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EVALUATION OF THE DECISION-MAKING PROCESS UNDERLYING THE NOVEL INITIAL OFF-LABEL USE OF VACCINES: A SCOPING REVIEW PROTOCOL

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Complete List of Authors:	Diallo, Dieynaba; Centre Hospitalier Universitaire Sainte-Justine, Centre de recherche; University of Montreal Faculty of Medicine, Microbiology, Infectious Diseases, and Immunology Quach, Caroline; Centre Hospitalier Universitaire Sainte-Justine, Centre de recherche; University of Montreal Faculty of Medicine, Microbiology, Infectious Diseases, and Immunology
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TITLE PAGE

Title of the article: Evaluation of the decision-making process underlying the novel initial off-label use of vaccines: a scoping review protocol

Corresponding author: Caroline Quach
Centre Hospitalier Universitaire Sainte-Justine, 3175 ch. Côte-Sainte-Catherine – B17.102, Montréal, Québec, Canada H3T 1C5. E-mail address: c.quach@umontreal.ca

Co-authors:
Dieynaba Diallo,[a,b,c] MScPH. ORCID iD : https://orcid.org/0000-0002-3650-5815
Centre Hospitalier Universitaire Sainte-Justine, 3175 ch. Côte-Sainte-Catherine – B17.003.14, Montréal, Québec, Canada H3T 1C5.
E-mail address: Dieynaba.diallo@umontreal.ca; Phone number:+1 438.827.4630

Caroline Quach,[a,b,d] MD, MSc. ORCID iD : https://orcid.org/0000-0002-1170-9475
Centre Hospitalier Universitaire Sainte-Justine, 3175 ch. Côte-Sainte-Catherine – B.17.102, Montréal, Québec Canada H3T 1C5.
Email address: c.quach@umontreal.ca; Phone number: +1 514.345.4931 #7430

a. Department of Microbiology, Infectious Diseases, and Immunology, Faculty of Medicine, University of Montreal, Montreal, Canada.
b. Research Institute – CHU Sainte-Justine, Montreal, Canada
c. Institut National de Santé Publique du Québec, Québec, Canada
d. Infection Prevention and Control, Department of Clinical Laboratory Medicine, Centre Hospitalier Universitaire Sainte-Justine, Montreal, Canada

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ABSTRACT

Introduction: Vaccination has become a central part of public health prevention. Vaccines are introduced after licensure by national regulatory authorities, whereas recommendations for use of licensed vaccines are made by national or international advisory committees and may include off-label use. The methodological and decision-making processes that are used to assess novel initial off-label vaccine use are unclear. This review aims to examine the off-label assessment processes to map evidence and concepts used in the decision-making process and present a common approach between all recommendations and specifics of each decision.

Methods and analysis: The methodological framework described at the Joanna Briggs Institute will be applied to this scoping review. A search strategy was developed, in collaboration with an experienced senior health research librarian, by combining Mesgarpour's highly sensitive search strategies. Peer-reviewed and grey literature will be systematically identified using PubMed, Medline, and EMBASE; governmental agency and pharmaceutical websites; and search engines, such as Google Scholar. Reports and studies on off-label vaccine use in public health will be included. Screening will be independently undertaken by two reviewers. Data will be extracted using a standard form. Results will be narratively summarized to highlight relevant findings and guide the development of an analytical framework for off-label vaccination recommendations.

Ethics and dissemination: This research does not require ethical approval. This scoping review will provide decision-making elements and a synthesis of knowledge on the off-label use of vaccines. Findings will be relevant to public health sectors and will be disseminated through peer-reviewed articles and conferences.

Words count: 249

Strengths and limitations of this study

►This review allows a comprehensive and in-depth mapping of off-label recommendations for vaccines.

►This review uses a proven scoping review methodology throughout the research.

►This review provides novel insights for the immunization assessment processes.

►This review will highlight key elements for public health stakeholders and decisionmakers.

►The findings of this review will be of global interest because, worldwide, all countries may face situations that require the use of off-label vaccines.

INTRODUCTION

Background and rationale

Infectious diseases are the commonest cause of deaths worldwide, killing more than 17 million people a year,[1] although many are preventable or curable diseases. In 2016, lower respiratory infections remained the deadliest communicable disease and were among the top 10 causes of deaths, with diarrhea and tuberculosis, and accounted for a total of 5.7 million deaths worldwide that year[2]: in low-income countries, more than half of all deaths were caused by conditions involving communicable diseases[1]. In Canada, infectious and parasitic diseases were responsible for 1.6% of all deaths in 2018.[3]

In the course of time, numerous vaccines have been developed to prevent diseases. In 2018, 85% of infants worldwide had received three doses of polio vaccine to protect them against poliomyelitis – a highly infectious viral disease that can cause irreversible paralysis.[4] In the same year, an estimated 35% of infants globally were protected against rotaviruses, the commonest cause of severe diarrheal disease among children worldwide. The global coverage of the third dose of the pneumococcal vaccine was estimated at 47% in 2018. Thus, vaccination has become a central part of public health preventive measures against morbidity, disability, and mortality.

The vaccine industry has become highly regulated through licensure.[5] The national regulatory authorities (NRA) license a vaccine after clinical trial data submitted by the manufacturer confirm the vaccine safety and efficacy for its intended use. Every vaccine has specific indications of use that are mentioned when introduced to the market. The vaccine's label provides information, such as the name, formulation, dosage, route of administration, age, indications and usage, and contraindications or other information unique to the vaccine.[6]

After vaccines are licensed, national immunization programs that are implemented by healthcare practitioners and clinicians may include these vaccines and will describe, for each vaccine, the NRA-approved prescribing information.[5] Subsequently, expert technical advisory committees – national or international – will make recommendations based on several additional elements, such as disease epidemiology (e.g., serotype distribution), vaccine effectiveness/efficacy, vaccine impact, cost, supply, or program optimization.[7] Very often, however, recommendations for the use of a licensed vaccine can be for off-label indications,[8] which involves the use of a licensed vaccine on a dosage, schedule, or within a population outside the indications approved by a regulatory body.

The unlabeled use of vaccines (unlicensed) is different from the off-label use, where the latter results from the recommendations for licensed vaccines and is supported by critically appraised evidence. There are known off-label recommendations that are reported in the literature. For example, at licensure, Prevnar-7 (PnC7 conjugated 7-valent pneumococcal vaccine) was approved in a 3 + 1 schedule. In Canada, the National Advisory Committee on Immunization (NACI) recommended an off-label schedule of 2 + 1 instead of the approved 3 + 1.[9] Another example is REPEVAX (diphtheria and tetanus toxoids, acellular pertussis adsorbed and inactivated poliovirus vaccine), which is not recommended for use during pregnancy because its effect on embryo-fetal development has not been assessed. REPEVAX has not been evaluated in fertility studies.[10] However, no teratogenic effect of vaccines containing diphtheria or tetanus toxoids, or inactivated poliovirus have been observed following use in pregnant women, and there is limited post-marketing information on the safety of

[1]Crude death rate per 100 000 population: lower respiratory infection 76; diarrhoeal diseases 58; HIV/AIDS 44.5; Malaria 38; Tuberculosis 34.5.

administering REPEVAX to pregnant women. Therefore, the recommendation for the use of this vaccine in this group in the UK is off-label, considering the approved summary of product characteristics (SmPC)[2].[11]

RotaTeq® (Rotavirus Vaccine, Live, Oral, Pentavalent) was licensed in February 2006[12 13] by the US Food and Drug Administration (FDA) for the prevention of rotavirus gastroenteritis, caused by types G1, G2, G3, and G4, in infants in the age range of 6–32 weeks, administered as a 3-dose series. In the United States, the Advisory Committee on Immunization Practices (ACIP) recommended routine oral vaccination of infants with 3 doses of this rotavirus vaccine at ages 2, 4, and 6 months.[14] Rotarix™ (Rotavirus vaccine, live, attenuated) was licensed in February 2006[15 16] by the European Medicines Agency (EMA) for use in the European Union in babies in age range of 6–24 weeks to protect them against gastroenteritis (diarrhea and vomiting) caused by rotavirus infection. Experts are investigating the possibility of waivers for patients younger than or older than 6 and 32 weeks of age, respectively,[17] or for different dosing schedules of rotavirus vaccines.[18]

Thus, off-label use of vaccines exists and is feasible when supported by scientific evidence. Among diverse populations and given the large number of vaccines, many considerations and elements should be assessed before any recommendation is made. However, for novel off-label vaccine use, the evaluation process does not rely on previous off-label recommendations of one vaccine and requires new evidence to support a recommendation.

Previous studies

We searched the literature to verify whether studies have examined the process for evaluating the initial off-label use of a vaccine or its recommendation. A pilot selection of databases and relevant studies identified mainly randomized controlled trials (RCTs) and systematic reviews on individual vaccines. Systematic reviews were conducted to evaluate the impact[19 20] and effectiveness[21-23] of vaccines, mortality[24], and morbidity.[25] Moreover, we searched the literature for off-label use of vaccine scoping reviews, to check whether similar work, as comprehensive as the research we intend to undertake, had been conducted. Several papers have reported off-label recommendations that have been implemented by public health decisionmakers,[8 9 18] but few have investigated the methodology behind the process of off-label recommendations.[26 27] To our knowledge, no scoping review has been conducted yet with a spectrum of data elements, synthesized for decision-making, considered in a recommendation for the off-label use of vaccines in a public health program. Further in-depth research is needed to map out approaches, evidence, and recommendations for the development for off-label vaccine use. Key elements of national and global importance will be highlighted in this review.[28 29]

Aims and objectives

Aim

To synthesize the knowledge around off-label use of vaccines in a novel initial assessment process at a global level. The scoping review method will allow us to examine peer-reviewed and grey literature and to map the broad topic of the off-label use of vaccine in a rigorous, systematic, and reproducible manner. A greater understanding of the nature of evidence that supports vaccine off-label use recommendations may lead to feasible and improved decision-making in public health. This scoping review is the first step in a three-phase research plan.

[2] The SmPC is used by healthcare professionals, such as doctors, nurses and pharmacists, and explains how to use and prescribe a medicine. SmPCs are written and updated by pharmaceutical companies and are based on their research and product knowledge

We define the initial assessment as the process that occurs after a vaccine has been licensed and wherein an off-label recommendation from an expert committee is implemented in a public program within a jurisdiction, before any other global off-label recommendation has been made for the same vaccine. To identify such processes, we will use the vaccine licensure date as a starting point and search for any published off-label recommendation that chronologically flows from it.

Objectives

1. To map the field of methods and concepts used in the decision-making process of a recommendation about off-label vaccination.
2. To identify and describe the different assessment processes that lead to a decision and its implementation of initial off-label vaccine use.
3. To identify and validate the recommendations on off-label vaccination that have been reported by advisory committees and which may help plan immunization programs.
4. To identify and summarize the range of evidence that inform the development of recommendations across different off-label types and characteristics.
5. To present a common approach between all initial off-label use of vaccine recommendations and the specific aspects of each decision.
6. To provide a clear definition of the off-label-use of vaccines.
7. To highlight relevant findings that will guide the conceptualization of an analytical framework for off-label vaccine use.

Review question

What are the evidences used by public health experts in recommending off-label use of vaccines in a vaccination program?

METHODS

Scoping review design

This study will follow the Joanna Briggs Institute (JBI)[30] methodological approaches for a scoping review, as described by Peters et al. in Chapter 11 of the 4th Edition of the reviewer's manual. The JBI framework involves:

1. Defining and aligning the objective/s and question/s
2. Developing and aligning the inclusion criteria with the objective/s and question/s
3. Describing the planned approach to evidence searching, selection,
4. Searching for the evidence
5. Selecting the evidence
6. Extracting the evidence
7. Charting the evidence
8. Summarizing the evidence in relation to the objective/s and question/s
9. Consultation of information scientists, librarians, and/or experts (throughout)

Vaccines that will be included in the ambit of this scoping review are being identified. This scoping review will be initiated as soon as the protocol is submitted for publication. Reporting will be conducted in accordance with the Preferred Reporting Items for Systematic Review and Meta-Analysis Extension for Scoping Reviews (PRISMA-ScR) checklist.[31]

Review registration

At present, scoping review (ScR) protocols are ineligible for registration in the PROSPERO database.

This review title has been registered with Open Science Framework[32]. The final version of this protocol will be submitted to *BMJ Open*.

Patient and public involvement

There will be no patient or public involvement in this review. However, patient/public involvement will be a part of the third phase of the research plan, during a focus-group interview to be conducted after the results of this review are reported.

Inclusion criteria

There are 26 vaccine-preventable diseases (VPD) for which a vaccine is available, and these will be included in our review:

- Cholera
- Dengue
- Diphtheria
- Hepatitis A
- Hepatitis B
- Hepatitis E
- Hemophilus influenzae type b (Hib)
- Human papillomavirus (HPV)
- Influenza
- Japanese encephalitis
- Malaria
- Measles
- Meningococcal meningitis
- Mumps
- Pertussis
- Pneumococcal invasive disease
- Poliomyelitis
- Rabies
- Rotavirus
- Rubella
- Tetanus
- Tick-borne encephalitis
- Tuberculosis
- Typhoid
- Varicella
- Yellow Fever

Population, Concept, and Context (PCC) elements

Table 1: Review inclusion criteria

	Inclusion	Exclusion
Types of participants	Public health immunization is a broad endeavor, and it is aimed at the entire population. All strata and categories of individuals will be suitable for inclusion: men and women of any age group, condition, or profession, as long as the off-label schedule is applicable to the group in a public health recommendation.	- Non-human subjects (e.g., preclinical studies) - Self-reporting of off-label-use of vaccine at the individual patient/physician level, as this is not representative of a public health approach (no case report).
Concept	Methodically, any indication of use that would be different from the prescribing information provided in the label of a vaccine should be considered off-label immunization. The most frequent off-label recommendations are for doses, population groups, indications, posology, or injection site,[7 8] but should not be limited to these aspects. An objective of our review is to identify all existing recommendations that address off-label vaccination in public health. The implementation of the recommendation for off-label vaccine use is considered an outcome when recommendations are part of published vaccination programs. The review uses the vaccine licensure as a starting point to	- Unlabeled vaccine use - Superfast-track approval is not considered off-label use. - Non-adherent behaviors that result in different dosing are not considered as off-label use

	determine the eligibility of a paper, and the label is considered the baseline for each vaccine. Various terms and definitions may have been used through the years. However, as "*off-label*" is a relatively new term that has been introduced in search engines in approximately 2010, the review intends to provide a clear definition for off-label vaccine use.	
Context	Off-label recommendations will be broadly sought from within the global context of immunization. There will be no limitation in the geographic location or in the settings. This review is intended to map the evidence that emerges from any context, including pandemics and shortages.	No exclusion criteria
Types of sources	Any and all documents included in the decision process of the initial off-label use of vaccine recommendations will be included in this review. The reference lists of identified reports will be manually searched for additional studies. All types of studies and documents: product monographs, official documents, recommendations (NITAG, SAGE, etc.), health authority vaccine updates, and accessible documentary evidence submitted for licensing (from clinical trials: quality, safety, and efficacy data), or from studies made after licensing. Any valuable written sources will be included to supplement the information on the vaccines. The period considered will be from the date of vaccine first licensing for the country, for each vaccine. Documents in all languages will be eligible at the initial phase. If short texts are available in languages other than English or French, they will be translated and included in the review.	Long documents will be excluded when not written in French or English: 3 pages or more.

