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PROTOCOL

Impact of the COVID-19 pandemic on adverse drug event reporting to health authorities: systematic review protocol

Impacto de la pandemia de COVID-19 en la notificación de eventos adversos por medicamentos a las autoridades sanitarias: protocolo de revisión sistemática

Impacto da pandemia COVID-19 nas notificações de eventos adversos de medicamentos às autoridades de saúde: protocolo de revisão sistemática

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Abstract

The aim was to outline the protocol for carrying out the systematic review, which will have the objective of evaluating the impact of the COVID-19 pandemic on notifications of adverse drug events to health authorities worldwide. This is a systematic review protocol consistent with PRISMA 2020 regulations and checklist, will be conducted in accordance with the recommendations of the Cochrane Manual, will include original observational studies, letters to editors and editorials containing summary information on adverse drug events before and during the COVID-19 pandemic. The search strategy was developed for the MEDLINE, Embase, CINALH, SciELO and gray literature databases, using the Health Sciences Descriptors (DECs) and the Medical Subject Heading (MeSH). Two independent reviewers will investigate the eligibility of the articles, extract the data and assess the risk of bias. The results of this review will contribute to identifying the impact of COVID-19 on adverse drug event reporting, this will be a significant step in informing and preventing such events and will provide an essential evidence base for the development of strategies and improvements that will contribute to patient safety worldwide.

Descriptors: Drug-Related Side Effects and Adverse Reactions; COVID-19; Pharmacovigilance; Patient Safety; Systematic Review.

Resumén

El objetivo fue perfilar el protocolo para la realización de la revisión sistemática, que tendrá como objetivo evaluar el impacto de la pandemia COVID-19 en las notificaciones de eventos adversos por medicamentos a las autoridades sanitarias a nivel mundial. Este es un protocolo de revisión sistemática consistente con las regulaciones y la lista de verificación de PRISMA 2020, se llevará a cabo de acuerdo con las recomendaciones del Manual Cochrane, incluirá estudios observacionales originales, cartas a los editores y editoriales que contienen información resumida sobre los eventos adversos de medicamentos antes y durante el COVID. -19 pandemia. La estrategia de búsqueda se desarrolló para las bases de datos MEDLINE, Embase, CINALH, SciELO y literatura gris, utilizando los descriptores de ciencias de la salud (DEC) y el encabezado de sujeto médico (MeSH). Dos revisores independientes investigarán la elegibilidad de los artículos, extraerán los datos y evaluarán el riesgo de sesgo. Los resultados de esta revisión contribuirán a identificar el impacto del COVID-19 en la notificación de eventos adversos por medicamentos, este será un paso significativo para informar y prevenir dichos eventos y proporcionará una base de evidencia esencial para el desarrollo de estrategias y mejoras que contribuirán a la seguridad del paciente en todo el mundo.

Descriptores: Efectos Colaterales y Reacciones Adversas Relacionados con Medicamentos; COVID-19; Farmacovigilancia; Seguridad del Paciente; Revisión Sistemática.

Resumo

Objetivou-se delinear o protocolo da realização da revisão sistemática que terá o objetivo de avaliar o impacto da pandemia COVID-19 nas notificações de eventos adversos a medicamentos às autoridades sanitárias em todo o mundo. Trata-se de um protocolo de revisão sistemática consistente com as normativas e *checklist* PRISMA 2020, será conduzido de acordo com as recomendações do Manual Cochrane, incluirá estudos observacionais originais, cartas aos editores e editoriais contendo informações resumidas sobre os eventos adversos a medicamentos antes e durante a pandemia COVID-19. A estratégia de busca foi desenvolvida para as bases de dados MEDLINE, Embase, CINALH, SciELO e literatura cinzenta, utilizando os Descritores em Ciências da Saúde (DECs) e no Medical Subject Heading (MeSH). Dois revisores independentes investigarão a elegibilidade dos artigos, extrairão os dados e avaliarão o risco de viés. Os resultados desta revisão contribuirão para identificar o impacto da COVID-19 nas notificações de eventos adversos a medicamentos, este será um passo significativo para informar e prevenir tais eventos e fornecerá uma base de evidências essenciais para o desenvolvimento de estratégias e melhorias que contribuirão para a segurança do paciente em nível mundial.

