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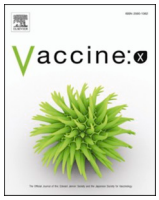

COVID-19 vaccine evidence monitoring assisted by artificial Intelligence: An emergency system implemented by the Public Health Agency of Canada to capture and describe the trajectory of evolving pandemic vaccine literature

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ABSTRACT

Background: The COVID-19 pandemic resulted in a rapid accumulation of novel vaccine research evidence. As a means to monitor this evidence, the Public Health Agency of Canada (PHAC) created the **E**vidence e**X**traction **T**eam for **R**esearch **A**nalysis (**EXTRA**), which contributed to situational awareness in Canada through a bibliographic repository used to support decision-making by the National Advisory Committee on Immunization. We describe the process by which this literature was identified and catalogued, and provide an overview of characteristics in the identified literature.

Methods: To expedite the process, PHAC leveraged an artificial intelligence (AI) tool to assist in the screening and selection of relevant articles. Literature search results were initially screened by AI, then manually reviewed for relevance. Relevant articles were tagged using controlled vocabulary and stored in a bibliographic repository. This repository was analyzed to identify trends in vaccine research over time according to several key characteristics.

Results: As of December 31, 2023, EXTRA's repository contained 19,050 articles relevant to PHAC's immunization mandate. The majority of these articles (63.9 %) were identified between August 2021 and January 2023, with an average of 20 relevant articles added daily during this period. Nearly 14,000 articles reported on mRNA vaccines. Safety outcomes were most frequently reported (n = 8,289), followed by immunogenicity (n = 7,269) and efficacy/effectiveness (n = 3,246). COVID-19 vaccine literature output started to decrease in mid-2023, two years after the initial dramatic increase in mid-2021.

Conclusions: This hybrid (AI and human) approach was critical for PHAC situational awareness and the development of timely vaccine guidance in Canada during the COVID-19 pandemic. Given the volume of data and analyses required, the AI-augmented processes made this massive undertaking manageable. Analysis of COVID-19 vaccine research patterns supports projections of research volume, type, and rate that will help predict resourcing and information needs to plan future emergency vaccine guidance activities.

1. Introduction

The collective efforts of the scientific community during the COVID-19 pandemic cultivated dramatic growth of vaccine evidence, unique in scope, scale, impact, and urgency. In 2020, submissions increased by more than 60 % to journals published by Elsevier [1], and within ten months of the first confirmed case of COVID-19, over 125,000 COVID-19-related scientific articles had been released [2]. By the end of 2022, the World Health Organization's COVID-19 database contained over 700,000 items [3]. In addition, considerable efforts were made by

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the scientific community to ensure that COVID-19 research was disseminated expeditiously, in order to reach key stakeholders and decision-makers quickly. The peer-review process, an often-lengthy one [4], had been considerably decreased by a number of publishers, in order to accelerate publication [5]. The use of pre-print servers, such as medRxiv and bioRxiv, also increased considerably during the COVID-19 pandemic, with several highly impactful scientific papers being originally housed on preprint servers [2]. This overwhelming and dynamic volume of literature presented unique challenges to public health officials and decision-makers across the globe, as COVID-19-related public health recommendations/decisions needed to be made swiftly.

The Public Health Agency of Canada (PHAC) ensures readiness for and responds to public health emergencies, such as the COVID-19 global pandemic [6]. Detailed information on the Government of Canada's COVID-19 Immunization Plan is available elsewhere [7]. In 2020, PHAC created the Evidence eXtraction Team for Research Analysis (EXTRA) to develop an emergency protocol to automate daily COVID-19 literature curation. This system was used for situational awareness and to create a bibliographic repository to support vaccine guidance development by the National Advisory Committee on Immunization (NACI), which has provided guidance on the use of vaccines in Canada since 1964. Prior to the COVID-19 pandemic, PHAC had identified the potential benefits of artificial intelligence (AI) and natural language processing (NLP) to facilitate public health intelligence and decision-making [8], and worked with health technology innovators on potential solutions to facilitate automated study selection and data extraction in relation to vaccine studies [9]. While historically there has been a general reluctance from the scientific community in relying on automated technologies to facilitate curation of health literature for decision-making [10], the pandemic provided the impetus for implementation in order to keep pace with the unprecedented volume of vaccine research evidence. In parallel, other groups have been experimenting with similar approaches [11], and guidance now exists to outline parameters for successful automation of living systematic reviews [12].

In the first year of the COVID-19 vaccine rollout in Canada, NACI and other immunization decision-makers were often challenged to make emergency decisions in advance of available published evidence or with limited evidence [13]. This was particularly challenging without the ability to anticipate when the global research community would be able to generate critical data to inform guidance on special populations (e.g. immunocompromised, pregnancy), dose optimising strategies (e.g. extended dose intervals, heterologous schedules, fractional dosing), or emerging vaccine safety signals (e.g. Vaccine-Induced Immune Thrombotic Thrombocytopenia [VITT], myocarditis).

The objectives of this report are two-fold: (1) to describe EXTRA's literature curation process, and (2) to describe key characteristics of the COVID-19 vaccine literature found to date.

2. Methods

PHAC surveillance of COVID-19 literature began in January 2020, with evidence summaries beginning in March 2020. The Medical Countermeasures (MCM) Daily Scan, which later became the EXTRA Scan in January 2021, was launched in May 2020, with the use of Zotero as a repository platform to house the scan results initiated in March 2021. Articles identified between May 2020 to March 2021 were retroactively added to Zotero for completeness. The repository is publicly accessible using the following link: https://www.zotero.org/groups/2826505/extra_covid-19_vaccine/library.