NITAG: National Immunization Technical Advisory Group; SAGE: WHO Strategic Advisory Group of Experts

Search strategy

Search terms and strategy:

A comprehensive and structured search of the literature will be conducted. For documents identification, two search strategies will be developed: one for the grey literature and the other for published studies.

For the grey literature,[33] a search will be conducted for each vaccine's product monograph from pharmaceuticals, licensure, national vaccine updates, or accessible documentary evidence submitted for licensing, identified by NRAs and organizations that proceeded to regulatory approval at the national or international level. Expert committees that make recommendations for off-label vaccines use will be identified.

A combination of terms – vaccine-preventable diseases, vaccine names, and licensure – will be used to search official publications and all documents on the evaluation process, recommendations, fundamental decisive factors, and program implementation. All documents describing the decision-making process of off-label vaccine recommendation in a public program, from the evaluation process

by the expert committee to the decisive elements that enabled the health authority to implement the recommendation, or otherwise, into the vaccination program. If necessary, we will contact the authors of the off-label decision for additional information.

The other search strategy will include a combination of two major concepts: off-label use (main concept) and vaccines (second concept). For the off-label concept, we will use Mesgarpour's[34 35] highly sensitive search strategy to retrieve as many documents as possible. The specificity of the search strategy will increase when combined with the second concept – *vaccines and each VPD name*. The outcome concept will not be included in the search strategy, as it could possibly restrict the number of papers. A medical librarian with experience in electronic database searches has worked with the research team and helped perfect the search strategy.

The exposure terms will be medical subject heading (MeSH) or EMBASE subject headings (EMTREE) that describe the off-label use, plus terms that describe vaccines, combined with the AND Boolean term. Word strings will be identified in the titles and abstracts of relevant documents. Variations of these words will be searched as free text. The complete search strategy with the terms to be entered into the databases are available in the supplementary materials.

Databases and other sources to be searched

The search will be conducted in the databases listed below for all documents and study types published from the date of the first vaccine licensure by using the prespecified search terms.

For the grey literature,[33] the sources to be searched are the World Health Organization [WHO] Immunization – Vaccines and Biologicals, US FDA, Health Canada (https://health-products.canada.ca/dpd-bdpp/index-eng.jsp), The Canadian Agency for Drugs and Technologies in Health (CADTH), European Medicines Agency (EMA), Therapeutic Goods Administration (TGA), Pharmaceuticals and Medical Devices Agency (PMDA), ImmunoFacts Vaccines and Immunologic drugs, Canadian Agency for Drugs and Technologies in Health, RxTx (The Canadian Pharmacists Association's e-Therapeutics+ and e-Therapeutics+ Complete products), and United States Pharmacopeia and National Formulary (USP), Merck Index, Google Scholar, WHO publications, Global NITAG Network center, Open Grey, and Ministries of Health publications. We may need to contact governmental agencies to gain access to some documents.

The databases that will be searched for studies will be PubMed, MEDLINE,[3] and EMBASE[4] to minimize retrieval bias. EMBASE is an international bibliographic science database for biomedical and pharmaceutical product with a comprehensive indexing policy for articles that deal with drugs, and it would be appropriate for this scoping review. For RCTs, www.clinicaltrials.gov and the International Clinical trials registry will be searched.

The data sources included in this review are deemed appropriate, given that the evidence will precede and inform the development of the recommendations, which would need to be published, to be considered.

[3] Ovid MEDLINE(R) and Epub Ahead of Print, In-Process & Other Non-Indexed Citations, Daily and Versions(R)
[4] Excerpta Medica Database (EMBASE) 1974 to 2020 June 26 (or last version)

Documents selection and screening

All monographs are eligible for inclusion. All documents and studies included in public health off-label recommendations – for considered vaccines – will be selected. Moreover, all documents supporting the implementation of the recommendations will be included.

All studies and documents identified in the search will be exported from databases or websites into the EndNote X9 reference manager to eliminate duplication. Unique citations will be exported into DistillerSR for screening. Studies and documents will be reviewed against the selection criteria specified in Table 1 for inclusion/exclusion in two stages: the first stage will comprise a review of the title and abstract, where two reviewers, at least one of whom is a content expert and the other a methodology expert, will independently conduct this review to minimize study selection bias; these reviewers will compare and discuss the results for consensus on the exclusion of studies after the first stage of review. Only studies and documents where both reviewers agree as clearly irrelevant to the search will be excluded from the search to maximize the study sensitivity. As the off-label recommendations might not have abstracts, they will be automatically included in the full-text screening.

In the second stage, the same two reviewers will independently review the full text of the included or uncertain studies and other documents to assess the study/document type, exposure, and outcomes. After a few reviews in the beginning, the two reviewers will meet just to calibrate inclusion/exclusion. Disagreements, if any, on inclusion/exclusion will be resolved through discussion after the second stage is completed. A third reviewer will arbitrate if a consensus cannot be reached about a given paper.

After the second stage of the review is completed, the reference lists of documents that are selected will be manually searched to check for articles or documents that were not identified initially. The reviewers will meet to compare results and to reach a consensus.

The scoping review methodology does not require an evaluation of the quality of studies. However, the quality of evidence is deemed to have been assessed when they were used in the development of recommendations. A report of this assessment is included in the stated objectives of this review and in the identification and summary of evidence.

The study and review processes will be presented in a PRISMA flowchart,[31] and reasons for exclusion will be provided in the final review report.

Extraction: charting the results

Data extraction from any type of evidence and research methodology and without being restricted to qualitative studies will be independently undertaken by the two reviewers. Data from all selected vaccine monographs will be extracted. However, for vaccines that have not been subject to off-label recommendations, there will be no data extraction of the evidence and they will not be considered for the rest of the review.

Before conducting a complete extraction, a pilot test will be undertaken with a random sample of studies to assess the quality and the consistency of the data collection by the reviewers and to familiarize themselves with the source of the results. Then, each reviewer will independently extract data by using the same checklist (Table 2) and will not be blinded to the authors of the

study/document. The reviewers will meet after data extraction for verification purposes: methods, text discrepancy, or missing information.

A draft charting table was developed to collect the relevant data items from the source and will be refined and continually updated at the review stage.

Table 2: Data extraction sheet

Licensure data:	Recommendations:	Evidence:
Monography Vaccine preventable disease: **Identification** • Trade name of vaccine • Abbreviation • Manufacturer • licensure date • date of implementation in a vaccination program • country of licensure **Typology** • therapeutic indication • posology, doses, number of shots in routine series • approved ages • specific population group**s,** sex • method of administration **Composition** • antigen • adjuvant • protein • other components • live or attenuated vaccine • bacteria, virus, toxoid, protozoan • wild strain or not, number of strains	**Committee identification** Name of the expert committee Country of the Committee NITAG member Yes/No **Recommendation** Title of the recommendation Date of publication of the recommendation Name of journal of publication, or not Implementation in an immunization program: Yes/No **Discussion structure** Use of a framework Yes/No Name of the framework Use of Theoretical concept Yes/No Name of the concept Use of a standard operation procedure Yes/No Name of the SOP **Decision elements, approach used** A. GRADE[536] ▪ GRADE Summary table available Yes/No ▪ Policy question - PICO ▪ Desirable effects ▪ Undesirable effects ▪ Desirable effects outweigh the undesirable effects ▪ Outcomes of interest (critical, important etc.) ▪ Number of studies per outcome ▪ Evidence retrieval / Exclusion criteria <u>Rating the quality of evidence</u> (each study): • Design (RCTs, Observational) • Risk of bias	<u>Qualitative information</u> **Study / document Information:** Authors Title of publication Year of Publication Type of document: ▪ Peer review literature ▪ Unpublished data ▪ Expert opinion ▪ Epidemiological data ▪ Article ▪ Other Journal name Study Design Aims/purpose Study period Country(s) in which it took place Calendar years in follow up period Conflicts of Interest declared by authors **Population under study:** Initial sample size recruited, N, records numbers, • N and % Males • N and % Females Age range Average age Sample size with full follow up data available • N and % Males • N and % Females Age range Average age Medical Comorbidities or Immunosuppressed condition (complete list if different) • HIV/AIDS; • Sickle cell disease, • Nephrotic syndrome, • Asplenia, • Cancer • Asthma

[5] Grading of Recommendations Assessment, Development and Evaluation (GRADE)

Contraindication • population • sex • age group • fertility, pregnancy and lactation **Immunogenicity** • serological threshold • antibody level **Other information →** accessible written evidence • vaccine updates • others	• Inconsistency • Indirectness • imprecision • Evidence type / level • Efficacy • Effectiveness • Impact • Number Needed to Vaccinate The final recommendation: B. ETR[6] • Evidence tables available Yes/No • Question - PICO • Background <u>Evidence for the following factors</u>: ▪ Statement of problem (for each criteria) ▪ Benefits & harms (for each criteria) ▪ Values and preferences of target population (for each criteria) ▪ Acceptability to stakeholders ▪ Resource use ▪ Feasibility ▪ Balance of consequences ▪ Type of recommendations ▪ Recommendation Additional considerations C. Other approach List the items evaluated	• COPD • Diabetes • Thyroid disorders • IBD Lifestyle factors: • Exposure to tobacco smoke. • Overweight • Malnutrition • Day care attendance • Lack of breastfeeding **Off-label Vaccine Intervention (Exposure):** Name of vaccine Quantity of type of strains protected against Dose per shot Number & timing of doses Measurement instrument/method, specific Calendar years intervention measured Immunization schedule Group of the population Off-label characteristics **Outcome Measure:** Immunogenicity serological threshold antibody levels Vaccine effectiveness (endpoint measure) Vaccine impact Vaccine safety Immunologic non-inferiority (indicate δ) Incidence of the disease Clinical criteria used for the disease Method of disease measurement/diagnosis **Methods:** Population description (inclusion/exclusion) Randomization process for RCTs (RCTs) Assessment of exposure status (cohort) Age groups: N, % in each • <2; • 2-5; • 5-12; • 12-18; Sex (N, % F - N, % M) Immunodepression Prior vaccination Vaccination interval different for intervention vs control arm

[6] Evidence to recommendations (EtR) framework

		Quantitative information (for studies) **Effect measures (yes/no)** OR, RR or HR rates n/N Standard deviation Confidence interval Variance Adjusted/unadjusted

Synthesis of the results

The main objective of this review is to synthesize the knowledge on the off-label use of vaccines in a novel initial assessment process. A deductive thematic data analysis will be conducted.

First, the review will commence with a perusal of the vaccine product monographs by presenting information on each vaccine at licensure, which is the study baseline. Then, the review will follow with a case-based analysis for each vaccine by describing the decision process for the initial off-label use of the vaccine and what methods were used; subsequently, off-label vaccine typology and vaccinated typology will be performed on the basis of published recommendations.

The synthesis of data from vaccine off-label recommendations will be either in narrative or tabulated form. For each vaccine, the elements of the decision used to develop the recommendation will be identified: priority questions, research evidence, important factors of evidence appraisal, benefits and harms, costs, feasibility, acceptability, values and preferences of clients or healthcare providers, and judgments about criterion or option. A concise summary of pivotal elements that led to the final option will be presented.

In the primary analysis, the study will stratify results by population in accordance with new risk groups with underlying conditions and the healthy population. At the second level, the review will stratify identified papers by study design or type of document, change of schedule, sex, special populations, number of doses, and time of introduction in the vaccination schedule. This analysis will examine the diversity and the possibility of clustering the elements. If any summary or effect measure is assessed and reported in a study, the synthesis will sum up the types of measures that were used and briefly discuss them. When comparing studies, RCTs and observational data will be analyzed separately.

Off-label vaccines will be pooled by characteristics: changes in the number of doses in their “exposure” arm, in the population, in the administration route, or in the indication, followed by pooling by the study design and the type of vaccine. Furthermore, the study will report whether the effect measures documented in studies were from the same calendar time (i.e., that the reference group received their vaccinations and were followed during the same calendar time period as the off-label groups).

If the data extracted from the included papers permit diagrammatic presentation, the results will be presented in a dendrogram format that relates to the objectives and question of the review. The results will be clustered by similar evidence, and a narrative description of the data will be presented for the:

- similarity of study population
- similarity of outcome measures
- similarity of evidence grade
- theoretical concept/no model

- similarity of methodology
- implementation/no implementation

Dissemination and Consultation

The results will be disseminated through (1) peer-reviewed articles; (2) at conferences. The relevant findings will guide the conceptualization of (3) an analytical framework for off-label vaccines that will also be submitted to a peer-reviewed journal. There will be a global consultation in the form of (4) a survey where the findings of the review will form the basis of the questionnaire and will be validated across stakeholder, policymaker, and public health actors in the second phase of the research plan. Iterative consultations are ongoing within the review team.

CONCLUSION

We present the protocol for a scoping review on the off-label use of vaccines in public programs, together with an in-depth review of the evidence and concepts from a novel initial analysis of off-label recommendations to identify the findings which are key to decision-making in off-label vaccination. To the best of our knowledge, this is the first review to undertake a comprehensive review on the off-label use of vaccines. This study will strengthen the knowledge base of vaccine assessment processes, which are central to the development of novel initial off-label use. Moreover, the mapping of published recommendations will provide an understanding of the extent of off-label vaccine use globally, and on how they facilitate the planning of immunization programs. The results of this review will enlighten and support researchers, public health actors, and policymakers globally by providing a clear definition of the off-label use of vaccines and guide the conceptualization of an analytical framework that will be used for the assessment of evidence in the development of future recommendations for the off-label use of vaccines in public programs. Furthermore, we anticipate that the findings of this scoping review will inspire research into the off-label use of agents beyond vaccination, where off-label indications play a considerable role.