Descritores: Efeitos Colaterais e Reações Adversas Relacionados a Medicamentos; COVID-19; Farmacovigilância; Segurança do Paciente; Revisão Sistemática.

Introduction

It is estimated that 421 million people are hospitalized each year around the world and that, on average, one in ten hospitalizations results in an adverse event (AE). Among the main AEs, medication errors stand out, which are considered one of the main causes of avoidable damage in health systems. Such pharmacological agents are widely used in the treatment of patients, but they can also compromise patient safety. In the US, approximately 1.3 million people are affected by adverse drug events (ASE) each year, the latter being responsible for nearly 700,000 emergency room visits and 100,000 admissions, in addition to the cost associated with Medication errors were estimated at US$42 billion annually, which corresponds to approximately 1% of total global health expenditures. It is noteworthy that, in the period from 2010 to 2013, 17 medication errors were reported in the Brazilian media and 14 resulted in serious damage[1-5].

The global burden of ADE and other health-related adverse events has not diminished over the past decade, despite the unprecedented priority the world has given to patient safety. Many of the harmful events are potentially preventable and the human cost to patients and families is of great concern. With the objective of mitigating risks, in 2017, the World Health Organization (WHO) launched the third global challenge for patient safety, the so-called Safe Medicines, in addition to establishing patient safety as a global health priority and an essential component for universal coverage during the 72nd World Health Assembly held in 2019[6-9].

The reporting of ADE plays an important role in patient and population safety, as it feeds the health authorities responsible for continuously evaluating the risk-benefit ratio of marketed drugs. However, one of the main problems related to drug safety is the underreporting of ADE to health authorities, through national reporting systems, especially in low- and middle-income countries, with health systems being challenged on a global scale during the COVID-19 pandemic, with recognition of increased risk for patients[2,7,10,11].

In this context, the WHO 2021-2030 global patient safety action plan suggests establishing or strengthening patient safety incident notification and learning systems to ensure a constant flow of information and knowledge to mitigate risks, reduce the avoidable harm level and improve the safety of care. Furthermore, the pharmacological management of drug users for patients remains uncertain and is the target of investigation for possible adverse events. In fact, the presence of ADEs in hospitals and in the community compromises patient safety, which is why it has become a subject of growing relevance in the literature[3,5,12].

Systematic literature reviews were carried out with the aim of analyzing current trends in reporting, monitoring and treatment related to ADE in the health system, another to assess the impact of different strategies aimed at improving ADE reporting. However, these studies have not analyzed global estimates of ADE, nor reports of ADE before and during the COVID-19 pandemic. Thus, this review, in addition to presenting a study that has not yet been carried out, will allow an analysis of previous ADEs, as well as emerging ones, including new drugs widely used in the COVID-19 context. This study will aim to answer the question what is the impact of the COVID-19 pandemic on the reports of adverse drug events to health authorities? The result will directly contribute to worldwide pharmacovigilance and drug and patient safety[13,14].

Methodology

Study designer

This systematic review protocol is consistent with the list of preferred reports for systematic review protocols in the PRISMA 2020 instruction – and will be conducted in accordance with the recommendations of the Cochrane Manual for Systematic Reviews of Interventions[15,16].

Eligibility criteria

Population

The study population will include humans using any type of pharmacological treatment (any formulation, administration, or doses).

Exhibition and Comparator

The exposure is the period of the COVID-19 pandemic, and the comparator is the pre-COVID-19 period.

Result

The main result is any EAM notified to the health authority.

Type of studies

This review will include original observational studies containing summary information about AEs before and during the COVID-19 pandemic. Letters to editors and editorials will also be included. Exclusion criteria will be legal review reports, consensus statements, single case reports, as well as any interventional studies, including clinical trials on the effectiveness of treatments against SARS-CoV-2. This criterion prioritizes studies that are close to reality, avoiding selection biases or excessive awareness of ADE that may occur in interventional studies. Animal studies will also be excluded.

