Interventions designed to improve vaccination uptake: scoping review of systematic reviews and meta-analyses - protocol

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Background:

Substantial differences exist in the uptake of vaccines by age, gender, ethnicity, geographical location, and socioeconomic status. In addition, the resources required to promote the uptake of effective vaccines varies widely by country and income level. As a result, immunization programmes often struggle to achieve optimal coverage of the target population.

A sizeable evidence base relevant to vaccine uptake exists: a search of PubMed reveals over a hundred systematic reviews. However, there is a need to curate this knowledge better to assess what works for whom and in what settings, particularly given the need to improve uptake for public health vaccines in those settings where resources are scarce.

Therefore, we plan to do a scoping review of systematic reviews of published evidence on interventions designed to increase vaccine uptake and categorise the interventions and their components across different populations and geographical regions. We will use the scoping review results to guide the implementation and evaluation of practical intervention tools to promote vaccine uptake.

Methods

Objectives: To conduct a scoping review of interventions designed to increase vaccination uptake.

The specific focus of the review:

- Population: 1) children under the age of 5, age 5-10 and adolescents age 10-19; [1] 2) adults, and 3) healthcare workers (including the care sector)
- Interventions: any intervention designed to improve participation in vaccination
- Outcomes: Uptake, Hesitancy, Knowledge, Confidence, Access, Provider recommendation, Social norms and Availability

Type of studies:

We will include systematic reviews and meta-analyses of interventional studies that address the question of vaccine uptake.

Search strategy:
We will search the following electronic databases: MEDLINE, Register of Controlled Trials (Cochrane CENTRAL), CINAHL, PsycINFO, EMBASE, Scopus, Epistemonikos, Web of Science, LILACs and TRIP database (which covers guidelines and the grey literature) up until 01 July 2021 and hand-searched the reference lists of included articles. The searches will combine free and MeSH search terms and keywords related to vaccine uptake (vaccine OR innocul OR immunis* OR immuniz*). In the first instance, we will use sensitive search filters developed by the Health Information Research Unit at McMaster University, Canada, to focus on systematic reviews and meta-analyses. [2] We will also search the bibliographies of retrieved systematic reviews. We will screen all titles and abstracts of retrieved citations for inclusion. Based on the results of the initial filter for systematic reviews we will review the need for further search terms that will include but not be limited to (vaccine OR innocul OR immunis* OR immuniz*) AND (uptake OR adherence OR compliance OR decision OR hesitanc* OR concern OR knowledge OR confidence OR access OR social norms OR refusal OR awareness OR behaviour* OR belief* OR accept* OR decision making). We will use sensitive search filters developed by the Health Information Research Unit at McMaster University, Canada, to focus on systematic reviews and meta-analyses. [2] We will also search the bibliographies of retrieved systematic reviews. We will screen all titles and abstracts of retrieved citations for inclusion. Two reviewers will independently evaluate the full text of articles potentially meeting eligibility criteria. Discrepancies will be resolved through discussion. Where a consensus cannot be reached, a third reviewer will arbitrate.

Eligibility criteria

We will include systematic reviews that comprise studies of all ages, including those with people with pre-existing ill-health conditions if they report quantitative data on the association between vaccine uptake, vaccine knowledge, confidence or hesitancy and or access. In addition, we will include systematic reviews that contain randomized controlled trials (RCTs) and quasi-experimental (including interrupted time series and before-and-after studies). We will exclude reviews that just assess vaccine efficacy and/or effectiveness.

Types of Interventions
Interventions that aim to increase vaccine uptake in a specific population or the overall population.

Quality Assessment

To assess the quality, we will use modified AMSTAR score items 3 and 7. [3] Item 3: “Was a comprehensive* literature search performed?” At least two electronic sources should be searched. The report must include years and databases used (e.g. Central, EMBASE, and MEDLINE), plus keywords and/or MESH terms. Item 7: “Was the scientific quality of the included studies assessed and documented?” 'A priori' assessment methods should be provided (e.g., for effectiveness studies if the author(s) chose to include only randomized, double-blind, placebo-controlled studies, or allocation concealment as inclusion* consistent with a systematic review search.