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Author Contributions
DD (PhD candidate) participated in conceptualization of the project, researched and developed all aspects of the project methodology, design and manuscript, and approved the final version as submitted. CQ (research director) participated in conceptualization of the project, critically reviewed and commented on the whole manuscript, and approved the final version of the protocol.

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SUPPLEMENTAL MATERIAL

Table 3: Search terms and strategy

Concept	Search terms	PubMed Search strategy_	MEDLINE Search Strategy[1]	EMBASE Search strategy[2]
Exposure wide	Off-label use Appropriate indication Drug administration Drug prescription Drug utilization Drug approval Drug without guideline Dose-response relationship Dose sparing Fda non approved Fractional dose Immunization schedule improper inappropriate indication use Licensure Label labeled Labelling license licensed non evidence based outside prescribed Product monograph Reduced dose registered schedule unapproved unlabeled unlicensed used proper	((("Off-Label Use"[Mesh]] OR (off[tiab] AND (label[tiab] OR labelling[tiab]) OR [illegible] [TIAB] OR "Unlabeled indication"[TIAB] OR "Unlabeled indications" [TIAB] OR "fractional dose"[TIAB] OR "fractional doses" [TIAB] OR "reduced [illegible][TIAB] OR "Unlabeled indications" [TIAB] OR "dose sparing" [TIAB])) OR (Off-label use[MH] OR ((off[TIAB] AND label[TIAB]) OR "Off label use"[TIAB] OR Unapprove*[TIAB] OR unlicense*[TIAB] OR (label[TIAB] AND indication*[TIAB]) OR (((no* licensed[TIAB] OR no* licenced[TIAB]) NOT (now licensed[TIAB] AND now licenced[TIAB]) AND use*[TIAB]) OR ((appropriate*[TIAB] AND prescri*[TIAB]) and indication[TIAB]) OR Off lisense[TIAB] OR Off license[TIAB] OR Off lisence[TIAB] OR Off licence[TIAB] OR nonapprove*[TIAB] OR unlabel* us*[TIAB] OR ((inappropriate us*[TIAB] AND indication[TIAB]) NOT (antibiotic*[TIAB] OR antimicrobial[TIAB])) OR unlabel* indication*[TIAB] OR inappropriate indication*[TIAB] OR labeled indication*[TIAB] OR (outside[TIAB] AND (licence*[TIAB] OR license*[TIAB])) OR registered	((off adj2 label).af. OR "Off label us*".af. OR Unapprove*.af. OR unlicense*.af. OR (label adj3 indication*).af. OR ((no* licen?ed for adj3 use*) not now licen?ed).af. OR ((appropriate* adj3 prescri*) and indication).af. OR Off li?en?e.af. OR nonapprove*.af. OR unlabel* us*.af. OR ((inappropriate us* and indication) not (antibiotic* or antimicrobial)).af. OR unlabel* indication*.af. OR inappropriate indication*.af. OR labeled indication*.af. OR (outside adj2 licen?e*).af. OR registered indication*.af. OR (out* adj4 licen?ed indication*).af. OR non fda approve*.af. OR ((no* licen?ed for adj3 indication*) not now licen?ed).af. OR (us* without adj2 indication*).af. OR (appropriate indication adj3 us*).af. OR non evidence base* us*.af. OR (improper adj1 indication*).af. OR (be???d* adj2 licen?ed indication*).af. OR out of label.af. OR without proper indication*.af. OR (prescri* outside adj4 guideline*).af. OR no* appropriate indication*.af. OR (drug* without adj2 indication*).af. OR (medication adj2 without adj2 indication*).af.) OR off label*.ab,ti.	(off label*.af. OR (off adj1 label).mp. OR (drug adj2 label adj2 us*).af. OR unlicense*.af. OR unapprove*.af. OR (label adj3 indication*).af. OR off li?en?e*.af. OR ((no* licen?ed for adj3 use*) not now licen?ed).af. OR ((inappropriate us* and indication) not (antibiotic* or antimicrobial)).af. OR ((appropriate* adj3 prescri*) and indication).af. OR (outside adj3 licen?e*).af. OR unlabel* us*.af. OR labeled indication*.af. OR (inappropriate indication*).af. OR nonapprove*.af. OR registered indication*.af. OR offlabel*.af. OR (out* adj4 licen?ed indication*).af. OR (unlabel* adj3 indication*).af. OR non fda approve*.af. OR ((no* licen?ed for adj3 indication*) not now licen?ed).af. OR (appropriate indication adj3 us*).af. OR (be???d* adj2 licen?ed indication*).af. OR (us* without adj2 indication*).af. OR (prescri* outside adj4 guideline*).af. OR (out of label).af. OR (improper adj1 indication*).af. OR (inappropriate adj5 indication adj2 us*).af. OR no* appropriate indication*.af. OR (non evidence base* us*).af. OR without proper indication*.af.) OR (drug* without adj2 indication*).af.

		indication*[TIAB] OR (out*[TIAB] AND (licenced indication*[TIAB] OR licensed indication*[TIAB])) OR non fda approve*[TIAB] OR (((no* licenced for[TIAB] OR no* licensed for[TIAB]) NOT (now licensed[TIAB] OR now licenced[TIAB])) AND indication*[TIAB]) OR (us* without[TIAB] AND indication*[TIAB]) OR (appropriate indication[TIAB] AND us*[TIAB]) OR non evidence base* us*[TIAB] OR (improper[TIAB] AND indication*[TIAB]) OR ((beyond [TIAB] OR beside*[TIAB]) AND (licensed indication*[TIAB] OR licenced indication*[TIAB])) OR out of label[TIAB] OR without proper indication*[TIAB] OR (prescri* outside[TIAB] AND guideline*[TIAB]) OR no* appropriate indication*[TIAB] OR (drug* without[TIAB] AND indication*[TIAB]) OR ((medication[TIAB] AND without[TIAB]) AND indication*[TIAB])) OR off label*[TIAB]))		
		PubMed	MEDLINE	EMBASE
Exposure specific	Cholera vaccine Dengue vaccine Diphtheria vaccine HAV vaccine HBV vaccine HEV vaccine Hib vaccine HPV vaccine	(("Cholera Vaccines"[Mesh] OR ((cholera OR cholerae) AND (vaccine OR vaccines))) OR ("Dengue Vaccines"[Mesh] OR ((breakbone OR break-bone OR dengues OR dengue) AND (vaccine OR vaccines))) OR	(Cholera Vaccines or ((cholera or cholerae) and (vaccine or vaccines))).af. OR (Dengue Vaccines or ((breakbone or break-bone or dengues or dengue) and (vaccine or vaccines))).af. OR (Diphtheria Toxoid or Diphtheria-Tetanus Vaccine or ((Diphtheria or	(Cholera Vaccines or ((cholera or cholerae) and (vaccine or vaccines))).af. OR (Dengue Vaccines or ((breakbone or break-bone or dengues or dengue) and (vaccine or vaccines))).af. OR (Diphtheria Toxoid or Diphtheria-Tetanus Vaccine or ((Diphtheria or

	Influenza vaccine Japanese encephalitis vaccine Malaria vaccine Measles vaccine Meningococcal meningitis vaccine Mumps vaccine Pertussis vaccine Pneumococcal vaccine Poliovirus vaccine Rabies vaccine Rotavirus vaccine Rubella vaccine Tetanus vaccine Tick-borne encephalitis vaccine Tuberculosis vaccine Typhoid vaccine Varicella vaccine Yellow Fever vaccine Pandemic vaccine Epidemic vaccine Shortage vaccination	(("Diphtheria Toxoid"[Mesh] OR "Diphtheria-Tetanus Vaccine"[Mesh]) OR ((Diphtheria OR diphtheriae OR DT) AND (vaccine OR vaccines))) OR [illegible] A Vaccines"[Mesh] OR ("Viral Hepatitis Vaccines"[Mesh] AND [illegible] A"[Mesh]) OR [illegible] vaccines"[Mesh] AND [illegible] A"[Mesh]) OR twinrix OR ((Hepatitis A OR HAV) AND (vaccine OR vaccines)) OR ((Hepatitis Viral Human OR Hepatitis Viruses) AND (hepatitis A) AND (vaccine OR vaccines)) OR [illegible] B Vaccines"[Mesh] OR ("Viral Hepatitis Vaccines"[Mesh] AND [illegible] B"[Mesh]) OR [illegible] vaccines"[Mesh] AND [illegible] B"[Mesh]) OR twinrix OR ((Hepatitis B OR HBV) AND (vaccine OR vaccines)) OR ((Hepatitis Viral Human OR Hepatitis Viruses) AND (hepatitis B) AND (vaccine OR vaccines)) OR ((Viral Hepatitis Vaccines AND [illegible] E"[Mesh]) OR [illegible] vaccines"[Mesh] AND [illegible] E"[Mesh]) OR ((Hepatitis E virus OR Hepatitis E OR HEV) AND (vaccine OR vaccines)) OR ((RNA Virus Infections OR Hepatitis Viral Human OR Hepatitis Viruses) AND (hepatitis E) AND (vaccine OR vaccines)) OR ("Haemophilus influenzae type b polysaccharide vaccine" [Supplementary Concept] OR ((hib	diphtheriae or DT) and (vaccine or vaccines))).af. OR (Hepatitis A Vaccines OR (Viral Hepatitis Vaccines AND Hepatitis A) OR (viral vaccines AND Hepatitis A) OR twinrix OR ((Hepatitis A OR HAV) AND (vaccine OR vaccines)) OR ((Hepatitis Viral Human OR Hepatitis Viruses) AND (hepatitis A) AND (vaccine OR vaccines))).af. OR (Hepatitis B Vaccines OR (Viral Hepatitis Vaccines AND Hepatitis B) OR (viral vaccines AND Hepatitis B) OR twinrix OR ((Hepatitis B OR HBV) AND (vaccine OR vaccines)) OR ((Hepatitis Viral Human OR Hepatitis Viruses) AND (hepatitis B) AND (vaccine OR vaccines))).af. (Hepatitis E vaccines or (Viral Hepatitis Vaccines and Hepatitis E) or (viral vaccines and Hepatitis E) or ((Hepatitis E virus or Hepatitis E or HEV) and (vaccine or vaccines)) or ((RNA Virus Infections or Hepatitis Viral Human or Hepatitis Viruses) and hepatitis E and (vaccine or vaccines))).af. OR (Haemophilus influenzae type b polysaccharide vaccine OR ((Haemophilus influenzae type b OR hib OR "Haemophilus influenzae") AND (vaccine OR vaccines))).af. OR (Papillomavirus Vaccines or ((hpv or Papillomavirus or Papilloma virus) and (vaccine or vaccines))).af. OR (Influenza Vaccines or ((flu or influenza or Influenza virus or LAIV) and (vaccine or vaccines))).af. OR	diphtheriae or DT) and (vaccine or vaccines))).af. OR (Hepatitis A Vaccines OR (Viral Hepatitis Vaccines AND Hepatitis A) OR (viral vaccines AND Hepatitis A) OR twinrix OR ((Hepatitis A OR HAV) AND (vaccine OR vaccines)) OR ((Hepatitis Viral Human OR Hepatitis Viruses) AND (hepatitis A) AND (vaccine OR vaccines))).af. OR (Hepatitis B Vaccines OR (Viral Hepatitis Vaccines AND Hepatitis B) OR (viral vaccines AND Hepatitis B) OR twinrix OR ((Hepatitis B OR HBV) AND (vaccine OR vaccines)) OR ((Hepatitis Viral Human OR Hepatitis Viruses) AND (hepatitis B) AND (vaccine OR vaccines))).af. (Hepatitis E vaccines or (Viral Hepatitis Vaccines and Hepatitis E) or (viral vaccines and Hepatitis E) or ((Hepatitis E virus or Hepatitis E or HEV) and (vaccine or vaccines)) or ((RNA Virus Infections or Hepatitis Viral Human or Hepatitis Viruses) and hepatitis E and (vaccine or vaccines))).af. OR (Haemophilus influenzae type b polysaccharide vaccine OR ((Haemophilus influenzae type b OR hib OR "Haemophilus influenzae") AND (vaccine OR vaccines))).af. OR (Papillomavirus Vaccines or ((hpv or Papillomavirus or Papilloma virus) and (vaccine or vaccines))).af. OR (Influenza Vaccines or ((flu or influenza or Influenza virus or LAIV) and (vaccine or vaccines))).af. OR