Research strategy and data extraction

The search strategy was developed with the help of an expert librarian from the Université Laval (Québec, Canada) for MEDLINE, Embase, CINALH and SciELO (Figure 1).

Health descriptors available in Health Science Descriptors (DECs) and Medical Subject Heading (MeSH) will be used and will include: "Drug-Related Side Effects and Adverse Reactions", "Medication Errors", "Health Services Research"," Government Agencies", "Public Health Administration", Adverse Drug Reaction Reporting Systems. We'll also search for gray literature, such as reports from health authorities, Institute for Safe Medicines Practices (ISMP) of Canada, Brazil, Spain and the United States, Food and Drug Administration (FDA), Medicines & Healthcare products Regulatory Agency (MHRA) of The Therapeutic

Goods Administration UK and The Therapeutic Goods Administration (TGA) Australia. Language restrictions will not apply, and translation will be performed if necessary. References will be imported into the Covidence software and duplicates will be removed directly in the software.

The title and abstract of articles identified with the search strategy will be investigated by two independent reviewers to determine eligibility for this study. Any disagreements will be resolved through discussion with a third reviewer. Then, the full texts of abstracts selected after the first round of review will be investigated by two independent reviewers to confirm eligibility for the present study.

Figure 1. Search strategy developed for Medline, Embase, CINAHL and SciELO. Québec, QC, Canada, 2021.

