The key factors that influence ADR reporting are HCP's knowledge, their underlying perspectives, and operational barriers. Several studies have shown that HCPs with better knowledge on what and how to report ADRs were more likely to do so, however the majority of them had very low knowledge on this topic.(7-9) HCP's perceptions also play a significant role in the under-reporting of ADRs with one survey showing that 87% of physicians believed that all serious reactions will be well documented by the time a drug is marketed and that 71% thought that a single case report will not contribute to medical knowledge.(10) Operational barriers such as lack of remuneration, competing priorities in patient care, and difficulty in accessing ADR reporting forms also significantly influence reporting rates. (11-14) A 2014 systematic review also summarised that the primary themes of indifference, diffidence, ignorance, insecurity and lack of time were the main causes of under-reporting.(13) These factors contribute significantly to the low rates of ADR reporting with studies showing that 50-97% of HCPs admitting that they have not reported any ADRs in the last 12 months.(15)

To address these barriers, a number of initiatives and interventions have been designed to help improve the ADR reporting rates. These have been traditionally in the form of providing educational sessions on ADR reporting, simplification of the ADR reporting process, providing

incentives such as continuing education points or remuneration, and enhancing the availability of reporting forms. A systematic review examined the evidence for the effectiveness of various interventions on improving ADR reporting and included all studies published until December 2010. (16) This was a comprehensive analysis of 43 studies which focussed on the traditional interventional strategies described above. However, there has been significant developments in the area of digital technology in the last decade across the healthcare sector with the introduction of a number of electronic health initiatives. These include e-prescribing, natural language processing tools to identify ADRs, electronic medical records, and health-related mobile apps, which can significantly improve the convenience of undertaking routine health related tasks and provide a streamlined process for medical administrative activities.(17-19)

### Objective

This literature review will provide a more recent assessment on the features and successes of the various strategies undertaken to improve ADR reporting by HCPs, and propose alternative initiatives that may enhance these existing methods. It will also examine whether the recent initiatives were more successful than previous strategies as reported in the earlier review.

## 2. Methods

### Search methodology

A literature search of MEDLINE and EMBASE databases from 01 Jul 2010 to 17 June 2019 was conducted following the PRISMA statement. (20)The following search terms were used in MEDLINE and EMBASE: ('adverse event'/exp OR 'adverse event' OR 'adverse drug reaction'/exp OR 'adverse drug reaction') AND ('drug surveillance program'/exp OR 'drug surveillance program'). All were Emtree search terms.

These dates were selected to avoid studies already identified in the previous systematic review and to allow for a potential 6 month publication delay. The inclusion criteria was any randomized studies on individual or aggregate levels (e.g. cluster randomized studies), quasi-experimental studies, and ecological time series studies that investigated the impact of an intervention to improve ADR reporting by HCPs. Studies that were already included in the Gonzalez-gonzalez systematic review were excluded. The other exclusion criteria included publications in non-English language, no full text availability, not providing sufficient description of the actual intervention, not reporting quantitative results of the intervention, and not including HCPs as the study population.

**Data extraction**

The abstracts of the retrieved scientific papers were initially screened by the primary author with a view to exclude review articles, conference presentations, editorials, or letters. The full text articles of the remaining publications papers were then independently reviewed by the primary author and included if it assessed an intervention that aimed to improve the rate of ADR reporting. All included articles were then independently reviewed by a second author to ensure they met the inclusion criteria. In case of disagreement, the publication was reviewed by a third author who made the final decision.

The following data were extracted for each of the included studies:

1) Study design: quasi-experimental, randomized controlled, cluster-randomized controlled and ecological time series.
2) Country where study was conducted
3) Type of intervention: educational sessions such as presentations or workshops to inform HCPs on the importance and process of ADR reporting, reminders, economic incentive, providing feedback to reported ADRs, making the ADR report form more available through distribution, telephone intervention, and electronic ADR reporting tools such as eHealth records, hyperlinks, or online reporting.
4) Study duration
5) Target population and setting: physicians, pharmacists or other healthcare professionals to whom the intervention is targeted in a primary care or hospital setting.
6) Sample size

**Data analysis**

An intervention was classified as successful if there were any quantitative increase in ADR reports after the intervention. The magnitude of this success was calculated as a ratio of the number of ADR reports post intervention versus pre intervention (x-fold) if this was not already reported in the included studies. The magnitude in increase of ADR reports for studies with multiple interventions was compared with studies investigating the impact of single interventions. The types of interventions identified in this systematic review were also compared with the types of interventions identified in a previous systematic review with a focus on the quantitative impact of the electronic reporting tools identified in both studies.