		OR "Haemophilus influenzae") AND (vaccine OR vaccines))) OR ("Papillomavirus Vaccines"[Mesh] OR ((hpv[tiab] OR Papillomavirus[tiab] OR Papilloma virus[tiab]) AND (vaccine OR vaccines))) OR ("Influenza Vaccines"[Mesh] OR ((flu OR influenza OR Influenza virus OR LAIV) AND (vaccine OR vaccines))) OR ("Japanese Encephalitis Vaccines"[Mesh] OR ((Japanese Encephalitis) AND (vaccine OR vaccines))) OR ("Malaria Vaccines"[Mesh]OR ((malarial OR malaria OR Remittent Fever OR Plasmodium Infection OR Marsh Fever OR Plasmodium Infections OR paludism) AND (vaccine OR vaccines))) OR ("Measles Vaccine"[Mesh]OR ((MMR OR rubeola OR morbilli OR Triviraten OR Priorix OR Trimovax OR Pluserix OR Virivac) AND (vaccine OR vaccines))) OR ("Meningococcal Vaccines"[Mesh] OR (Meningococcal Meningitis AND (vaccine OR vaccines))) OR ("Mumps Vaccine"[Mesh] OR -Mumps-Rubella Vaccine"[Mesh] OR ((mumps OR Parotitis OR Parotitides OR Measles-Mumps-Rubella) AND (vaccine OR vaccines))) OR ("Pertussis Vaccine"[Mesh] OR "Diphtheria-Tetanus-Pertussis Vaccine"[Mesh] OR "Diphtheria-Tetanus-acellular Pertussis	(Japanese Encephalitis Vaccines or (Japanese Encephalitis and (vaccine or vaccines))).af. OR (Malaria Vaccines or ((malarial or malaria or Remittent Fever or Plasmodium Infection or Marsh Fever or Plasmodium Infections or paludism or Plasmodium falciparum) and (vaccine or vaccines))).af. OR ((Measles and (Vaccine or vaccines)) or ((MMR or rubeola or morbilli or Triviraten or Priorix or Trimovax or Pluserix or Virivac) and (vaccine or vaccines))).af. OR ((Meningococcal or Meningococcal Meningitis) and (vaccine or vaccines)).af. OR (Mumps Vaccine or Measles-Mumps-Rubella Vaccine OR ((mumps or Measles-Mumps-Rubella or Parotitis or Parotitides) and (vaccine or vaccines))).af. OR (Pertussis Vaccine or Diphtheria-Tetanus-Pertussis Vaccine or Diphtheria-Tetanus-acellular Pertussis Vaccines or ((DTaP or ACEL IMUNE Tripedia or ACELIMUNE or Infanrix or dtwp or DPT or Di Te Per or Pertussis or Whooping Cough or bordetella) and (vaccine or vaccines))).af. OR (Pneumococcal Vaccines or ((Pneumococcal or Pnu Imune or PnuImune or Pneumovax or PncOMPC or PNCRM7 or PCV7 or PCV13 or PCV10 or Prevenar or Prevnar or Pneumococcal	(Japanese Encephalitis Vaccines or (Japanese Encephalitis and (vaccine or vaccines))).af. OR (Malaria Vaccines or ((malarial or malaria or Remittent Fever or Plasmodium Infection or Marsh Fever or Plasmodium Infections or paludism or Plasmodium falciparum) and (vaccine or vaccines))).af. OR ((Measles and (Vaccine or vaccines)) or ((MMR or rubeola or morbilli or Triviraten or Priorix or Trimovax or Pluserix or Virivac) and (vaccine or vaccines))).af. OR ((Meningococcal or Meningococcal Meningitis) and (vaccine or vaccines)).af. OR (Mumps Vaccine or Measles-Mumps-Rubella Vaccine OR ((mumps or Measles-Mumps-Rubella or Parotitis or Parotitides) and (vaccine or vaccines))).af. OR (Pertussis Vaccine or Diphtheria-Tetanus-Pertussis Vaccine or Diphtheria-Tetanus-acellular Pertussis Vaccines or ((DTaP or ACEL IMUNE Tripedia or ACELIMUNE or Infanrix or dtwp or DPT or Di Te Per or Pertussis or Whooping Cough or bordetella) and (vaccine or vaccines))).af. OR (Pneumococcal Vaccines or ((Pneumococcal or Pnu Imune or PnuImune or Pneumovax or PncOMPC or PNCRM7 or PCV7 or PCV13 or PCV10 or Prevenar or Prevnar or Pneumococcal

		Vaccines"[Mesh] OR ((DTaP OR ACEL IMUNE Tripedia OR ACELIMUNE OR Infanrix OR dtwp OR DPT OR Di Te Per OR Pertussis or Whooping Cough or bordetella) AND (vaccine OR vaccines))) OR ("Pneumococcal Vaccines"[Mesh] OR ((Pneumococcal OR Pnu Imune OR PnuImune OR Pneumovax OR PncOMPC OR PNCRM7 OR PCV7 OR PCV13 OR PCV10 OR Prevenar OR Prevnar or Pneumococcal Polysaccharide) AND (vaccine OR vaccines))) OR ("Poliovirus Vaccines"[Mesh] OR ((Poliomyelitis or poliovirus OR Salk OR sabin OR Brunhilde OR Lansing OR Leon OR Polioviruses) AND (vaccine OR vaccines))) OR ("Rabies Vaccines"[Mesh]OR ((rabies OR lyssa OR lyssas or rabies virus) AND (vaccine OR vaccines))) OR ("Rotavirus Vaccines"[Mesh] OR ((rotavirus) AND (vaccine OR vaccines))) OR ("Rubella Vaccine"[Mesh]OR ((Rubela OR rubelas or Rubella virus) AND (vaccine OR vaccines))) OR ("Tetanus Toxoid"[Mesh] OR ((tetatus OR tetani) AND (vaccine OR vaccines))) OR ("Encephalitis, Tick-Borne"[Mesh] OR (enchephalitis AND (tick borne OR Russian Spring-Summer OR Far Eastern Russian OR Louping OR Powassan OR Central European) AND (vaccine OR vaccines))) OR	Polysaccharide) and (vaccine or vaccines))).af. OR (Poliovirus Vaccines or ((Poliomyelitis or poliovirus or Salk or sabin or Brunhilde or Lansing or Leon or Polioviruses) and (vaccine or vaccines)).af. OR (Rabies Vaccines or ((rabies or lyssa or lyssas or rabies virus) and (vaccine or vaccines))).af. OR (Rotavirus Vaccines or (rotavirus and (vaccine or vaccines))).af. OR (Rubella Vaccine or ((rubellas or Rubela or rubelas or Rubella virus) and (vaccine or vaccines))).af. OR (Tetanus Toxoid or ((tetatus or tetani) and (vaccine or vaccines))).af. OR (Encephalitis, Tick-Borne or (encephalitis and (tick borne or Russian Spring-Summer or Far Eastern Russian or Louping or Powassan or Central European) and (vaccine or vaccines))).af. OR (Tuberculosis Vaccines or ((tuberculosis or bcg or Calmette* or Kochs) and (vaccine or vaccines))).af. OR (typhoid vaccine or Ty21a typhoid vaccine or Typhoid-Paratyphoid Vaccines or ((typhoid or Paratyphoid or enteric or typhus or typhi or Typhoids or M01ZH09 or Typhoid fever) and (vaccine or vaccines))).af. OR ((varicella or Chickenpox or varivax) and (vaccine or vaccines)).af.OR	Polysaccharide) and (vaccine or vaccines))).af. OR (Poliovirus Vaccines or ((Poliomyelitis or poliovirus or Salk or sabin or Brunhilde or Lansing or Leon or Polioviruses) and (vaccine or vaccines)).af. OR (Rabies Vaccines or ((rabies or lyssa or lyssas or rabies virus) and (vaccine or vaccines))).af. OR (Rotavirus Vaccines or (rotavirus and (vaccine or vaccines))).af. OR (Rubella Vaccine or ((rubellas or Rubela or rubelas or Rubella virus) and (vaccine or vaccines))).af. OR (Tetanus Toxoid or ((tetatus or tetani) and (vaccine or vaccines))).af. OR (Encephalitis, Tick-Borne or (encephalitis and (tick borne or Russian Spring-Summer or Far Eastern Russian or Louping or Powassan or Central European) and (vaccine or vaccines))).af. OR (Tuberculosis Vaccines or ((tuberculosis or bcg or Calmette* or Kochs) and (vaccine or vaccines))).af. OR (typhoid vaccine or Ty21a typhoid vaccine or Typhoid-Paratyphoid Vaccines or ((typhoid or Paratyphoid or enteric or typhus or typhi or Typhoids or M01ZH09 or Typhoid fever) and (vaccine or vaccines))).af. OR ((varicella or Chickenpox or varivax) and (vaccine or vaccines)).af.OR

		("Tuberculosis Vaccines"[Mesh] or ((tuberculosis or bcg or Calmette* OR Kochs) AND (vaccine OR vaccines))) OR ("typhoid vaccine M01ZH09" [Supplementary Concept] OR "Ty21a typhoid vaccine" [Supplementary Concept] OR "Typhoid-Paratyphoid Vaccines"[Mesh] OR ((typhoid OR Paratyphoid OR enteric OR typhus OR typhi OR Typhoids) AND (vaccine OR vaccines))) OR ("measles, mumps, rubella, varicella vaccine" [Supplementary Concept] OR "Chickenpox Vaccine"[Mesh] OR ((varicella OR Chickenpox OR varivax) AND (vaccine OR vaccines))) OR ("Yellow Fever Vaccine"[Mesh] OR ((yellow fever) AND (vaccine OR vaccines))) OR [illegible] vaccines or vaccination)) OR Shortage vaccination)	((Yellow Fever or yellow fever virus) and (vaccine or vaccines)).af. OR ((pandemics or epidemics) and (vaccine or vaccines or vaccination)).af. OR (Shortage vaccination).af.	((Yellow Fever or yellow fever virus) and (vaccine or vaccines)).af. OR ((pandemics or epidemics) and (vaccine or vaccines or vaccination)).af. OR (Shortage vaccination).af.

1. Mesgarpour B, Muller M, Herkner H. Search strategies-identified reports on "off-label" drug use in MEDLINE. *J Clin Epidemiol* 2012;65(8):827-34. doi: 10.1016/j.jclinepi.2012.01.020 [published Online First: 2012/06/26]
2. Mesgarpour B, Müller M, Herkner H [illegible] *BMC Med Res Methodol* 2012;12(1):[illegible]. doi: 10.1186/1471-2288-12-190

OvidSP MEDLINE Off-label High Sensitivity Search Strategy

1. (off adj2 label).af.
2. "Off label us*".af.
3. Unapprove*.af.
4. unlicense*.af.
5. (label adj3 indication*).af.
6. ((no* licen?ed for adj3 use*) not now licen?ed).af.
7. ((appropriate* adj3 prescri*) and indication).af.
8. Off li?en?e.af.
9. nonapprove*.af.
10. unlabel* us*.af.
11. ((inappropriate us* and indication) not (antibiotic* or antimicrobial)).af.
12. unlabel* indication*.af.
13. inappropriate indication*.af.
14. labeled indication*.af.
15. (outside adj2 licen?e*).af.
16. registered indication*.af.
17. (out* adj4 licen?ed indication*).af.
18. non fda approve*.af.
19. ((no* licen?ed for adj3 indication*) not now licen?ed).af.
20. (us* without adj2 indication*).af.
21. (appropriate indication adj3 us*).af.
22. non evidence base* us*.af.
23. (improper adj1 indication*).af.
24. (be???d* adj2 licen?ed indication*).af.
25. out of label.af.
26. without proper indication*.af.
27. (prescri* outside adj4 guideline*).af.
28. no* appropriate indication*.af.
29. (drug* without adj2 indication*).af.
30. (medication adj2 without adj2 indication*).af.
31. 1 or 2 or 3 or 4 or 5 or 6 or 7 or 8 or 9 or 10 or 11 or 12 or 13 or 14 or 15 or 16 or 17 or 18 or 19 or 20 or 21 or 22 or 23 or 24 or 25 or 26 or 27 or 28 or 29 or 30
32. off label*.ab,ti.
33. 31 or 32

APPENDIX

SECTION	ITEM	PRISMA-ScR CHECKLIST ITEM	REPORTED ON PAGE #
TITLE			
Title	1	Identify the report as a scoping review.	1
ABSTRACT			
Structured summary	2	Provide a structured summary that includes (as applicable): background, objectives, eligibility criteria, sources of evidence, charting methods, results, and conclusions that relate to the review questions and objectives.	2
INTRODUCTION			
Rationale	3	Describe the rationale for the review in the context of what is already known. Explain why the review questions/objectives lend themselves to a scoping review approach.	4-5
Objectives	4	Provide an explicit statement of the questions and objectives being addressed with reference to their key elements (e.g., population or participants, concepts, and context) or other relevant key elements used to conceptualize the review questions and/or objectives.	6
METHODS			
Protocol and registration	5	Indicate whether a review protocol exists; state if and where it can be accessed (e.g., a Web address); and if available, provide registration information, including the registration number.	6
Eligibility criteria	6	Specify characteristics of the sources of evidence used as eligibility criteria (e.g., years considered, language, and publication status), and provide a rationale.	7-8
Information sources	7	Describe all information sources in the search (e.g., databases with dates of coverage and contact with authors to identify additional sources), as well as the date the most recent search was executed.	9
Search	8	Present the full electronic search strategy for at least 1 database, including any limits used, such that it could be repeated.	8
Selection of sources of evidence	9	State the process for selecting sources of evidence (i.e., screening and eligibility) included in the scoping review.	9-10
Data charting process	10	Describe the methods of charting data from the included sources of evidence (e.g., calibrated forms or forms that have been tested by the team before their use, and whether data charting was done independently or in duplicate) and any processes for obtaining and confirming data from investigators.	10
Data items	11	List and define all variables for which data were sought and any assumptions and simplifications made.	11-12
Critical appraisal of individual sources of evidence	12	If done, provide a rationale for conducting a critical appraisal of included sources of evidence; describe the methods used and how this information was used in any data synthesis (if appropriate).	n/a
Synthesis of results	13	Describe the methods of handling and summarizing the data that were charted.	13

SECTION	ITEM	PRISMA-ScR CHECKLIST ITEM	REPORTED ON PAGE #
RESULTS			
Selection of sources of evidence	14	Give numbers of sources of evidence screened, assessed for eligibility, and included in the review, with reasons for exclusions at each stage, ideally using a flow diagram.	n/a
Characteristics of sources of evidence	15	For each source of evidence, present characteristics for which data were charted and provide the citations.	n/a
Critical appraisal within sources of evidence	16	If done, present data on critical appraisal of included sources of evidence (see item 12).	n/a
Results of individual sources of evidence	17	For each included source of evidence, present the relevant data that were charted that relate to the review questions and objectives.	n/a
Synthesis of results	18	Summarize and/or present the charting results as they relate to the review questions and objectives.	n/a
DISCUSSION			
Summary of evidence	19	Summarize the main results (including an overview of concepts, themes, and types of evidence available), link to the review questions and objectives, and consider the relevance to key groups.	n/a
Limitations	20	Discuss the limitations of the scoping review process.	3
Conclusions	21	Provide a general interpretation of the results with respect to the review questions and objectives, as well as potential implications and/or next steps.	14
FUNDING			
Funding	22	Describe sources of funding for the included sources of evidence, as well as sources of funding for the scoping review. Describe the role of the funders of the scoping review.	15

BMJ Open

EVALUATION OF THE DECISION-MAKING PROCESS UNDERLYING THE INITIAL OFF-LABEL USE OF VACCINES: A SCOPING REVIEW PROTOCOL

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Primary Subject Heading:	Public health
Secondary Subject Heading:	Evidence based practice
Keywords:	PUBLIC HEALTH, IMMUNOLOGY, INFECTIOUS DISEASES

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TITLE PAGE

Title of the article: Evaluation of the decision-making process underlying the initial off-label use of vaccines: a scoping review protocol

Corresponding author: Caroline Quach
Centre Hospitalier Universitaire Sainte-Justine, 3175 ch. Côte-Sainte-Catherine – B17.102, Montréal, Québec, Canada H3T 1C5. E-mail address: c.quach@umontreal.ca

Co-authors:
Dieynaba Diallo,[a,b,c] MScPH. ORCID iD : https://orcid.org/0000-0002-3650-5815
Centre Hospitalier Universitaire Sainte-Justine, 3175 ch. Côte-Sainte-Catherine – B17.003.14, Montréal, Québec, Canada H3T 1C5.
E-mail address: Dieynaba.diallo@umontreal.ca; Phone number:+1 438.827.4630

Caroline Quach,[a,b,d] MD, MSc. ORCID iD : https://orcid.org/0000-0002-1170-9475
Centre Hospitalier Universitaire Sainte-Justine, 3175 ch. Côte-Sainte-Catherine – B.17.102, Montréal, Québec Canada H3T 1C5.
Email address: c.quach@umontreal.ca; Phone number: +1 514.345.4931 #7430

a. Department of Microbiology, Infectious Diseases, and Immunology, Faculty of Medicine, University of Montreal, Montreal, Canada.
b. Research Institute – CHU Sainte-Justine, Montreal, Canada
c. Institut National de Santé Publique du Québec, Québec, Canada
d. Infection Prevention and Control, Department of Clinical Laboratory Medicine, Centre Hospitalier Universitaire Sainte-Justine, Montreal, Canada

Keywords: Off-label, vaccines, public health, decision-making, VPD, Immunization, recommendations.