One reviewer will record and assess the reporting of the quality of included systematic reviews and report the assessments, and a second reviewer will independently check the quality ratings. Disagreements will be resolved through discussion; a third reviewer will arbitrate where a consensus cannot be reached. We will rate the quality of the evidence in included reviews using the “Grade of Recommendations Assessment, Development and Evaluation” (GRADE). [4] We will downgrade or upgrade the quality of the evidence, based on the amount of potential bias due to study design and other criteria specified in the GRADE, and provide a summary of findings tables by the outcomes of interest. GRADE assessment will be based on assessing the risk of bias and an evaluation of inconsistency, indirectness, and imprecision of the results and other factors (see the GRADE Table in the appendix for more information). Where GRADE has been used to assess primary studies included in the reviews, we will check the rating. Where another tool has been used to assess quality,

one reviewer will convert this to a GRADE assessment, and a second reviewer will independently check the assessment.

Data extraction:
We will conduct the review according to PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-Analyses) guidelines. [7] Data from included reviews will be extracted by one reviewer and independently checked by a second reviewer. We will structure the outcomes by intervention type and create categories using an iterative process to extract objectives and self-reported outcomes. In addition, we will extract data on the population, study characteristics (e.g., number of trials, location etc.) and the intervention and comparator and the outcomes of interest as well as the type of meta-analysis effect model used in the meta-analysis (fixed or random) and between-study heterogeneity estimates (I^2 values).

Where two reviews cover the same intervention and outcome with overlapping studies, we will select the most relevant reviews (i.e. more comprehensive and up-to-date) for inclusion; we will ~~and~~ include the historical reviews as an appendix. We will also use the Jadad decision algorithm to interpret discordant reviews and select the most appropriate review evidence for interventions (see figure 1). Two authors will independently apply the algorithm to reach a consensus over which review/meta-analysis is included. [5]

Outcomes of interest
We will prioritize outcomes according to the WHO handbook for guideline development [6] as High (critical for decision making), Moderate (important for decision making) and Low (not important for decision making).

Table 1. Outcomes of interest and prioritization

Priority	Construct	Definition	Includes
High	Uptake	Receipt of vaccine	Initiation, completion, coverage and behaviour
Moderate	Hesitancy	Motivational state of being conflicted about, or opposed to, getting vaccinated	Intentions, willingness, openness, stage
Moderate	Knowledge	An accurate understanding of facts about vaccination.	It does not include awareness, but we will assess it where reported
Moderate	Confidence	Attitudes and beliefs that vaccines work are safe and are part of a trustworthy medical system.	Perceived importance, benefit, and effectiveness. Concerns about safety, harm, side effects, and adverse events.
Moderate	Access	Perceived and actual access to immunization services	Distance, travel, timing, location, ease, convenience
Low	Provider recommendation	Advice from a health care worker to receive vaccination	Advice in clinical and non-clinical settings
Low	Social norms	Shared expectations of acceptable vaccination behaviour by a group	Descriptive norms, injunctive norms
Low	Availability	Low/unavailable stocks may play a role in vaccine uptake	

We will use summary tables to present the evidence for four population subgroups: 1) children under the age of 5, 5-10 and adolescents 10-19, 2) adults, and 3) healthcare workers (including care workers). We will specifically look for interventions trialled in Low-income settings reporting studies by geographical regions, the intervention components, and vaccine uptake effects. We will also subgroup data by type of vaccination, income level (High, Low Middle and Low-income Countries) and report whether specific interventions affect multiple vaccinations and age groups.

We will present the data as reported in the paper and use RevMan version 5 to reconstruct the forest plots when necessary. Where significant heterogeneity exists, we will extract the reasons and consider whether further subgroup analyses are required. Given the complex nature of the interventions, we will report the outcomes using a random-effects analysis which allows for differences in the treatment effect from study to study.

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Authors' contributions

All authors contributed in equal part to the conceptualization and development of the content. TJ and CH wrote the first draft and edited this version. All authors contributed to the subsequent drafts and approved the final version.