**Quality analysis**

As there are significant limitations in the current tools that are used to assess the quality of studies included in systematic reviews, we have used the following criteria to classify the quality of our included studies.(21)

1) Quasi-experimental and time series studies: these were classified as high risk of bias as the lack of a control group can influence the results. Some confounding factors include seasonal variation in reporting, media reports of ADRs of interest, public health campaigns, or changes in reporting protocols which may inflate the number of ADRs collected.
2) Randomized/non-randomized controlled studies: these were classified as medium risk of bias as there was no randomization or the process for randomization was not described. This can bias the selection of participants but controls for external influences mentioned above.
3) Cluster-randomized controlled studies: these were classified as low risk of bias as the authors clearly specified the method of randomization and the use of spatial clusters across different hospital networks that prevented the possibility of cross-contamination between the intervention and control groups.

**Statistical analysis**

Statistical analysis of the magnitude of increase in ADR reporting was performed using IBM SPSS (version 25.0) with significance levels set at $P<0.05$. The non-parametric Mann Whitney U test was used for comparing the ADR reporting rates between multifaceted versus single interventions as well as electronic reporting interventions versus traditional methods.

**Ethics approval**

As this is a systematic review of studies containing fully anonymized data, no ethics approval was required.

## 3. Results

**Publication selection**

Using the keywords in the computerized searches in MEDLINE and EMBASE, a total of 10,021 publications were identified. After removing duplicates and excluding publications

based on language, full text availability, and article type, 2688 abstracts were screened for relevance to the topic. The full texts of 58 publications were then reviewed for potential inclusion based on the inclusion criteria. There were 48 publications excluded for inadequate description of the intervention, not providing sufficient results of the intervention, not including HCPs as the study population, or the study did not aim to investigate the impact of the intervention. A horizontal review of the remaining papers' references resulted in 3 additional studies identified. Consequently, a total of 13 publications were included in this review. (22-34) Table 1 provides a summary of the publications that met the inclusion criteria.

**Setting and population**

The majority of the included studies were conducted in Europe (61.5%) with 2 in Asia (15.4%), 2 in North America (15.4%) and 1 in Africa (7.7%). Almost two thirds of the studies were undertaken exclusively in the hospital setting (61.5%) while two were reported in the primary care environment (15.4%). Three of the studies (23.1%) were also carried out in both a hospital and primary care setting. (22, 30, 32)Just over half of the studies (61.5%) involved multiple HCPs (physicians, pharmacists and/or nurses) while 30.8% exclusively targeted physicians. (23, 26, 30, 31)The duration of these studies ranged from 5 to 102 months. (24, 29)

**Study designs and measures**

The most common study design of the included publications was quasi-experimental (53.8%), followed by randomized controlled studies (30.8%), and ecological time series studies (7.7%). All publications included quantitative parameters as a measure of the success of each intervention such as the increase in the absolute number of ADRs reported or the rate of ADR reporting. The majority of these publications (53.8%) also included qualitative parameters such as quantity of new ADRs, serious ADRs, unexpected ADRs and high causality ADRs. (24-27, 30, 32, 33)

**Quality assessment of included studies**

Table 2 below presents the results of the quality assessment of the included studies. There were 3 that were classified as low risk of bias (26, 30, 32), one study as medium risk (27), and 9 studies were classified as high risk. (22-25, 28, 29, 31, 33, 34).

**Interventions and outcomes**

The majority of the studies (61.5%) examined the effectiveness of a single form of intervention to improve ADR reporting while the rest investigated the impact of multifaceted approaches. (24-26, 31, 32) As the authors of 5 papers included 2 or more activities as part of their intervention, we included a total of 19 interventions from the 13 publications for this analysis. (24-26, 31, 32)The most common strategy was the provision of educational session(s) such as a presentation or workshop (31.6%) (25, 26, 30-32, 34), while using an electronic reporting tool to improve ADR reporting was also a popular strategy utilized in 26.3% of the studies. (22, 24, 28, 29, 33) Other initiatives include sending reminders (15.8%), offering an economic incentive (10.5%), using telephone interventions (10.5%), and providing feedback to reported ADRs (5.3%). (23-27, 31, 32) The results showed that all interventions were effective in increasing the absolute number of ADRs reports, or the percentage or rate of ADR reporting. The median increase in reporting rates was higher for multifaceted approaches versus single interventions (9.26 fold vs 7.18 fold, P=0.42), although this was not statistically significant. The median increase in ADR reporting rates for electronic reporting tools was also higher than traditional educational methods (13.68 fold versus 5.39 fold, P=). Out of the 4 randomized controlled studies that were included in this review, all interventions resulted in a statistically significant increase in the quantity of ADR reports. (26, 27, 30, 32)