ABSTRACT

Introduction: Vaccination has become a central part of public health prevention. Vaccines are introduced after licensure by national regulatory authorities, whereas recommendations for use of licensed vaccines are made by national or international advisory committees and may include off-label use. The methodological and decision-making processes that are used to assess novel initial off-label vaccine use are unclear. This review aims to examine the off-label assessment processes to map evidence and concepts used in the decision-making process and present a common approach between all recommendations and specifics of each decision.

Methods and analysis: The methodological framework described at the Joanna Briggs Institute will be applied to this scoping review. A search strategy was developed, in collaboration with an experienced senior health research librarian, by combining Mesgarpour's highly sensitive search strategies. Peer-reviewed and grey literature will be systematically identified using PubMed, Medline, and EMBASE; governmental agency and pharmaceutical websites; and search engines, such as Google Scholar. Reports and studies on off-label vaccine use in public health will be included. Screening will be independently undertaken by two reviewers. Data will be extracted using a standard form. Results will be narratively summarized to highlight relevant findings and guide the development of an analytical framework for off-label vaccination recommendations.

Ethics and dissemination: This research does not require ethical approval. This scoping review will provide decision-making elements and a synthesis of knowledge on vaccines off-label use. Findings will be relevant to decision-makers/advisory committees and public health. These will be disseminated through peer-reviewed articles and conferences.

Words count: 249

Strengths and limitations of this study

►Strengths of this review comprise the substantial significance of mapping the decision-making processes and methods used for off-label vaccine recommendations,

►the use of recognized scoping review methodology,

►a search strategy developed in collaboration with an experienced senior health research librarian,

►systematic screening and extraction of data independently conducted in duplicate.

► Off-label vaccine use established practices, not published in an official form by national authorities, potentially represent a limitation for this review.

INTRODUCTION

Background and rationale

Infectious diseases are the commonest cause of deaths worldwide, killing more than 17 million people a year,[1] although many are preventable or curable diseases. In 2016, lower respiratory infections remained the deadliest communicable disease and were among the top 10 causes of deaths, with diarrhea and tuberculosis, and accounted for a total of 5.7 million deaths worldwide that year[2]: in low-income countries, more than half of all deaths were caused by conditions involving communicable diseases[1]. In Canada, infectious and parasitic diseases were responsible for 1.6% of all deaths in 2018.[3]

In the course of time, numerous vaccines have been developed to prevent diseases. In 2018, 85% of infants worldwide had received three doses of polio vaccine to protect them against poliomyelitis − a highly infectious viral disease that can cause irreversible paralysis.[4] In the same year, an estimated 35% of infants globally were protected against rotaviruses, the commonest cause of severe diarrheal disease among children worldwide. The global coverage of the third dose of the pneumococcal vaccine was estimated at 47% in 2018. Thus, vaccination has become a central part of public health preventive measures against morbidity, disability, and mortality.

The vaccine industry has become highly regulated through licensure.[5] The national regulatory authorities (NRA) license a vaccine after clinical trial data submitted by the manufacturer confirm the vaccine safety and efficacy for its intended use. Every vaccine has specific indications of use that are mentioned when introduced to the market. The vaccine's label provides information, such as the name, formulation, dosage, route of administration, age, indications and usage, and contraindications or other information unique to the vaccine.[6]

After vaccines are licensed, national immunization programs that are implemented by healthcare practitioners and clinicians may include these vaccines and will describe, for each vaccine, the NRA-approved prescribing information.[5] Subsequently, expert technical advisory committees – national or international – will make recommendations based on several additional elements, such as disease epidemiology (e.g., serotype distribution), vaccine effectiveness/efficacy, vaccine impact, cost, supply, or program optimization.[7] Very often, however, recommendations for the use of a licensed vaccine can be for off-label indications,[8] which involves the use of a licensed vaccine on a dosage, schedule, or within a population outside the indications approved by a regulatory body.

The unlabeled use of vaccines (unlicensed) is different from off-label use, which results from recommendations for licensed vaccines and is supported by critically appraised evidence. There are known off-label recommendations that are reported in the literature. For example, at licensure, Prevnar-7 (PnC7 conjugated 7-valent pneumococcal vaccine) was approved in a 3 + 1 schedule. In Canada, the National Advisory Committee on Immunization (NACI) recommended an off-label schedule of 2 + 1 instead of the approved 3 + 1.[9] Another example is REPEVAX (diphtheria and tetanus toxoids, acellular pertussis adsorbed and inactivated poliovirus vaccine), which is not indicated for use during pregnancy because its effect on embryo-fetal development has not been assessed. REPEVAX has not been evaluated in fertility studies.[10] However, no teratogenic effect of vaccines containing diphtheria or tetanus toxoids, or inactivated poliovirus have been observed following use in pregnant women, and there is some post-marketing information on the safety of

[1]Crude death rate per 100 000 population: lower respiratory infection 76; diarrhoeal diseases 58; HIV/AIDS 44.5; Malaria 38; Tuberculosis 34.5.

administering REPEVAX to pregnant women. Therefore, its use for pregnant women in the UK is off-label, but considered the approved summary of product characteristics (SmPC)[2].[11]

RotaTeq® (Rotavirus Vaccine, Live, Oral, Pentavalent) was licensed in February 2006[12 13] by the US Food and Drug Administration (FDA) for the prevention of rotavirus gastroenteritis, caused by types G1, G2, G3, and G4, in infants in the age range of 6–32 weeks, administered as a 3-dose series. In the United States, the Advisory Committee on Immunization Practices (ACIP) recommended routine oral vaccination of infants with 3 doses of this rotavirus vaccine at ages 2, 4, and 6 months.[14] Rotarix™ (Rotavirus vaccine, live, attenuated) was licensed in February 2006[15 16] by the European Medicines Agency (EMA) for use in the European Union in babies 6–24 weeks of age to protect them against gastroenteritis (diarrhea and vomiting) caused by rotavirus infection. Experts are investigating the possibility of waivers for patients younger than or older than 6 and 32 weeks of age, respectively,[17] or for different dosing schedules of rotavirus vaccines.[18]

Thus, off-label use of vaccines exists and is feasible when supported by scientific evidence. Among diverse populations and given the large number of vaccines, many considerations and elements should be assessed before a recommendation is made. However, for novel off-label vaccine use, the evaluation process does not rely on previous off-label recommendations of one vaccine and requires new evidence to support a recommendation.

Previous studies

We searched the literature to verify whether studies had examined the process for evaluating the initial off-label use of a vaccine or its recommendation. A pilot selection of databases and relevant studies identified mainly randomized controlled trials (RCTs) and systematic reviews on individual vaccines. Systematic reviews were conducted to evaluate the impact[19 20] and effectiveness[21-23] of vaccines, mortality[24], and morbidity.[25] Moreover, we searched the literature for scoping reviews of off-label use of vaccine, to check whether similar work, as comprehensive as the research we intend to undertake, had been conducted. Several papers reported off-label recommendations that had been implemented by public health decision-makers,[8 9 18] but few have investigated the methodology behind the process for off-label recommendations.[26 27] To our knowledge, no scoping review has thus far been conducted with a spectrum of data elements, synthesized for decision-making, considered in a recommendation for the off-label use of vaccines in a public health program. Further in-depth research is needed to map out approaches, evidence, and recommendations for off-label vaccine use. Key elements of national and global importance will be highlighted in this review.[28 29]

Aims and objectives

Aim

To synthesize the knowledge around off-label use of vaccines in an initial assessment process at a global level. The scoping review method will allow us to examine peer-reviewed and grey literature and to map the broad topic of the off-label use of vaccine in a rigorous, systematic, and reproducible manner. A greater understanding of the nature of evidence that supports vaccine off-label use recommendations may lead to feasible and improved decision-making in public health. This scoping review is the first step of a three-phase research plan which includes a survey and a focus group in

[2] The SmPC is used by healthcare professionals, such as doctors, nurses and pharmacists, and explains how to use and prescribe a medicine. SmPCs are written and updated by pharmaceutical companies and are based on their research and product knowledge

the second and third phase respectively toward the development of an analytical framework for off-label vaccine recommendations.

We define the initial assessment as the process that occurs after a vaccine has been licensed and wherein an off-label recommendation from an expert committee is implemented in a public program within a jurisdiction, before any other global off-label recommendation has been made for the same vaccine. To identify such processes, we will use the vaccine licensure date as a starting point and search for any published off-label recommendation that chronologically flows from it.

Objectives

1. To map the field of methods and concepts used in the decision-making process of a recommendation about off-label vaccination.
2. To identify and describe the different assessment processes that lead to a decision and its implementation of initial off-label vaccine use.
3. To identify and validate the recommendations on off-label vaccination that have been reported by advisory committees and which may help plan immunization programs.
4. To identify and summarize the range of evidence that inform the development of recommendations across different off-label types and characteristics.
5. To present a common approach between all initial off-label use of vaccine recommendations and the specific aspects of each decision.
6. To provide a clear definition of the off-label-use of vaccines.
7. To highlight relevant findings that will guide the conceptualization of an analytical framework for off-label vaccine use.

Review question

What are the evidences used by public health experts in recommending off-label use of vaccines in a vaccination program?

METHODS AND ANALYSIS

Scoping review design

This study will follow the Joanna Briggs Institute (JBI)[30] methodological approaches for a scoping review, as described by Peters et al. in Chapter 11 of the 4th Edition of the reviewer's manual. The JBI framework involves:

1. Defining and aligning the objective/s and question/s
2. Developing and aligning the inclusion criteria with the objective/s and question/s
3. Describing the planned approach to evidence searching, selection,
4. Searching for the evidence
5. Selecting the evidence
6. Extracting the evidence
7. Charting the evidence
8. Summarizing the evidence in relation to the objective/s and question/s
9. Consultation of information scientists, librarians, and/or experts (throughout)

Vaccines that will be included in the ambit of this scoping review have been identified. This scoping review has been initiated as the protocol was submitted for publication. Reporting will be conducted in accordance with the Preferred Reporting Items for Systematic Review and Meta-Analysis Extension for Scoping Reviews (PRISMA-ScR) checklist.[31]

Review registration

At present, scoping review (ScR) protocols are ineligible for registration in the PROSPERO database. This review title has been registered with Open Science Framework[32].

Patient and public involvement

There will be no patient or public involvement in this review. However, patient/public involvement will be a part of the third phase of the research plan, during a focus-group interview to be conducted after the results of this review are reported.

Inclusion criteria

There are 26 vaccine-preventable diseases (VPD) that are part of a routine immunization program for which a vaccine is available, and these will be included in our review:

- Cholera
- Dengue
- Diphtheria
- Hepatitis A
- Hepatitis B
- Hepatitis E
- Hemophilus influenzae type b (Hib)
- Human papillomavirus (HPV)
- Influenza
- Japanese encephalitis
- Malaria
- Measles
- Meningococcal meningitis
- Mumps
- Pertussis
- Pneumococcal invasive disease
- Poliomyelitis
- Rabies
- Rotavirus
- Rubella
- Tetanus
- Tick-borne encephalitis
- Tuberculosis
- Typhoid
- Varicella
- Yellow Fever

Population, Concept, and Context (PCC) elements

Table 1: Review inclusion criteria

	Inclusion	Exclusion
Types of participants	Public health immunization is a broad endeavor, and it is aimed at the entire population. All strata and categories of individuals will be suitable for inclusion: males and females of any age group, condition, or profession, as long as the off-label schedule is applicable to the group in a public health recommendation.	- Non-human subjects (e.g., preclinical studies). Phase I, II or III clinical trials, unless it is used as an evidence in a recommendation - Self-reporting of off-label-use of vaccine at the individual patient/physician level, as this is not representative of a public health approach (no case report).
Concept	Methodically, any indication of use that would be different from the prescribing information provided in the label of a vaccine should be considered off-label immunization. The most frequent off-label recommendations are for doses, population groups, indications, posology, or injection site,[7 8] but should not be limited to these aspects. An objective of our review is to identify all existing recommendations that address off-label vaccination in public health. The implementation of the	- Unlabeled vaccine use - Superfast-track approval is not considered off-label use. - Non-adherent behaviors that result in different dosing are not considered as off-label use

	recommendation for off-label vaccine use is considered an outcome when recommendations are part of published vaccination programs. The review uses the vaccine licensure as a starting point to determine the eligibility of a paper, and the label is considered the baseline for each vaccine. Various terms and definitions may have been used through the years. However, as "*off-label"* is a relatively new term that has been introduced in search engines in approximately 2010, the review intends to provide a clear definition for off-label vaccine use.	
Context	Off-label recommendations will be broadly sought from within the global context of immunization. There will be no limitation in the geographic location or in the settings. This review is intended to map the evidence that emerges from any context, including pandemics and shortages, and to provide findings that support the development of an analytical framework applicable to any context.	No exclusion criteria
Types of sources	Any and all documents included in the decision process of the initial off-label use of vaccine recommendations will be included in this review. The reference lists of identified reports will be manually searched for additional studies. All types of studies and documents: product monographs, official documents, recommendations (NITAG, SAGE, etc.), health authority vaccine updates, and accessible documentary evidence submitted for licensing (from clinical trials: quality, safety, and efficacy data), or from studies made after licensing. Any valuable written sources will be included to supplement the information on the vaccines. The period considered will be from the date of vaccine first licensing for the country, for each vaccine. Documents in all languages will be eligible at the initial phase. If texts are available in languages other than English or French, they will be translated and included in the review.	No exclusion criteria

NITAG: National Immunization Technical Advisory Group; SAGE: WHO Strategic Advisory Group of Experts

Search strategy

Search terms and strategy:

A comprehensive and structured search of the literature will be conducted. For documents identification, two search strategies will be developed: one for the grey literature and the other for published studies.