MEDLINE	
#1	*"Drug-Related Side Effects and Adverse Reactions"/ or "Safety-Based Drug Withdrawals"/ or *"Medical Errors"/ or "Long Term Adverse Effects"/ or *"Medication Errors"/ or "Drug Monitoring"/
#2	(((Drug* or Fatal*) adj3 ("Side Effect*" or "Adverse* Effect*")) or ("Adverse* Drug*" adj3 (Reaction* or Event* or Effect*)) or ("Long Term*" adj3 "Adverse* Effect*") or (Safet* adj3 "Drug* Withdrawal*") or (Medical* adj3 (Mistake* or Error* or Incident*)) or (("Wrong-Procedure*" or "Health Care*" or Healthcare* or Medication* or Drug*) adj3 Error*) or (Drug* adj3 (Fatalit* or Mortalit* or Complication* or Disease* or Injur* or Iatrogeni* or Monitoring)) or "Wrong Drug Administration*" or "Medication Monitoring" or "Fatal Adverse* Reaction*" or "Never Event*"). ab,kf,ti.
#3	exp "United Nations"/ or "United States Food and Drug Administration"/ or "United States Office of National Drug Control Policy"/ or *"United States Dept. of Health and Human Services"/ or "Federal Government"/ or *"Health Services Research"/ or *"Government Agencies"/ or "Public Health Administration"/ or "Government Regulation"/ or exp "Policy Making"/ or *"Population Surveillance"/ or "Prescription Drug Monitoring Programs"/ or Pharmacovigilance/ or Pharmacoepidemiology/ OR "Sentinel Surveillance"/ OR "Adverse Drug Reaction Reporting Systems"/
#4	(ANVISA or "National Health Surveillance Agency" or "World Health Organization" or "Institute for Safe Medication Practices" or ISMP or "Food and Drug Administration" or FDA or USFDA or "Medicines and Healthcare Products Regulatory Agency" or MHRA or "Therapeutic Goods Administration" or "African Medicines Regulatory Harmonization" or AMRH or "United Nations" or UNHCR or UNICEF or UNESCO or "Pan American Health Organization" or PAHO or "Health Services Research*" or "Health Services Evaluation*" or "Medical Care Research*" or "Health Care Research*" or "Healthcare Research*" or Government* or "Population Surveillanc*" or "Department of Health and Human Services" or "Office of National Drug Control Polic*" or "Advisory Committee*" or "Drug Surveillance Program*" or "Drug Monitoring Program*" or "Prescription Monitoring" or "Vaccine Adverse Events Report*" or VAERS or "Drug Enforcement Administration" or "Centers for Medicare and Medicaid Services" or "Centers for Disease Control and Prevention" or "Health Department*" or "National Health Care*" or pharmacovigilance* or "pharmaco-vigilance*" or "sentinel surveillance*" or pharmacoepidemiolog* or pharmaco-epidemiolog* or "Adverse Drug Reaction Reporting System*" or ("Public Health" adj1 (Care* or Center* or Centre* or Practic* or Service* or Administration* or Surveillance*))).ab,kf,ti (#1 OR #2) AND (#3 OR #4)
Embase	
#1	'adverse drug reaction'/de OR 'drug fatality'/de OR 'drug induced disease'/de OR 'drug recall'/de OR 'medical error'/de OR 'medication error'/de OR 'drug monitoring'/de