Conflict of interest statements

TJ was in receipt of a Cochrane Methods Innovations Fund grant to develop guidance on the use of regulatory data in Cochrane reviews (2015 to 2018). In 2014 to 2016, he was a member of three advisory boards for Boehringer Ingelheim. TJ was a member of an independent data monitoring committee for a Sanofi Pasteur clinical trial on an influenza vaccine. TJ is occasionally interviewed by market research companies about phase I or II pharmaceutical products for which he receives fees (current). TJ was a member of three advisory boards for Boehringer Ingelheim (2014 to 16). TJ was a member of an independent data monitoring committee for a Sanofi Pasteur clinical trial on an influenza vaccine (2015 to 2017). TJ is a relator in a False Claims Act lawsuit on behalf of the United States that involves sales of Tamiflu for pandemic stockpiling. If resolved in the United States favour, he would be entitled to a percentage of the recovery. TJ is coholder of a Laura and John Arnold Foundation grant for the development of a RIAT support centre (2017 to 2020) and Jean Monnet Network Grant, 2017 to 2020 for The Jean Monnet Health Law and Policy Network. TJ is an unpaid collaborator to the project Beyond Transparency in Pharmaceutical Research and Regulation led by Dalhousie University and funded by the Canadian Institutes of Health Research (2018 to 2022). TJ consulted for Illumina LLC on next-generation gene sequencing (2019 to 2020). TJ was the consultant scientific coordinator for the HTA Medical Technology programme of the Agenzia per i Servizi Sanitari Nazionali (AGENAS) of the Italian MoH (2007 to 2019). TJ is Director Medical Affairs for BC Solutions, a market access company for medical devices in Europe. TJ was funded by NIHR UK and the World Health Organization (WHO) to update Cochrane review A122, Physical Interventions to interrupt the spread of respiratory viruses. TJ is funded by Oxford University to carry out a living review on the transmission epidemiology of COVID 19. Since 2020, TJ receives fees for articles published by The Spectator and other media outlets. TJ is part of a review group carrying out a Living rapid literature review on the modes of transmission of SARS CoV 2 (WHO Registration 2020/1077093 0). He is a member of the WHO COVID 19 Infection Prevention and Control Research Working Group, for which he receives no funds. TJ is funded to co-author rapid reviews on the impact of Covid restrictions by the Collateral Global Organisation.

CJH holds grant funding from the NIHR, the NIHR School of Primary Care Research, the NIHR BRC Oxford and the World Health Organization for a series of Living rapid reviews on the modes of transmission of SARs CoV 2 reference WHO registration No2020/1077093. He has received financial remuneration from an asbestos

case and given legal advice on mesh and hormone pregnancy tests cases. He has received expenses and fees for his media work, including occasional payments from BBC Radio 4 Inside Health and The Spectator. He receives expenses for teaching EBM and is also paid for his GP work in NHS out of hours (contract Oxford Health NHS Foundation Trust). He has also received income from the publication of a series of toolkit books and appraising treatment recommendations in non-NHS settings. He is the Director of CEBM, an NIHR Senior Investigator and an advisor to Collateral Global.

DE holds grant funding from the Canadian Institutes for Health Research and Li Ka Shing Institute of Virology relating to the development of Covid 19 vaccines and the Canadian Natural Science and Engineering Research Council concerning Covid 19 aerosol transmission. He is a recipient of World Health Organization and Province of Alberta funding which supports the provision of BSL3 based SARS CoV 2 culture services to regional investigators. He also holds public and private sector contract funding relating to the development of poxvirus based Covid 19 vaccines, SARS CoV 2 inactivation technologies, and serum neutralization testing.