**Comparison with previous systematic review**

The use of electronic reporting tools to improve ADR reporting was more commonly identified as an interventional strategy in this systematic review. In the Gonzalez-Gonzalez review, only 3 of the 46 interventions (6.5%) identified from 1986 to 2010 investigated the impact of an electronic ADR reporting tool whereas this review identified 5 out of 19 interventions (26.3%) over a period of less than 10 years. (16) The electronic reporting tools identified in this review included the use of electronic health records, which resulted in a median 11 fold increase in ADR reporting as opposed to earlier electronic reporting tools, which only achieved a modest 2 fold increase in the previous systematic review.

## 4. Discussion

This review showed that all strategies were effective in increasing the ADR reporting rate and the magnitude of this increase was significant with 53.8% of the studies reporting at least a 3 fold improvement. (24, 26, 28, 29, 31, 32, 34)This is not surprising as the literature showed that under-reporting of ADRs was extremely high and therefore at pre-intervention, there were very low numbers of ADRs reported. Compared to previous systematic reviews, the use of electronic reporting tools was more commonly identified as an interventional strategy and this demonstrates an important advance in utilizing digital technology to facilitate the reporting of ADRs. For example, Linder et al captured electronic health records using an application to trigger an ADR report when a clinician discontinued a medication due to the ADR. (29) It took the clinicians a mean of 53 seconds to send each report and this resulted in a 35 fold increase in reporting rates. Therefore, the integration of electronic health data and automatic capture of this information to facilitate ADR reporting appears to be an extremely successful strategy, however higher quality randomized controlled studies are required to fully investigate its benefits. It is also important to note that other electronic methods identified in this review only achieved a more modest 1.45 to 5.4 fold increase in ADR reporting rates.(22, 28, 33) This can be attributed to the fact that electronic reporting tools are only a passive facilitator that improves the convenience of reporting ADRs, whereas traditional methods such as educational sessions and/or reminders are active facilitators that directly promote ADR reporting. Therefore, a multifaceted interventional approach utilizing both strategies would be paramount to its success. This was demonstrated in a study where educational sessions in combination with reminders, providing feedback, and making reporting forms more accessible resulted in a 14 fold increase in reporting.(31) Studies that investigated single forms of intervention in education and reminders only achieved a modest 2.3 fold and 1.5 fold increase respectively.(27, 30) This can be explained by the fact that different interventions may have different effects on individual HCPs and that some interventions may work synergistically with each other. However, it is difficult to characterize the exact influence of each individual intervention as part of a multifaceted strategy on the final outcome.

There were no studies identified in this review that were conducted in the Oceania region. In Australia, a pharmacy software vendor integrated an Adverse Event Recording module into the dispensing software of community pharmacists that allowed them to report ADRs directly to the local regulator. (36) This program was initially successful as the volume of ADRs reported in the first three quarters of 2014 was almost as high as the total number of ADRs

reported by community pharmacists in the previous year. (37) However, ADR reporting rates fell again in 2015 indicating that this initiative did not provide a long-term solution. (38) Other strategies such as educational sessions may be useful as one study reported that almost 90% of community pharmacists in Australia would be encouraged to report more ADRs if education was provided on this topic. (14) Based on the results of this review, a multi-faceted approach including education, reminders, and electronic reporting would likely to be the most successful.

It is also important to note that improvements in the quality of ADR reports are also a critical measure, and unfortunately this was not investigated in any of the included studies. Studies have shown that the filling quality of ADR reports in national pharmacovigilance databases are extremely poor resulting in the inability to apply algorithms to determine any possible causal relationships between the medicine and ADR. (39, 40) This may be due to constraints within global pharmacovigilance legislations that mandate ADR reporting for pharmaceutical companies, who would focus on reporting ADRs just to comply with these regulations, even for cases with minimal information.(41, 42) The same studies showed that the quality of ADR reports from HCPs are much higher than those received from the pharmaceutical companies indicating that those who choose to report are more motivated or had better knowledge of pharmacovigilance. (39, 40)Therefore, the focus of strategies should be to address the barriers associated with the voluntary nature of HCP reporting to increase the quantity of reports that are of high quality.