#2	(((drug* OR fatal*) NEAR/3 ('side effect*' OR 'adverse* effect*')):ab,kw,ti) OR (('adverse* drug*' NEAR/3 (reaction* OR event* OR effect*)):ab,kw,ti) OR (('long term*' NEAR/3 'adverse* effect*'):ab,kw,ti) OR ((safet* NEAR/3 'drug* withdrawal*'):ab,kw,ti) OR ((medical* NEAR/3 (mistake* OR error* OR incident*)):ab,kw,ti) OR ((('wrong-procedure*' OR 'health care*' OR healthcare* OR medication* OR drug*) NEAR/3 error*):ab,kw,ti) OR ((drug* NEAR/3 (fatalit* OR mortalit* OR complication* OR disease* OR injur* OR iatrogeni* OR monitoring)):ab,kw,ti) OR 'wrong drug administration*':ab,kw,ti OR 'medication monitoring':ab,kw,ti OR 'fatal adverse* reaction*':ab,kw,ti OR 'never event*':ab,kw,ti
#3	'pharmacovigilance'/exp OR 'pharmacoepidemiology'/de or 'United Nations'/exp or 'Food and Drug Administration'/de or 'government'/de or 'health services research'/de or 'public health service'/de or 'government regulation'/de or 'population surveillance'/de or 'prescription drug monitoring program'/de or 'drug surveillance program'/de OR 'sentinel surveillance'/de
#4	anvisa:ab,kw,ti OR 'national health surveillance agency':ab,kw,ti OR 'world health organization':ab,kw,ti OR 'institute for safe medication practices':ab,kw,ti OR ismp:ab,kw,ti OR 'food and drug administration':ab,kw,ti OR fda:ab,kw,ti OR usfda:ab,kw,ti OR 'medicines and healthcare products regulatory agency':ab,kw,ti OR mhra:ab,kw,ti OR 'therapeutic goods administration':ab,kw,ti OR 'african medicines regulatory harmonization':ab,kw,ti OR amrh:ab,kw,ti OR 'united nations':ab,kw,ti OR unhcr:ab,kw,ti OR unicef:ab,kw,ti OR unesco:ab,kw,ti OR 'pan american health organization':ab,kw,ti OR paho:ab,kw,ti OR 'health services research*':ab,kw,ti OR 'health services evaluation*':ab,kw,ti OR 'medical care research*':ab,kw,ti OR 'health care research*':ab,kw,ti OR 'healthcare research*':ab,kw,ti OR government*:ab,kw,ti OR 'population surveillanc*':ab,kw,ti OR 'department of health and human services':ab,kw,ti OR 'office of national drug control polic*':ab,kw,ti OR 'advisory committee*':ab,kw,ti OR 'drug surveillance program*':ab,kw,ti OR 'drug monitoring program*':ab,kw,ti OR 'prescription monitoring':ab,kw,ti OR 'vaccine adverse events report*':ab,kw,ti OR vaers:ab,kw,ti OR 'drug enforcement administration':ab,kw,ti OR 'centers for medicare and medicaid services':ab,kw,ti OR 'centers for disease control and prevention':ab,kw,ti OR 'health department*':ab,kw,ti OR 'national health care*':ab,kw,ti OR pharmacovigilance*:ab,kw,ti OR 'pharmaco-vigilance*':ab,kw,ti OR 'sentinel surveillance*':ab,kw,ti OR pharmacoepidemiolog*:ab,kw,ti OR 'pharmaco epidemiolog*':ab,kw,ti OR 'adverse drug reaction reporting system*':ab,kw,ti OR (('public health' NEAR/1 (care* OR center* OR centre* OR practic* OR service* OR administration* OR surveillance*)):ab,kw,ti) (#1 OR #2) AND (#3 OR #4)
CINAHL	
#1	(MH "Adverse Drug Event") or (MH "Substance Withdrawal, Controlled") or (MH "Treatment Errors") or (MH "Medication Errors") or (MH "Drug Monitoring")