JMC holds grants from the Canadian Institutes for Health Research on acute and primary care preparedness for COVID 19 in Alberta, Canada and was the primary local Investigator for a Staphylococcus aureus vaccine study funded by Pfizer, for which all funding was provided only to the University of Calgary. He is a co-investigator on a WHO funded study using integrated human factors and ethnography approaches to identify and scale innovative IPC guidance implementation supports in primary care with a focus on low resource settings and using drone aerial systems to deliver medical supplies and PPE to remote First Nations communities during the COVID 19 pandemic. He also received support from the Centers for Disease Control and Prevention (CDC) to attend an Infection Control Think Tank Meeting. He is a member of the WHO Infection Prevention and Control Research and Development Expert Group for COVID 19 and the WHO Health Emergencies Programme (WHE) Ad hoc COVID 19 IPC Guidance Development Group, both of which provide multidisciplinary advice to the WHO, for which no funding is received and from which no funding recommendations are made for any WHO contracts or grants. He is also a member of the Cochrane Acute Respiratory Infections Group.

JB is a major shareholder in the Trip Database search engine (www.tripdatabase.com) as well as being an employee. In relation to this work, Trip has worked with a large number of organisations over the years; none have any links with this work. The main current projects are with AXA and Collateral Global.

ECR was a member of the European Federation of Neurological Societies(EFNS) / European Academy of Neurology (EAN) Scientist Panel, Subcommittee of Infectious Diseases (2013 to 2017). Since 2021, she is a member of the International Parkinson and Movement Disorder Society (MDS) Multiple System Atrophy Study Group, the Mild Cognitive Impairment in Parkinson Disease Study Group, and the Infection Related Movement Disorders Study Group. She was an External Expert and sometimes Rapporteur for COST proposals (2013, 2016, 2017, 2018, 2019) for Neurology projects.

IJO, EAS, and AP have no interests to disclose.

Ethics committee approval.

No approval was necessary.

Data Availability

All data included in the review will be provided in the tables and text.