**Limitations of this review**

One of the key limitations of this review is publication bias with one study showing that statistically significant results are almost 3 times more likely to be published. (43) Therefore, the effectiveness of the interventions to improve ADR reporting may have been overestimated. In addition, there is significant heterogeneity in the designs and sample sizes of the included studies making it difficult to compare their results without adjusting for confounding variables. Furthermore, the quality of the included studies were poor with the majority lacking a control group.

**Future directions**

With the development of digital technologies and automation, there is a great opportunity to utilize these methods to assist with improving ADR reporting rates. This can include the development of systems such as mobile apps or software in personal digital assistants that can

integrate with existing databases so that it reduces manual input of data. These novel approaches can decrease the time it takes submit an ADR report, minimize manual entry errors and therefore encourage timely and high quality reports. Another area for further research would be to investigate whether interventions also improved the quality of ADR reports as this would significantly assist with signal detection activities to identify or confirm a potentially new safety issue. s.

## 5. Conclusion

To address the high rate of underreporting, multiple strategies have been studied and found to be effective in increasing the ADR reporting rates by HCPs. However, ensuring the improved ADR reporting rates are maintained after ceasing the intervention remains a significant challenge. Developing mobile apps and software that integrate with existing databases presents an opportunity to create a more permanent solution but would require high quality studies to investigate the impact of this novel approach.

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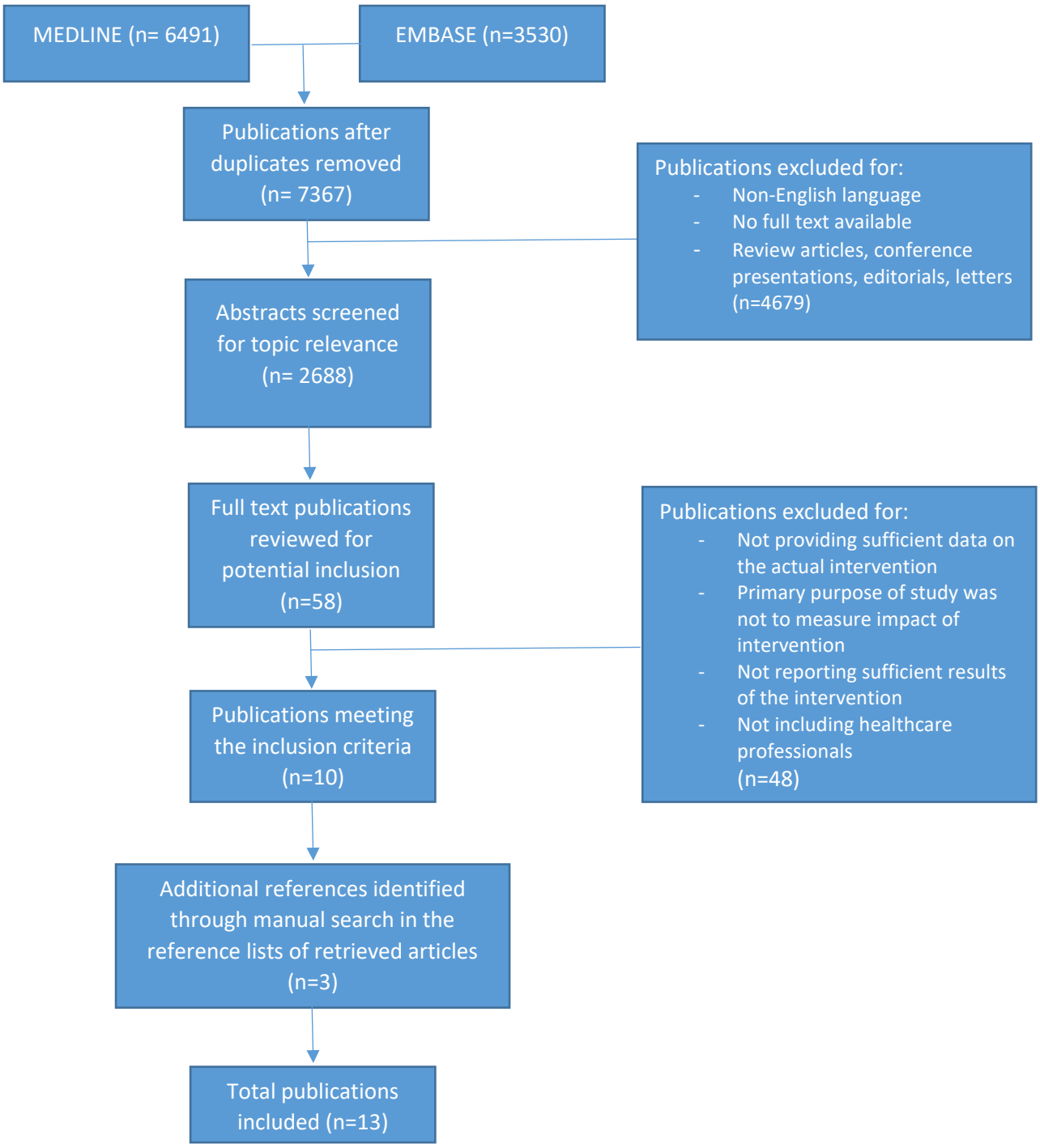