For the grey literature,[33] a search will be conducted for each vaccine's product monograph from pharmaceuticals, licensure, national vaccine updates, or accessible documentary evidence submitted for licensing, identified by NRAs and organizations that proceeded to regulatory approval at the

national or international level. Expert committees that make recommendations for off-label vaccines use will be identified.

A combination of terms – vaccine-preventable diseases, vaccine names, and licensure – will be used to search official publications and all documents on the evaluation process, recommendations, fundamental decisive factors, and program implementation. All documents describing the decision-making process of off-label vaccine recommendation in a public program, from the evaluation process by the expert committee to the decisive elements that enabled the health authority to implement the recommendation, or otherwise, into the vaccination program. If necessary, we will contact the authors of the off-label decision for additional information.

The other search strategy will include a combination of two major concepts: off-label use (main concept) and vaccines (second concept). For the off-label concept, we will use Mesgarpour's[34 35] highly sensitive search strategy to retrieve as many documents as possible. The specificity of the search strategy will increase when combined with the second concept – *vaccines and each VPD name*. The outcome concept will not be included in the search strategy, as it could possibly restrict the number of papers. A medical librarian with experience in electronic database searches has worked with the research team and helped perfect the search strategy (Supplementary).

The exposure terms will be medical subject heading (MeSH) or EMBASE subject headings (EMTREE) that describe the off-label use, plus terms that describe vaccines, combined with the AND Boolean term. Word strings will be identified in the titles and abstracts of relevant documents. Variations of these words will be searched as free text.

Databases and other sources to be searched

The search will be conducted in the databases listed below for all published documents, without date or study type restrictions, by using the prespecified search terms.

For the grey literature,[33] the sources to be searched are the World Health Organization [WHO] Immunization – Vaccines and Biologicals, US FDA, Health Canada (https://health-products.canada.ca/dpd-bdpp/index-eng.jsp), The Canadian Agency for Drugs and Technologies in Health (CADTH), European Medicines Agency (EMA), Therapeutic Goods Administration (TGA), Pharmaceuticals and Medical Devices Agency (PMDA), ImmunoFacts Vaccines and Immunologic drugs, Canadian Agency for Drugs and Technologies in Health, RxTx (The Canadian Pharmacists Association's e-Therapeutics+ and e-Therapeutics+ Complete products), and United States Pharmacopeia and National Formulary (USP), Merck Index, Google Scholar, WHO publications, Global NITAG Network center, Open Grey, and Ministries of Health publications. We may need to contact governmental agencies and committees to gain access to some documents.

The databases that will be searched for studies will be PubMed, MEDLINE,[3] and EMBASE[4] to minimize retrieval bias. EMBASE is an international bibliographic science database for biomedical and pharmaceutical product with a comprehensive indexing policy for articles that deal with drugs, and it would be appropriate for this scoping review. For RCTs, www.clinicaltrials.gov and the International Clinical trials registry will be searched.

[3] Ovid MEDLINE(R) and Epub Ahead of Print, In-Process & Other Non-Indexed Citations, Daily and Versions(R)
[4] Excerpta Medica Database (EMBASE) 1974 to 2020 June 26 (or last version)

The data sources included in this review are deemed appropriate, given that the evidence will precede and inform the development of the recommendations, which would need to be published, to be considered.

Documents selection and screening

All monographs are eligible for inclusion and have been uploaded in a file. An Excel sheet gathers vaccine names and weblinks of downloaded monographs. These will be automatically included during third stage of the review where data extraction for off-label vaccines will be performed.

All documents and studies included in public health off-label recommendations – for considered vaccines – will be selected. Moreover, all documents supporting the implementation of the recommendations will be included.

All studies and documents identified in the search will be exported from databases or websites into the EndNote X9 reference manager to eliminate duplication. Unique citations will be exported into DistillerSR for screening. Studies and documents will be reviewed against the selection criteria specified in Table 1 for inclusion/exclusion in two stages: the first stage will comprise a review of the title and abstract, where two reviewers, at least one of whom is a content expert and the other a methodology expert, will independently conduct this review to minimize study selection bias; these reviewers will compare and discuss the results for consensus on the exclusion of studies after the first stage of review. Only studies and documents where both reviewers agree as clearly irrelevant to the search will be excluded from the search to maximize the study sensitivity. As the off-label recommendations might not have abstracts, they will be automatically included in the second stage full-text screening.

In the second stage, the same two reviewers will independently review the full text of the included or uncertain studies and other documents to assess the study/document type, exposure, and outcomes. After the first 10 reviews, the two reviewers will meet to calibrate inclusion/exclusion. Disagreements, if any, will be resolved through discussion once the second stage is completed. A third reviewer will arbitrate if a consensus cannot be reached about a given paper.

After the second stage of the review is completed, bibliographic information of selected articles will be manually searched to find any missing or non-indexed literature. The reviewers will meet to compare results and reach a consensus.

The scoping review methodology does not require an evaluation of the quality of studies. However, the quality of evidence is deemed to have been assessed when they were used in the development of recommendations. A report of this assessment is included in the stated objectives of this review and in the identification and summary of evidence.

The study and review processes will be presented in a PRISMA flowchart,[31] and reasons for exclusion will be provided in the final review report.

Extraction: charting the results

Data extraction from any type of evidence and research methodology, without restriction to qualitative studies, will be independently undertaken by the two reviewers. A preliminary data extraction of vaccine's indication, concentration of bacteria or virus, route/site, doses and schedule will be performed from all included monographs followed by more extensive data extraction for off-

label vaccine used only. Therefore, data will not be extracted and not be included in this scoping review if vaccines have not been subject to off-label recommendations.

Before conducting a complete extraction, a pilot test will be undertaken with a random sample of studies/documents to assess the quality and the consistency of the data collection by the reviewers and to familiarize themselves with the source of the results. Then, each reviewer will independently extract data by using the same checklist (Table 2) and will not be blinded to the authors of the study/document. The reviewers will meet after data extraction for verification purposes: methods, text discrepancy, or missing information. This step is paramount in building the final analytical framework considering that data extracted will constitute its mainstays.

A draft charting table was developed to collect the relevant data items from the source and will be refined and continually updated at the review stage.

Table 2: Data extraction sheet

Licensure data:	Recommendations:	Evidence:
Monography Vaccine preventable disease: **Identification** • Trade name of vaccine • Abbreviation • Manufacturer • licensure date • date of implementation in a vaccination program • country of licensure **Typology** • therapeutic indication • posology, doses, number of shots in routine series • approved ages • specific population group**s,** sex • method of administration **Composition** • antigen • adjuvant • protein • other components	**Committee identification** Name of the Advisory committee Country of the Committee NITAG member: Yes/No **Recommendation** Title of the recommendation Date of publication of the recommendation Name of journal of publication, or not Implementation in an immunization program: Yes/No **Discussion structure** Use of a framework Yes/No Name of the framework Use of Theoretical concept Yes/No Name of the concept Use of a standard operation procedure Yes/No Name of the SOP **Decision elements, approach used** A. GRADE[5][36] ▪ GRADE Summary table available Yes/No ▪ Policy question - PICO ▪ Desirable effects ▪ Undesirable effects ▪ Desirable effects outweigh the undesirable effects ▪ Outcomes of interest (critical,	<u>Qualitative information</u> **Study / document Information:** Authors Title of publication Year of Publication Type of document: ▪ Peer review literature ▪ Unpublished data ▪ Expert opinion ▪ Epidemiological data ▪ Article ▪ Other Journal name Study Design Aims/purpose Study period Country(s) in which it took place Calendar years in follow up period Conflicts of Interest declared by authors **Population under study:** Initial sample size recruited, N, records numbers, • N and % Males • N and % Females Age range Average age Sample size with full follow up data available • N and % Males • N and % Females Age range Average age

[5] Grading of Recommendations Assessment, Development and Evaluation (GRADE)

• live or attenuated vaccine • bacteria, virus, toxoid, protozoan • wild strain or not, number of strains **Contraindication** • population • sex • age group • fertility, pregnancy and lactation **Immunogenicity** • serological threshold • antibody level **Other information →** accessible written evidence • vaccine updates • others	▪ Number of studies per outcome ▪ Evidence retrieval / Exclusion criteria Rating the quality of evidence (each study): • Design (RCTs, Observational) • Risk of bias • Inconsistency • Indirectness • imprecision • Evidence type / level • Efficacy • Effectiveness • Impact • Number Needed to Vaccinate The final recommendation: B. ETR[6] • Evidence tables available Yes/No • Question - PICO • Background Evidence for the following factors: ▪ Statement of problem (for each criteria) ▪ Benefits & harms (for each criteria) ▪ Values and preferences of target population (for each criteria) ▪ Acceptability to stakeholders ▪ Resource use ▪ Feasibility ▪ Balance of consequences ▪ Type of recommendations ▪ Recommendation Additional considerations C. Other approach List the items evaluated	Medical Comorbidities or Immunosuppressed condition (complete list if different) • HIV/AIDS; • Sickle cell disease, • Nephrotic syndrome, • Asplenia, • Cancer • Asthma • COPD • Diabetes • Thyroid disorders • IBD Lifestyle factors: • Exposure to tobacco smoke. • Overweight • Malnutrition • Day care attendance • Lack of breastfeeding **Off-label Vaccine Intervention (Exposure):** Name of vaccine Quantity of type of strains protected against Dose per shot Number & timing of doses Measurement instrument/method, specific Calendar years intervention measured Immunization schedule Group of the population Off-label characteristics **Outcome Measure:** Immunogenicity serological threshold antibody levels Vaccine effectiveness (endpoint measure) Vaccine impact Vaccine safety Immunologic non-inferiority (indicate δ) Incidence of the disease Clinical criteria used for the disease Method of disease measurement/diagnosis **Methods:** Population description (inclusion/exclusion) Randomization process for RCTs (RCTs) Assessment of exposure status (cohort) Age groups: N, % in each • <1; 1-4; 5-9; 10-14; 15-18;

[6] Evidence to recommendations (EtR) framework

		• 19-24; 25-29; 30-39; 40-59; • ≥60; Sex (N, % F - N, % M) Immunodepression Prior vaccination Vaccination interval different for intervention vs control arm Quantitative information (for studies) **Effect measures (yes/no)** OR, RR or HR rates n/N Standard deviation Confidence interval Variance Adjusted/unadjusted

Synthesis of the results

The main objective of this review is to synthesize the knowledge on the off-label use of vaccines in a novel initial assessment process ultimately to guide the development of analytical framework for off-label vaccine recommendations. A deductive thematic data analysis will be conducted.

First, the review will commence with a perusal of the vaccine product monographs by presenting information on each vaccine at licensure, which is the study baseline. Then, the review will follow with a case-based analysis for each vaccine by describing the decision process for the initial off-label use of the vaccine and what methods were used; subsequently, off-label vaccine typology and vaccinated typology will be performed on the basis of published recommendations.

The synthesis of data from vaccine off-label recommendations will be either in narrative or tabulated form. For each vaccine, the elements of the decision used to develop the recommendation will be identified: priority questions, research evidence, important factors of evidence appraisal, benefits and harms, costs, feasibility, acceptability, values and preferences of clients or healthcare providers, and judgments about criterion or option. A concise summary of pivotal elements that led to the final option will be presented.

In the primary analysis, the study will stratify results by population in accordance with new risk groups with underlying conditions and the healthy population. At the second level, the review will stratify identified papers by study design or type of document, change of schedule, sex, special populations, number of doses, and time of introduction in the vaccination schedule. This analysis will examine the diversity and the possibility of clustering the elements. If any summary or effect measure is assessed and reported in a study, the synthesis will sum up the types of measures that were used and briefly discuss them. When comparing studies, RCTs and observational data will be analyzed separately.

Off-label vaccines will be pooled by characteristics: changes in the number of doses in their “exposure” arm, in the population, in the administration route, or in the indication, followed by pooling by the study design and the type of vaccine. Furthermore, the study will report whether the effect measures documented in studies were from the same calendar time (i.e., that the reference group received their vaccinations and were followed during the same calendar time period as the off-label groups).

If the data extracted from the included papers permit diagrammatic presentation, the results will be presented in a dendrogram format that relates to the objectives and question of the review. The results will be clustered by similar evidence, and a narrative description of the data will be presented for the:

- similarity of study population
- similarity of outcome measures
- similarity of evidence grade
- theoretical concept/no model
- similarity of methodology
- implementation/no implementation

ETHICS AND DISSEMINATION

Ethics approval is not required for this scoping review although this manuscript will be part of an entire protocol which will be submitted to the ethics committee. This scoping review is the first step for the 3 phases of this research program, for a PhD degree. The second phase is a survey where public health experts will answer a questionnaire. Phase three includes a focus group in which decision-makers, pharmaceutical industry and the patient/public will be involved. The results will be disseminated through (1) peer-reviewed articles; (2) at conferences. The relevant findings will guide the conceptualization of (3) an analytical framework for off-label vaccines that will also be submitted to a peer-reviewed journal. Within the global consultation, findings of the review (4) will be presented to stakeholder, policymaker, and public health actors for validation. Iterative consultations are ongoing within the review team.

CONCLUSION

We present the scoping review protocol on the off-label use of vaccines in public programs, together with an in-depth review of the evidence and concepts from a novel initial analysis of off-label recommendations to identify the findings which are key to decision-making in off-label vaccination. To the best of our knowledge, this is the first review to undertake a comprehensive review on the off-label use of vaccines. This study will strengthen the knowledge base of vaccine assessment processes, which are central to the development of novel initial off-label use. Moreover, the mapping of published recommendations will provide an understanding of the extent of off-label vaccine use globally, and on how they facilitate the planning of immunization programs. The results of this review will enlighten and support researchers, expert committees, public health actors, and policymakers globally by providing a clear definition of the off-label use of vaccines and guide the conceptualization of an analytical framework that will be used for the assessment of evidence in the development of future recommendations for the off-label use of vaccines in public programs. Furthermore, we anticipate that the findings of this scoping review will inspire research into the off-label use of agents beyond vaccination, where off-label indications play a considerable role.