#2	TI (((Drug* or Fatal*) N2 ("Side Effect*" or "Adverse* Effect*")) or ("Adverse* Drug*" N2 (Reaction* or Event* or Effect*)) or ("Long Term*" N2 "Adverse* Effect*") or (Safet* N2 "Drug* Withdrawal*") or (Medical* N2 (Mistake* or Error* or Incident*)) or (("Wrong-Procedure*" or "Health Care*" or Healthcare* or Medication* or Drug*) N2 Error*) or (Drug* N2 (Fatalit* or Mortalit* or Complication* or Disease* or Injur* or Iatrogeni* or Monitoring)) or "Wrong Drug Administration*" or "Medication Monitoring" or "Fatal Adverse* Reaction*" or "Never Event*")
#3	AB (((Drug* or Fatal*) N2 ("Side Effect*" or "Adverse* Effect*")) or ("Adverse* Drug*" N2 (Reaction* or Event* or Effect*)) or ("Long Term*" N2 "Adverse* Effect*") or (Safet* N2 "Drug* Withdrawal*") or (Medical* N2 (Mistake* or Error* or Incident*)) or (("Wrong-Procedure*" or "Health Care*" or Healthcare* or Medication* or Drug*) N2 Error*) or (Drug* N2 (Fatalit* or Mortalit* or Complication* or Disease* or Injur* or Iatrogeni* or Monitoring)) or "Wrong Drug Administration*" or "Medication Monitoring" or "Fatal Adverse* Reaction*" or "Never Event*")
#4	(MH "United Nations+") or (MH "United States Food and Drug Administration") or (MH "United States Department of Health and Human Services") or (MH "Federal Government") or (MH "Health Services Research") or (MH "Government Agencies") or (MH "Public Health Administration") or "Government Regulations") or (MH "Policy Making") or (MH "Population Surveillance") or (MH "Prescription Drug Monitoring Programs") or (MH "Pharmacovigilance") or (MH "Sentinel Event")
#5	TI (ANVISA or "National Health Surveillance Agency" or "World Health Organization" or "Institute for Safe Medication Practices" or ISMP or "Food and Drug Administration" or FDA or USFDA or "Medicines and Healthcare Products Regulatory Agency" or MHRA or "Therapeutic Goods Administration" or "African Medicines Regulatory Harmonization" or AMRH or "United Nations" or UNHCR or UNICEF or UNESCO or "Pan American Health Organization" or PAHO or "Health Services Research*" or "Health Services Evaluation*" or "Medical Care Research*" or "Health Care Research*" or "Healthcare Research*" or Government* or "Population Surveillanc*" or "Department of Health and Human Services" or "Office of National Drug Control Polic*" or "Advisory Committee*" or "Drug Surveillance Program*" or "Drug Monitoring Program*" or "Prescription Monitoring" or "Vaccine Adverse Events Report*" or VAERS or "Drug Enforcement Administration" or "Centers for Medicare and Medicaid Services" or "Centers for Disease Control and Prevention" or "Health Department*" or "National Health Care*" or pharmacovigilance* or "pharmaco-vigilance*" or "sentinel surveillance*" or pharmacoepidemiolog* or pharmaco-epidemiolog* or "Adverse Drug Reaction Reporting System*" or ("Public Health" N1 (Care* or Center* or Centre* or Practic* or Service* or Administration* or Surveillance*)))
#6	AB (ANVISA or "National Health Surveillance Agency" or "World Health Organization" or "Institute for Safe Medication Practices" or ISMP or "Food and Drug Administration" or FDA or USFDA or "Medicines and Healthcare Products Regulatory Agency" or MHRA or "Therapeutic Goods Administration" or "African Medicines Regulatory Harmonization" or AMRH or "United Nations" or UNHCR or UNICEF or UNESCO or "Pan American Health Organization" or PAHO or "Health Services Research*" or "Health Services Evaluation*" or "Medical Care Research*" or "Health Care Research*" or "Healthcare Research*" or Government* or "Population Surveillanc*" or "Department of Health and Human Services" or "Office of National Drug Control Polic*" or "Advisory Committee*" or "Drug Surveillance Program*" or "Drug Monitoring Program*" or "Prescription Monitoring" or "Vaccine Adverse Events Report*" or VAERS or "Drug Enforcement Administration" or "Centers for Medicare and Medicaid Services" or "Centers for Disease Control and Prevention" or "Health Department*" or "National Health Care*" or pharmacovigilance* or "pharmaco-vigilance*" or "sentinel surveillance*" or pharmacoepidemiolog* or pharmaco-epidemiolog* or "Adverse Drug Reaction Reporting System*" or ("Public Health" N1 (Care* or Center* or Centre* or Practic* or Service* or Administration* or Surveillance*))) (#1 OR #2 OR #3) AND (#4 OR #5 OR #6)
SciELO	
#1	TS=(((Drug* or Fatal*) NEAR/2 ("Side Effect*" or "Adverse* Effect*")) or ("Adverse* Drug*" NEAR/2 (Reaction* or Event* or Effect*)) or ("Long Term*" NEAR/2 "Adverse* Effect*") or (Safet*NEAR/2 "Drug* Withdrawal*") or (Medical* NEAR/2 (Mistake* or Error* or Incident*)) or (("Wrong-Procedure*" or "Health Care*" or Healthcare* or Medication* or Drug*) NEAR/2 Error*) or (Drug* NEAR/2 (Fatalit* or Mortalit* or Complication* or Disease* or Injur* or Iatrogeni* or Monitoring)) or "Wrong Drug Administration*" or "Medication Monitoring" or "Fatal Adverse* Reaction*" or "Never Event*")
#2	ts=(ANVISA or "National Health Surveillance Agency" or "World Health Organization" or "Institute for Safe Medication Practices" or ISMP or "Food and Drug Administration" or FDA or USFDA or "Medicines and Healthcare Products Regulatory Agency" or MHRA or "Therapeutic Goods Administration" or "African Medicines Regulatory Harmonization" or AMRH or "United Nations" or UNHCR or UNICEF or UNESCO or "Pan American Health Organization" or PAHO or "Health Services Research*" or "Health Services Evaluation*" or "Medical Care Research*" or "Health Care Research*" or "Healthcare Research*" or Government* or "Population Surveillanc*" or "Department of Health and Human Services" or "Office of National Drug Control Polic*" or "Advisory Committee*" or "Drug Surveillance Program*" or "Drug Monitoring Program*" or "Prescription Monitoring" or "Vaccine Adverse Events Report*" or VAERS or "Drug Enforcement Administration" or "Centers for Medicare and Medicaid Services" or "Centers for Disease Control and Prevention" or "Health Department*" or "National Health Care*" or pharmacovigilance* or "pharmaco-vigilance*" or "sentinel surveillance*" or pharmacoepidemiolog* or pharmaco-epidemiolog* or "Adverse Drug Reaction Reporting System*" or ("Public Health" NEAR/1 (Care* or Center* or Centre* or Practic* or Service* or Administration* or Surveillance*))) #1 AND #2