Figures

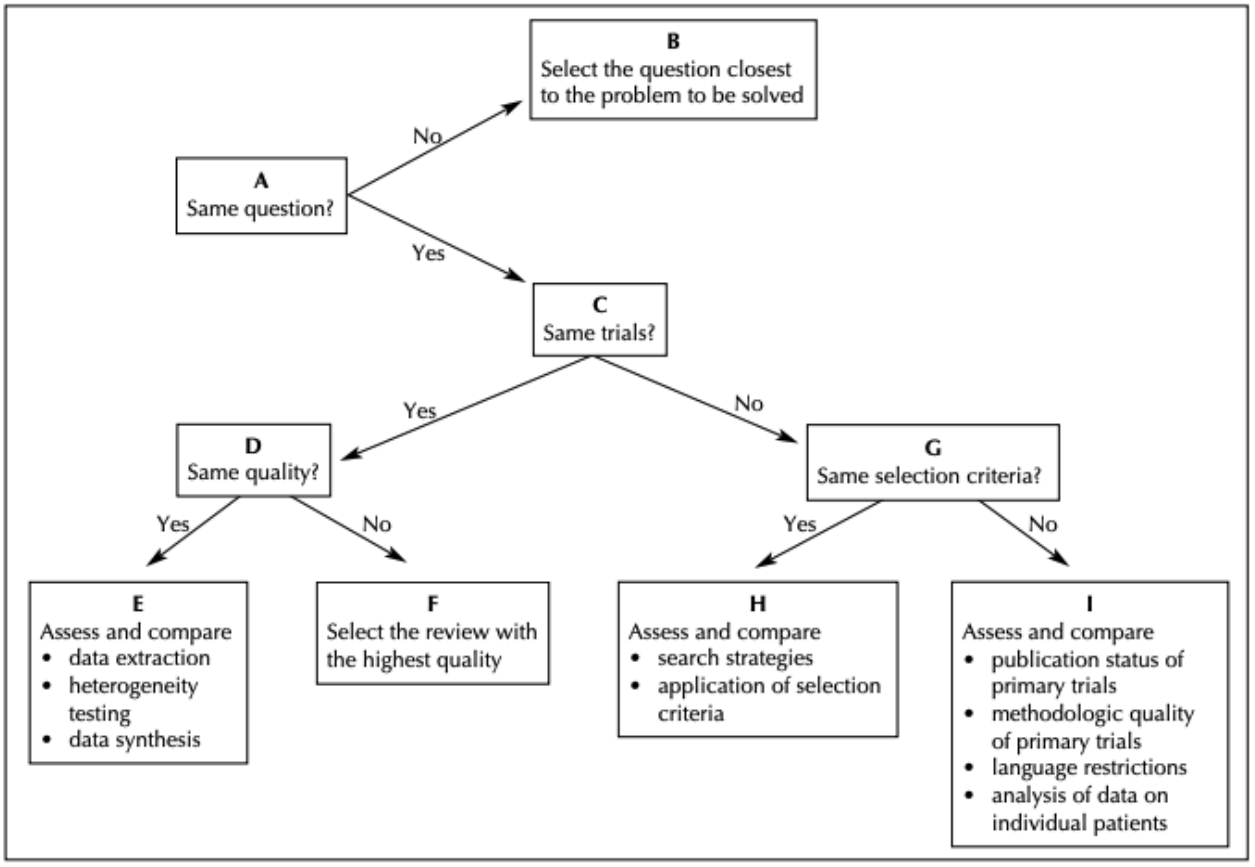

Fig. 1: A decision algorithm for interpreting discordant reviews (assuming that the reviews have few and minimal flaws).

CAN MED ASSOC J • MAY 15, 1997; 156 (10) 1413

Jadad AR, Cook DJ, Browman GP. A guide to interpreting discordant systematic reviews. CMAJ1997;156:1411-6.pmid:9164400

Appendix

GRADE tables.

Quality assessment							Summary of findings					Importance
							No of patients		Effect		Quality	
No of studies	Design	Limitations	Inconsistency	Indirectness	Imprecision	Other considerations	Intervention	Usual care	Relative (95% CI)	Absolute		
Intervention (ID)												
Outcome 1												
Outcome 2												

- **Limitations - assessing risk of bias**
  - Lack of allocation concealment: Those enrolling patients are aware of the group (or period in a crossover trial) to which the next enrolled patient will be allocated (major problem in “pseudo” or “quasi” randomized trials with allocation by day of week, birth date, chart number, etc)
  - Lack of blinding: Patient, care givers, those recording outcomes, those adjudicating outcomes, or data analysts are aware of the arm to which patients are allocated (or the medication currently being received in a crossover trial)
  - Incomplete accounting of patients and outcome events: Loss to follow-up and failure to adhere to the intention-to-treat principle in superiority trials; or in non-inferiority trials, loss to follow-up, and failure to conduct both analyses considering only those who adhered to treatment, and all patients for whom outcome data are available
  - Selective outcome reporting bias: Incomplete or absent reporting of some outcomes and not others on the basis of the results
  - Other limitations: Stopping early for benefit; Use of unvalidated outcome measures (e.g., patient-reported outcomes); Carryover effects in crossover trial; Recruitment bias in cluster-randomized trials
- **Inconsistency**
  - Reviewers should consider rating down for inconsistency when: 1.Point estimates vary widely across studies; 2.Confidence intervals (CIs) show minimal or no overlap;3.The statistical test for heterogeneity—which tests the null hypothesis that all studies in a meta-analysis have the same underlying magnitude of effect—shows a low P-value; 4.The I2—which quantifies the proportion of the variation in point estimates due to among-study differences—is large.
- **Indirectness**
  - We are more confident in the results when we have direct evidence. By direct evidence, we mean research that directly compares the interventions in which we are interested delivered to the populations in which we are interested and measures the outcomes important to patients. Thus, we can have concerns about indirectness when the population, intervention, or outcomes differ from those in which we are interested. In general, evidence based on surrogate outcomes should usually trigger rating down, whereas the other types of indirectness will require a more considered judgment.
- **Imprecision**
  - When considering the quality of evidence, the issue is whether the CI around the estimate of treatment effect is sufficiently narrow. If it is not, we rate down the evidence quality by one level (for instance, from high to moderate). If the CI is very wide, we might rate down by two levels.
- **Other**
  - A number of factors may rate the quality of evidence up or down. These include presence or absence of publication bias, when a large magnitude of effect exists, when there is a dose–response gradient, and when all plausible confounders or other biases increase our confidence in the estimated effect.

Reference

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