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Author Contributions
DD (PhD candidate) participated in conceptualization of the project, researched and developed all aspects of the project methodology, design and manuscript, and approved the final version as submitted. CQ (research director) participated in conceptualization of the project, critically reviewed and commented on the whole manuscript, and approved the final version of the protocol.

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SUPPLEMENTAL MATERIAL

Search terms and strategy

Concept	Search terms	PubMed Search strategy (Translated from MEDLINE)	MEDLINE Search Strategy (1)	EMBASE Search strategy(2)
Exposure wide	Off-label use Appropriate indication Drug administration Drug prescription Drug utilization Drug approval Drug without guideline Dose-response relationship Dose sparing Fda non approved Fractional dose Immunization schedule improper inappropriate indication use Licensure Label labeled Labelling license licensed non evidence based outside prescribed Product monograph Reduced dose registered schedule unapproved unlabeled unlicensed used proper	(("Off-Label Use"[Mesh]) OR (off[tiab] AND (label[tiab] OR labelling[tiab])) OR “reduced dose” [TIAB] OR "Unlabeled indication"[TIAB] OR "Unlabeled indications" [TIAB] OR "fractional dose"[TIAB] OR "fractional doses"[TIAB] OR "reduced doses”[TIAB] OR "Unlabeled indications"[TIAB] OR "dose sparing"[TIAB] OR (Off-label use[MH] OR (off[TIAB] AND label[TIAB]) OR "Off label use"[TIAB] OR Unapprove*[TIAB] OR unlicense*[TIAB] OR (label[TIAB] AND indication*[TIAB]) OR ((no licensed[TIAB] OR not licensed[TIAB] OR no licenced[TIAB] OR not licenced[TIAB]) NOT (now licensed[TIAB] OR now licenced[TIAB]) AND (use [TIAB] OR used [TIAB]) OR usage [TIAB])) OR ((appropriate*[TIAB] AND prescri*[TIAB]) and indication[TIAB]) OR Off lisense[TIAB] OR Off license[TIAB] OR Off lisence[TIAB] OR Off licence[TIAB] OR nonapprove*[TIAB] OR (unlabel* [TIAB] AND (use[TIAB] OR used[TIAB])) OR (((inappropriate [TIAB] AND (use[TIAB] OR used[TIAB])) AND indication[TIAB]) NOT (antibiotic*[TIAB] OR	((off adj2 label) or "Off label us*" or Unapprove* or unlicense* or (label adj3 indication*) or ((no* licen?ed for adj3 use*) not now licen?ed) or ((appropriate* adj3 prescri*) and indication) or Off li?en?e or nonapprove* or unlabel* us* or ((inappropriate us* and indication) not (antibiotic* or antimicrobial)) or unlabel* indication* or inappropriate indication* or labeled indication* or (outside adj2 licen?e*) or registered indication* or (out* adj4 licen?ed indication*) or non fda approve* or ((no* licen?ed for adj3 indication*) not now licen?ed) or (us* without adj2 indication*) or (appropriate indication adj3 us*) or non evidence base* us* or (improper adj1 indication*) or (be???d* adj2 licen?ed indication*) or out of label or without proper indication* or (prescri* outside adj4 guideline*) or no* appropriate indication* or (drug* without adj2 indication*) or (medication adj2 without adj2 indication*)).af. or off label*.ab,ti.	(off label*.af. OR (off adj1 label).mp. OR (drug adj2 label adj2 us*).af. OR unlicense*.af. OR unapprove*.af. OR (label adj3 indication*).af. OR off li?en?e*.af. OR ((no* licen?ed for adj3 use*) not now licen?ed).af. OR ((inappropriate us* and indication) not (antibiotic* or antimicrobial)).af. OR ((appropriate* adj3 prescri*) and indication).af. OR (outside adj3 licen?e*).af. OR unlabel* us*.af. OR labeled indication*.af. OR (inappropriate indication*).af. OR nonapprove*.af. OR registered indication*.af. OR offlabel*.af. OR (out* adj4 licen?ed indication*).af. OR (unlabel* adj3 indication*).af. OR non fda approve*.af. OR ((no* licen?ed for adj3 indication*) not now licen?ed).af. OR (appropriate indication adj3 us*).af. OR (be???d* adj2 licen?ed indication*).af. OR (us* without adj2 indication*).af. OR (prescri* outside adj4 guideline*).af. OR (out of label).af. OR (improper adj1 indication*).af. OR (inappropriate adj5 indication adj2 us*).af. OR no* appropriate indication*.af. OR (non evidence base* us*).af. OR without proper indication*.af.) OR (drug* without adj2 indication*).af.

		antimicrobial[TIAB])) OR unlabel* indication*[TIAB] OR inappropriate indication*[TIAB] OR labeled indication*[TIAB] OR (outside[TIAB] AND (licence*[TIAB] OR license*[TIAB])) OR registered indication*[TIAB] OR (outside[TIAB] AND (licenced indication*[TIAB] OR licensed indication*[TIAB])) OR non fda approve*[TIAB] OR (((not licenced for[TIAB] OR not licensed for[TIAB]) NOT (now licensed[TIAB] OR now licenced[TIAB])) AND indication*[TIAB]) OR (((use[TIAB] OR used[TIAB] OR usage[TIAB]) AND without[TIAB]) AND indication*[TIAB]) OR (appropriate indication[TIAB] AND (use[TIAB] OR used[TIAB] OR usage[TIAB])) OR (non evidence base* AND (use[TIAB] OR used[TIAB] OR usage[TIAB])) OR (improper[TIAB] AND indication*[TIAB]) OR ((beyond [TIAB] OR beside*[TIAB]) AND (licensed indication*[TIAB] OR licenced indication*[TIAB])) OR out of label[TIAB] OR without proper indication*[TIAB] OR (prescri* outside[TIAB] AND guideline*[TIAB]) OR ((no[TIAB] OR not[TIAB]) AND appropriate indication*[TIAB]) OR (drug* without[TIAB] AND indication*[TIAB]) OR ((medication[TIAB] AND without[TIAB]) AND indication*[TIAB]) OR off label*[TIAB])		

		PubMed	MEDLINE (Translated from PubMed)	EMBASE (Translated from PubMed)
Exposure specific	Cholera vaccine Dengue vaccine Diphtheria vaccine HAV vaccine HBV vaccine HEV vaccine Hib vaccine HPV vaccine Influenza vaccine Japanese encephalitis vaccine Malaria vaccine Measles vaccine Meningococcal meningitis vaccine Mumps vaccine Pertussis vaccine Pneumococcal vaccine Poliovirus vaccine Rabies vaccine Rotavirus vaccine Rubella vaccine Tetanus vaccine Tick-borne encephalitis vaccine Tuberculosis vaccine Typhoid vaccine Varicella vaccine Yellow Fever vaccine Pandemic vaccine Epidemic vaccine Shortage vaccination	(("Cholera Vaccines"[Mesh] OR ((cholera OR cholerae) AND (vaccine OR vaccines))) OR ("Dengue Vaccines"[Mesh] OR ((breakbone OR break-bone OR dengues OR dengue) AND (vaccine OR vaccines))) OR (("Diphtheria Toxoid"[Mesh] OR "Diphtheria-Tetanus Vaccine"[Mesh]) OR ((Diphtheria OR diphtheriae OR DT) AND (vaccine OR vaccines))) OR (“Hepatitis A Vaccines"[Mesh] OR ("Viral Hepatitis Vaccines"[Mesh] AND “Hepatitis A"[Mesh]) OR (“viral vaccines"[Mesh] AND “Hepatitis A"[Mesh]) OR twinrix OR ((Hepatitis A OR HAV) AND (vaccine OR vaccines)) OR ((Hepatitis Viral Human OR Hepatitis Viruses) AND (hepatitis A) AND (vaccine OR vaccines))) OR “Hepatitis B Vaccines"[Mesh] OR ("Viral Hepatitis Vaccines"[Mesh] AND “Hepatitis B"[Mesh]) OR (“viral vaccines"[Mesh] AND “Hepatitis B"[Mesh]) OR twinrix OR ((Hepatitis B OR HBV) AND (vaccine OR vaccines)) OR ((Hepatitis Viral Human OR Hepatitis Viruses) AND (hepatitis B) AND (vaccine OR vaccines)) OR ((Viral Hepatitis Vaccines AND “Hepatitis E"[Mesh]) OR (“viral vaccines"[Mesh] AND “Hepatitis E"[Mesh]) OR ((Hepatitis E virus OR Hepatitis E OR HEV) AND (vaccine OR	(Cholera Vaccines or ((cholera or cholerae) and (vaccine or vaccines))).af. OR (Dengue Vaccines or ((breakbone or break-bone or dengues or dengue) and (vaccine or vaccines))).af. OR (Diphtheria Toxoid or Diphtheria-Tetanus Vaccine or ((Diphtheria or diphtheriae or DT) and (vaccine or vaccines))).af. OR (Hepatitis A Vaccines OR (Viral Hepatitis Vaccines AND Hepatitis A) OR (viral vaccines AND Hepatitis A) OR twinrix OR ((Hepatitis A OR HAV) AND (vaccine OR vaccines)) OR ((Hepatitis Viral Human OR Hepatitis Viruses) AND (hepatitis A) AND (vaccine OR vaccines))).af. OR (Hepatitis B Vaccines OR (Viral Hepatitis Vaccines AND Hepatitis B) OR (viral vaccines AND Hepatitis B) OR twinrix OR ((Hepatitis B OR HBV) AND (vaccine OR vaccines)) OR ((Hepatitis Viral Human OR Hepatitis Viruses) AND (hepatitis B) AND (vaccine OR vaccines))).af. OR (Hepatitis E vaccines or (Viral Hepatitis Vaccines and Hepatitis E) or (viral vaccines and Hepatitis E) or ((Hepatitis E virus or Hepatitis E or HEV) and (vaccine or vaccines)) or ((RNA Virus Infections or Hepatitis Viral Human or Hepatitis Viruses) and hepatitis E and (vaccine or vaccines))).af. OR (Haemophilus influenzae type b polysaccharide vaccine OR ((Haemophilus influenzae type b OR hib OR "Haemophilus	(Cholera Vaccines OR ((cholera OR cholerae) and (vaccine or vaccines))).af. OR (Dengue Vaccines OR ((breakbone OR break-bone or dengues or dengue) and (vaccine or vaccines))).af. OR (Diphtheria Toxoid OR Diphtheria-Tetanus Vaccine OR ((Diphtheria OR diphtheriae OR DT) and (vaccine or vaccines))).af. OR (Hepatitis A Vaccines OR (Viral Hepatitis Vaccines AND Hepatitis A) OR (viral vaccines AND Hepatitis A) OR twinrix OR ((Hepatitis A OR HAV) AND (vaccine OR vaccines)) OR ((Hepatitis Viral Human OR Hepatitis Viruses) AND (hepatitis A) AND (vaccine OR vaccines))).af. OR (Hepatitis B Vaccines OR (Viral Hepatitis Vaccines AND Hepatitis B) OR (viral vaccines AND Hepatitis B) OR twinrix OR ((Hepatitis B OR HBV) AND (vaccine OR vaccines)) OR ((Hepatitis Viral Human OR Hepatitis Viruses) AND (hepatitis B) AND (vaccine OR vaccines))).af. OR (Hepatitis E vaccines OR (Viral Hepatitis Vaccines and Hepatitis E) OR (viral vaccines and Hepatitis E) OR ((Hepatitis E virus OR Hepatitis E OR HEV) and (vaccine OR vaccines)) OR ((RNA Virus Infections OR Hepatitis Viral Human OR Hepatitis Viruses) and hepatitis E and (vaccine OR vaccines))).af. OR

		vaccines)) OR ((RNA Virus Infections OR Hepatitis Viral Human OR Hepatitis Viruses) AND (hepatitis E) AND (vaccine OR vaccines)) OR ("Haemophilus influenzae type b polysaccharide vaccine" [Supplementary Concept] OR ((hib OR "Haemophilus influenzae") AND (vaccine OR vaccines))) OR ("Papillomavirus Vaccines"[Mesh] OR ((hpv[tiab] OR Papillomavirus[tiab] OR Papilloma virus[tiab]) AND (vaccine OR vaccines))) OR ("Influenza Vaccines"[Mesh] OR ((flu OR influenza OR Influenza virus OR LAIV) AND (vaccine OR vaccines))) OR ("Japanese Encephalitis Vaccines"[Mesh] OR ((Japanese Encephalitis) AND (vaccine OR vaccines))) OR ("Malaria Vaccines"[Mesh]OR ((malarial OR malaria OR Remittent Fever OR Plasmodium Infection OR Marsh Fever OR Plasmodium Infections OR paludism) AND (vaccine OR vaccines))) OR ("Measles Vaccine"[Mesh]OR ((MMR OR rubeola OR morbilli OR Triviraten OR Priorix OR Trimovax OR Pluserix OR Virivac) AND (vaccine OR vaccines))) OR ("Meningococcal Vaccines"[Mesh] OR (Meningococcal Meningitis AND (vaccine OR vaccines))) OR ("Mumps Vaccine"[Mesh] OR “Measles-Mumps-Rubella Vaccine"[Mesh] OR ((mumps OR	influenzae") AND (vaccine OR vaccines))).af. OR (Papillomavirus Vaccines or ((hpv or Papillomavirus or Papilloma virus) and (vaccine or vaccines))).af. OR (Influenza Vaccines or ((flu or influenza or Influenza virus or LAIV) and (vaccine or vaccines))).af. OR (Japanese Encephalitis Vaccines or (Japanese Encephalitis and (vaccine or vaccines))).af. OR (Malaria Vaccines or ((malarial or malaria or Remittent Fever or Plasmodium Infection or Marsh Fever or Plasmodium Infections or paludism or Plasmodium falciparum) and (vaccine or vaccines))).af. OR ((Measles and (Vaccine or vaccines)) or ((MMR or rubeola or morbilli or Triviraten or Priorix or Trimovax or Pluserix or Virivac) and (vaccine or vaccines))).af. OR ((Meningococcal or Meningococcal Meningitis) and (vaccine or vaccines)).af. OR (Mumps Vaccine or Measles-Mumps-Rubella Vaccine OR ((mumps or Measles-Mumps-Rubella or Parotitis or Parotitides) and (vaccine or vaccines))).af. OR (Pertussis Vaccine or Diphtheria-Tetanus-Pertussis Vaccine or Diphtheria-Tetanus-acellular Pertussis Vaccines or ((DTaP or ACEL IMUNE Tripedia or ACELIMUNE or Infanrix or dtwp or DPT or Di Te Per or Pertussis or Whooping Cough or bordetella) and (vaccine or vaccines))).af. OR (Pneumococcal Vaccines or	(Haemophilus influenzae type b polysaccharide vaccine OR ((Haemophilus influenzae type b OR hib OR "Haemophilus influenzae") AND (vaccine OR vaccines))).af. OR (Papillomavirus Vaccines OR ((hpv OR Papillomavirus OR Papilloma virus) and (vaccine OR vaccines))).af. OR (Influenza Vaccines OR ((flu OR influenza OR Influenza virus OR LAIV) and (vaccine OR vaccines))).af. OR (Japanese Encephalitis Vaccines OR (Japanese Encephalitis and (vaccine OR vaccines))).af. OR (Malaria Vaccines OR ((malarial OR malaria OR Remittent Fever OR Plasmodium Infection OR Marsh Fever OR Plasmodium Infections OR paludismOR Plasmodium falciparum) and (vaccine OR vaccines))).af. OR ((Measles and (Vaccine OR vaccines))OR ((MMR OR rubeola OR morbilli OR Triviraten OR Priorix OR Trimovax OR Pluserix OR Virivac) and (vaccine OR vaccines))).af. OR ((Meningococcal OR Meningococcal Meningitis) and (vaccine OR vaccines)).af. OR (Mumps Vaccine OR Measles-Mumps-Rubella Vaccine OR ((mumps OR Measles-Mumps-Rubella OR Parotitis OR Parotitides) and (vaccine OR vaccines))).af. OR (Pertussis Vaccine OR Diphtheria-Tetanus-Pertussis Vaccine OR Diphtheria-Tetanus-acellular Pertussis Vaccines OR ((DTaP OR