Data and Variables

The following variables will be extracted from the selected studies:

- Variables related to the study and the emergence of the COVID-19 pandemic: country, type of study, period covered, qualitative interpretation of the authors regarding the research question.
- Demographic variables of the patients involved: sex, age, presence of comorbidities and number of comorbidities, number of medications in use and main medical diagnosis.
- Drug class involved in the reported ADE: no prophylactic class or life-threatening level will be differentiated, as it intends to analyze all possible variables with low, medium, and high complexity levels of multi-causality. Therefore, this proposal expands the comparative possibility between the previous periods and during the pandemic; type of study drugs before/during the

COVID-19 pandemic, the definition of exposure.

- Variables related to EAM reporting: reporting country/state/region; consequence of ADE for the patient according to the WHO classification: none, mild, moderate, severe, death; type of health service according to the levels of health care that make up the Health Care Network (RAS): outpatient; hospital; exclusive urgent and emergency service; others.

Quantitative data will be extracted from selected studies using Excel spreadsheets. This will be done independently by two researchers from our group. Likewise, qualitative data from editorials and letters to the editor will be extracted and summarized[17].

Bias risk assessment

The risk of bias in the non-randomized intervention studies tool (ROBINS-I) will be used for the scientific literature. This tool provides a framework for assessing the risk of bias in a single study (an estimate of the effect of an intervention and experimental observation compared to another intervention on a specific outcome. In summary, the domains and bias covered by this tool are: 1) Pre-intervention (bias due to confusion, bias in the selection of study participants); 2) Intervention/exposure (bias in the classification of interventions/exposure); 3) Post-intervention (bias due to deviations from intended interventions, bias due to lack of data, bias in outcome measurement, bias in selection of reported outcome). Each domain will be judged on whether its risk of bias is low, moderate, severe, critical or "no information" if applicable[18,19].

Studies from gray literature, letter to the editors, and editorials will be evaluated using the Authority, Accuracy, Coverage, Objectivity, Date and Significance (AACODS) checklist. Two independent reviewers will assess the risk of bias in all selected studies[20].

Statistical analysis

Descriptive analyzes will be performed to summarize the quantitative variables extracted from the selected studies using frequency tables with absolute values (n) and percentages (%), distribution measures (mean, median, minimum, and maximum) and dispersion (standard deviation, interquartile range).

Qualitative data from the original studies (ie: authors' final interpretation with confidence intervals) and editorials will be extracted and classified as: 1) Increased ADE reports; 2) Decrease in EAM reports; 3) EAM reports were unchanged during vs. before the COVID-19 pandemic. If possible, the annual ADE rate will be calculated as the number of ADE reported to health authorities in each country divided by the population of the country that originated the cases and reported to 100,000 inhabitants. This will be graphically represented. Adverse event rate trends reported to health authorities during vs. before the COVID-19 pandemic will be quantified and compared using linear join point regression program models version 4.8.0.1. Statistical significance will be judged according to 95% confidence intervals.

The results will be described according to the PRISMA flow diagram guidelines and submitted for publication in a peer-reviewed journal.

Prospero: Registration ID: CRD42021251011 on July 23, 2021 - Under review.

Strengths and limitations of the study

The electronic databases used in this review will be searched without language limitation, minimizing the risk of selection bias. However, it is possible that we find only a low number of published and peer-reviewed studies that may be associated with information or publication bias. However, as far as we know, this systematic review will provide the first comprehensive assessment of ADE reports and the impact of the COVID-19 pandemic on those reports. The results will then contribute to worldwide pharmacovigilance.

Expected Results

It is hoped that with the preparation of this systematic review, the real impact of the COVID-19 pandemic on notifications of ADE reported to health authorities at the global level, before and during the human health crisis, will be identified. This will be a significant step in informing and preventing such events, as to our knowledge, this will be the first systematic review evaluating the worldwide impact of the COVID-19 pandemic on the number of AE reports to health authorities. This review will also provide an essential evidence base for developing strategies and improving the number of ADE reports to directly contribute to pharmacovigilance and patient safety worldwide.

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