**Figure 1: Flow chart of literature selection process**

**Table 1: Characteristics of included studies**

| Reference and country | Study population and setting | Study period | Sample size | Study design | Type of intervention | Increase in reporting (fold) |
|---|---|---|---|---|---|---|
| Linder et al, 2010, USA | Healthcare professionals in hospital | 5 months | 26 | Quasi-experimental | Electronic ADR reporting | 36.17 |
| Johansson et al, 2011, Sweden | Physicians and nurses in hospital | 12 months | 151 | Randomized controlled | Reminders | 1.52 |
| Ribeiro-Vaz et al, 2011, Portugal | Pharmacists in hospital and primary healthcare | 12 months | 1467 | Cluster randomized controlled | Educational session Telephone intervention | 3.22 |
| Herdeiro et al, 2012, Portugal | Physicians in primary care | 20 months | 6579 | Cluster randomized controlled | Educational session Telephone intervention | 3.97 |
| Ribeiro-Vaz et al, 2012, Portugal | Healthcare professionals in hospital | 48 months | Not reported | Ecological time series | Electronic ADR reporting | 2.50 |
| Lander et al, 2013, Denmark | Healthcare professionals in hospital | 12 months | 140 | Quasi-experimental | Electronic ADR reporting | 5.4 |
| Biagi et al, 2013, Italy | Physicians in primary care | 24 months | 737 | Quasi-experimental | Reminders | 1.49 |
| Abadie et al, 2014, France | Healthcare professionals in primary care and hospital | 18 months | Not reported | Quasi-experimental | Electronic ADR reporting | 1.45 |
| Lopez-Gonzalez et al, 2015, Spain | Physicians in hospital and primary care | 22 months | 7498 | Cluster randomized controlled | Educational session | 2.31 |

| | | | | | | |
|---|---|---|---|---|---|---|
| Morales Rios et al, 2016, Mexico | Physicians in paediatric emergency department of hospital | 16 months | 62 | Quasi-experimental | Educational session<br>Reminders<br>Inclusion of reporting form<br>Feedback | 14.68 |
| Chang et al, 2017, China | Physicians and pharmacists in hospital | 102 months | Not reported | Ecological time series | Economic incentive<br>Electronic ADR reporting | 22.96 |
| Fang et al, 2017, China | Physicians, pharmacists and nurses in hospital | 66 months | 943 | Quasi-experimental | Educational session<br>Economic incentive | 1.49 |
| Terblanche et al, 2018, South Africa | Healthcare professionals in hospital | 18 months | 547 | Quasi-experimental | Educational session | 6.7 |

**Table 2: Quality assessment of included studies**

| **Reference** | **Study design** | **Method of randomization described** | **Risk of bias** |
|---|---|---|---|
| Ribeiro-Vaz et al, 2011 | Randomized controlled | Yes, spatial cluster | Low |
| Herdeiro et al, 2012 | Randomized controlled | Yes, spatial cluster | Low |
| Lopez-Gonzalez et al, 2015 | Randomized controlled | Yes, spatial cluster | Low |
| Johansson et al, 2011 | Randomized controlled | No | Medium |
| Linder et al, 2010 | Quasi-experimental | N/A | High |
| Lander et al, 2013 | Quasi-experimental | N/A | High |
| Biagi et al, 2013 | Quasi-experimental | N/A | High |
| Abadie et al, 2014 | Quasi-experimental | N/A | High |
| Morales Rios et al, 2016 | Quasi-experimental | N/A | High |
| Fang et al, 2017 | Quasi-experimental | N/A | High |

| | | | |
|---|---|---|---|
| Terblanche et al, 2018 | Quasi-experimental | N/A | High |
| Ribeiro-Vaz et al, 2012 | Ecological time series | N/A | High |
| Chang et al, 2017 | Ecological time series | N/A | High |