		Parotitis OR Parotitides OR Measles-Mumps-Rubella) AND (vaccine OR vaccines))) OR ("Pertussis Vaccine"[Mesh] OR "Diphtheria-Tetanus-Pertussis Vaccine"[Mesh] OR "Diphtheria-Tetanus-acellular Pertussis Vaccines"[Mesh] OR ((DTaP OR ACEL IMUNE Tripedia OR ACELIMUNE OR Infanrix OR dtwp OR DPT OR Di Te Per OR Pertussis or Whooping Cough or bordetella) AND (vaccine OR vaccines))) OR ("Pneumococcal Vaccines"[Mesh] OR ((Pneumococcal OR Pnu Imune OR PnuImune OR Pneumovax OR PncOMPC OR PNCRM7 OR PCV7 OR PCV13 OR PCV10 OR Prevenar OR Prevnar or Pneumococcal Polysaccharide) AND (vaccine OR vaccines))) OR ("Poliovirus Vaccines"[Mesh] OR ((Poliomyelitis or poliovirus OR Salk OR sabin OR Brunhilde OR Lansing OR Leon OR Polioviruses) AND (vaccine OR vaccines))) OR ("Rabies Vaccines"[Mesh]OR ((rabies OR lyssa OR lyssas or rabies virus) AND (vaccine OR vaccines))) OR ("Rotavirus Vaccines"[Mesh] OR ((rotavirus) AND (vaccine OR vaccines))) OR ("Rubella Vaccine"[Mesh]OR ((Rubela OR rubelas or Rubella virus) AND (vaccine OR vaccines))) OR	((Pneumococcal or Pnu Imune or PnuImune or Pneumovax or PncOMPC or PNCRM7 or PCV7 or PCV13 or PCV10 or Prevenar or Prevnar or Pneumococcal Polysaccharide) and (vaccine or vaccines))).af. OR (Poliovirus Vaccines or ((Poliomyelitis or poliovirus or Salk or sabin or Brunhilde or Lansing or Leon or Polioviruses) and (vaccine or vaccines))).af. OR (Rabies Vaccines or ((rabies or lyssa or lyssas or rabies virus) and (vaccine or vaccines))).af. OR (Rotavirus Vaccines or (rotavirus and (vaccine or vaccines))).af. OR (Rubella Vaccine or ((rubellas or Rubela or rubelas or Rubella virus) and (vaccine or vaccines))).af. OR (Tetanus Toxoid or ((tetatus or tetani) and (vaccine or vaccines))).af. OR (Encephalitis, Tick-Borne or (encephalitis and (tick borne or Russian Spring-Summer or Far Eastern Russian or Louping or Powassan or Central European) and (vaccine or vaccines))).af. OR (Tuberculosis Vaccines or ((tuberculosis or bcg or Calmette* or Kochs) and (vaccine or vaccines))).af. OR (typhoid vaccine or Ty21a typhoid vaccine or Typhoid-Paratyphoid Vaccines or ((typhoid or Paratyphoid or enteric or typhus or typhi or Typhoids or M01ZH09 or Typhoid fever) and (vaccine or vaccines))).af. OR ((varicella or Chickenpox or varivax) and (vaccine	ACEL IMUNE Tripedia OR ACELIMUNE OR Infanrix OR dtwp OR DPT OR Di Te Per OR Pertussis OR Whooping Cough OR bordetella) and (vaccine OR vaccines))).af. OR (Pneumococcal Vaccines OR ((Pneumococcal OR Pnu Imune OR PnuImune OR Pneumovax OR PncOMPC OR PNCRM7 OR PCV7 OR PCV13 OR PCV10 OR Prevenar OR Prevnar OR Pneumococcal Polysaccharide) and (vaccine OR vaccines))).af. OR (Poliovirus Vaccines OR ((Poliomyelitis OR poliovirus OR Salk OR sabin OR Brunhilde OR Lansing OR Leon OR Polioviruses) and (vaccine OR vaccines))).af. OR (Rabies Vaccines OR ((rabies OR lyssa OR lyssas OR rabies virus) and (vaccine OR vaccines))).af. OR (Rotavirus Vaccines OR (rotavirus and (vaccine OR vaccines))).af. OR (Rubella Vaccine OR ((rubellas OR Rubela OR rubelas OR Rubella virus) and (vaccine OR vaccines))).af. OR (Tetanus Toxoid OR ((tetatus OR tetani) and (vaccine OR vaccines))).af. OR (Encephalitis, Tick-Borne OR (encephalitis and (tick borne OR Russian Spring-Summer OR Far Eastern Russian OR Louping OR Powassan OR Central European) and (vaccine OR vaccines))).af. OR (Tuberculosis Vaccines OR ((tuberculosis OR bcg OR Calmette*

		("Tetanus Toxoid"[Mesh] OR ((tetatus OR tetani) AND (vaccine OR vaccines))) OR ("Encephalitis, Tick-Borne"[Mesh] OR (enchephalitis AND (tick borne OR Russian Spring-Summer OR Far Eastern Russian OR Louping OR Powassan OR Central European) AND (vaccine OR vaccines))) OR ("Tuberculosis Vaccines"[Mesh] or ((tuberculosis or bcg or Calmette* OR Kochs) AND (vaccine OR vaccines))) OR ("typhoid vaccine M01ZH09" [Supplementary Concept] OR "Ty21a typhoid vaccine" [Supplementary Concept] OR "Typhoid-Paratyphoid Vaccines"[Mesh] OR ((typhoid OR Paratyphoid OR enteric OR typhus OR typhi OR Typhoids) AND (vaccine OR vaccines))) OR ("measles, mumps, rubella, varicella vaccine" [Supplementary Concept] OR "Chickenpox Vaccine"[Mesh] OR ((varicella OR Chickenpox OR varivax) AND (vaccine OR vaccines))) OR ("Yellow Fever Vaccine"[Mesh] OR ((yellow fever) AND (vaccine OR vaccines))) OR (“pandemics"[Mesh] OR “epidemics"[Mesh] AND (vaccine OR vaccines or vaccination)) OR Shortage vaccination)	or vaccines)).af. OR ((Yellow Fever or yellow fever virus) and (vaccine or vaccines)).af. OR ((pandemics or epidemics) and (vaccine or vaccines or vaccination)).af. OR (Shortage vaccination).af.	OR Kochs) and (vaccine OR vaccines))).af. OR (typhoid vaccine OR Ty21a typhoid vaccine OR Typhoid-Paratyphoid Vaccines OR ((typhoid OR Paratyphoid OR enteric OR typhus OR typhi OR Typhoids OR M01ZH09 OR Typhoid fever) and (vaccine OR vaccines))).af. OR ((varicella OR Chickenpox OR varivax) and (vaccine OR vaccines)).af. OR ((Yellow Fever OR yellow fever virus) and (vaccine OR vaccines)).af. OR ((pandemics OR epidemics) and (vaccine OR vaccines OR vaccination)).af. OR (Shortage vaccination).af.

1. Mesgarpour B, Muller M, Herkner H. Search strategies-identified reports on "off-label" drug use in MEDLINE. J Clin Epidemiol. 2012;65(8):827-34.
2. Mesgarpour B, Müller M, Herkner H. Search strategies to identify reports on “off-label” drug use in EMBASE. BMC Med Res Methodol. 2012;12(1):190.

Databases used:

PubMed: 1 January 1925 to 14 August 2020
MEDLINE: Ovid MEDLINE(R) ALL 1946 to August 14, 2020
EMBASE: Embase 1974 to 2020 August 14

OvidSP MEDLINE Off-label High Sensitivity Search Strategy

1. (off adj2 label).af.
2. "Off label us*".af.
3. Unapprove*.af.
4. unlicense*.af.
5. (label adj3 indication*).af.
6. ((no* licen?ed for adj3 use*) not now licen?ed).af.
7. ((appropriate* adj3 prescri*) and indication).af.
8. Off li?en?e.af.
9. nonapprove*.af.
10. unlabel* us*.af.
11. ((inappropriate us* and indication) not (antibiotic* or antimicrobial)).af.
12. unlabel* indication*.af.
13. inappropriate indication*.af.
14. labeled indication*.af.
15. (outside adj2 licen?e*).af.
16. registered indication*.af.
17. (out* adj4 licen?ed indication*).af.
18. non fda approve*.af.
19. ((no* licen?ed for adj3 indication*) not now licen?ed).af.
20. (us* without adj2 indication*).af.
21. (appropriate indication adj3 us*).af.
22. non evidence base* us*.af.
23. (improper adj1 indication*).af.
24. (be???d* adj2 licen?ed indication*).af.
25. out of label.af.
26. without proper indication*.af.
27. (prescri* outside adj4 guideline*).af.
28. no* appropriate indication*.af.
29. (drug* without adj2 indication*).af.
30. (medication adj2 without adj2 indication*).af.
31. 1 or 2 or 3 or 4 or 5 or 6 or 7 or 8 or 9 or 10 or 11 or 12 or 13 or 14 or 15 or 16 or 17 or 18 or 19 or 20 or 21 or 22 or 23 or 24 or 25 or 26 or 27 or 28 or 29 or 30
32. off label*.ab,ti.
33. 31 or 32

APPENDIX

SECTION	ITEM	PRISMA-ScR CHECKLIST ITEM	REPORTED ON PAGE #
TITLE			
Title	1	Identify the report as a scoping review.	1
ABSTRACT			
Structured summary	2	Provide a structured summary that includes (as applicable): background, objectives, eligibility criteria, sources of evidence, charting methods, results, and conclusions that relate to the review questions and objectives.	2
INTRODUCTION			
Rationale	3	Describe the rationale for the review in the context of what is already known. Explain why the review questions/objectives lend themselves to a scoping review approach.	4-5
Objectives	4	Provide an explicit statement of the questions and objectives being addressed with reference to their key elements (e.g., population or participants, concepts, and context) or other relevant key elements used to conceptualize the review questions and/or objectives.	6
METHODS			
Protocol and registration	5	Indicate whether a review protocol exists; state if and where it can be accessed (e.g., a Web address); and if available, provide registration information, including the registration number.	6
Eligibility criteria	6	Specify characteristics of the sources of evidence used as eligibility criteria (e.g., years considered, language, and publication status), and provide a rationale.	7-8
Information sources	7	Describe all information sources in the search (e.g., databases with dates of coverage and contact with authors to identify additional sources), as well as the date the most recent search was executed.	9
Search	8	Present the full electronic search strategy for at least 1 database, including any limits used, such that it could be repeated.	8
Selection of sources of evidence	9	State the process for selecting sources of evidence (i.e., screening and eligibility) included in the scoping review.	9-10
Data charting process	10	Describe the methods of charting data from the included sources of evidence (e.g., calibrated forms or forms that have been tested by the team before their use, and whether data charting was done independently or in duplicate) and any processes for obtaining and confirming data from investigators.	10
Data items	11	List and define all variables for which data were sought and any assumptions and simplifications made.	11-12
Critical appraisal of individual sources of evidence	12	If done, provide a rationale for conducting a critical appraisal of included sources of evidence; describe the methods used and how this information was used in any data synthesis (if appropriate).	n/a
Synthesis of results	13	Describe the methods of handling and summarizing the data that were charted.	13

SECTION	ITEM	PRISMA-ScR CHECKLIST ITEM	REPORTED ON PAGE #
RESULTS			
Selection of sources of evidence	14	Give numbers of sources of evidence screened, assessed for eligibility, and included in the review, with reasons for exclusions at each stage, ideally using a flow diagram.	n/a
Characteristics of sources of evidence	15	For each source of evidence, present characteristics for which data were charted and provide the citations.	n/a
Critical appraisal within sources of evidence	16	If done, present data on critical appraisal of included sources of evidence (see item 12).	n/a
Results of individual sources of evidence	17	For each included source of evidence, present the relevant data that were charted that relate to the review questions and objectives.	n/a
Synthesis of results	18	Summarize and/or present the charting results as they relate to the review questions and objectives.	n/a
DISCUSSION			
Summary of evidence	19	Summarize the main results (including an overview of concepts, themes, and types of evidence available), link to the review questions and objectives, and consider the relevance to key groups.	n/a
Limitations	20	Discuss the limitations of the scoping review process.	3
Conclusions	21	Provide a general interpretation of the results with respect to the review questions and objectives, as well as potential implications and/or next steps.	14
FUNDING			
Funding	22	Describe sources of funding for the included sources of evidence, as well as sources of funding for the scoping review. Describe the role of the funders of the scoping review.	15