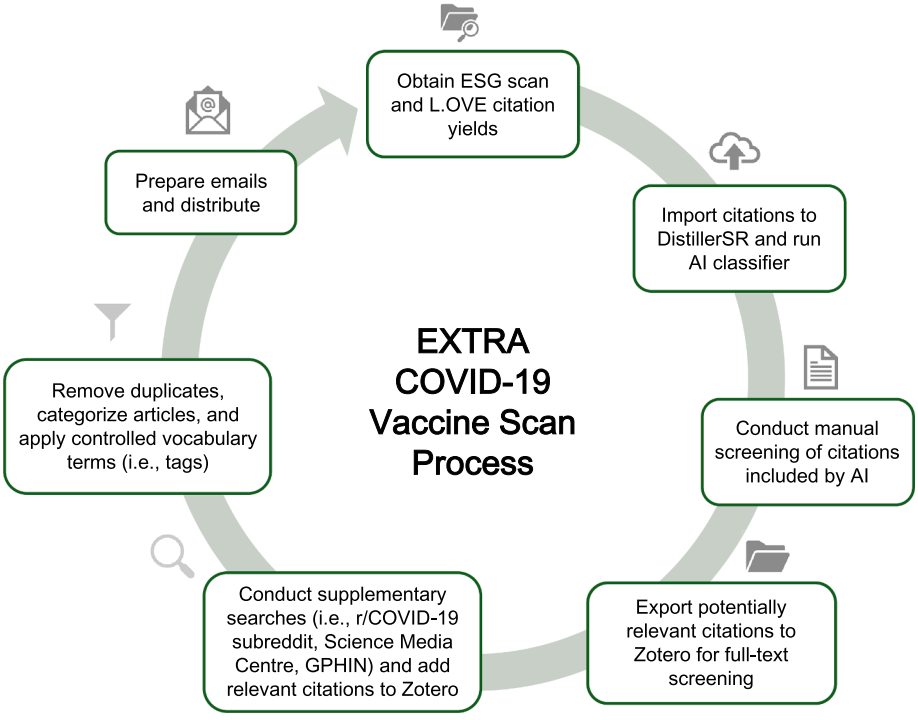

Fig. 1.

2.1. Research team and training

The number of individuals required to support the EXTRA scan fluctuated over the course of the surveillance period. The project team consisted of PHAC staff and students with expertise in information sciences, epidemiology, and immunology. During peak resource requirements, five PHAC employees and four students contributed a total of 3.5 full-time equivalent positions (FTE), equating to 26.5 hours per day over a five-day work week. Over time, the support required to maintain the repository reduced to 2.5 FTE positions (equating to 18.75 hours per day over a five-day work week) largely owing to efficiencies gained by streamlining the scanning process. During the peak period, EXTRA met weekly, in addition to numerous ad-hoc meetings, to strategize approaches for optimizing efficiency that would continue to meet emerging information needs as the pandemic evolved. To ensure consistency across reviewers, standard operating procedures were developed and updated as needed.

2.2. Search strategy

Electronic databases including PubMed, Scopus and EuropePMC-medRxiv, bioRxiv,Arxiv, SSRN and Research Square were regularly searched by PHAC's Emerging Sciences Group (ESG) and citations on all COVID-19 literature during each search period (two weeks prior to the search date) were shared with EXTRA. Details regarding ESG's search strategy have been describe previously [14]. A supplemental search was also performed by EXTRA, leveraging additional information sources including Epistemonikos' L·OVE platform (https://iloveevidence.com/), Science Media Centre (Roundups and Rapid Reactions, https://www.sciencemediacentre.org/), Global Public Health Intelligence Network (GPHIN) daily reports (https://gphin.canada.ca/cepr/listarticles.jsp?language=en_CA), social media sites (e.g. COVID-19 subreddit) and press releases from vaccine manufacturers containing scientific data. Citations from ESG were retrieved daily until April 2022, when decision-making urgency for the pandemic vaccine program diminished, and then the frequency of ESG searches reduced to twice weekly, and then once weekly as of March 2023. Citations from L·OVE were received daily via email subscription to the following thread: Sars-cov-2 vaccines for COVID-19 (any population). Remaining sources were searched daily until July 2023 at which point the supplemental search was discontinued (apart from L·OVE) due to limited benefit at the time.

2.3. Eligibility criteria

Publications were selected for inclusion according to criteria specified in Table 1. Briefly, articles reporting on COVID-19 vaccine safety, efficacy/effectiveness, or immunogenicity were included. Articles published in journals or as preprints, press releases and position statements were eligible for inclusion (hereafter referred to as "articles" unless otherwise specified). As the evidence base evolved, changes to the eligibility criteria were made to meet information needs for guideline development and to maintain feasibility of the literature curation process. For example, while studies on non-COVID-19 vaccines (e.g. Bacilli Calmette-Guerin [BCG]) were initially included because they were studied for indirect benefits to prevent COVID-19, these were no longer relevant when studies of COVID-19 vaccines became available. Similarly, in the absence of clinical evidence on new COVID-19 vaccine formulations authorized in Canada (i.e., bivalent mRNA vaccines targeting the Omicron BA.4/5 variant), preclinical studies conducted by vaccine manufacturers were included until clinical evidence for such vaccines became readily available. Shifts in eligibility were applied prospectively; previously included articles were not removed from the EXTRA COVID-19 Zotero library.

2.4. Citation screening

Title screening was performed in DistillerSR, an online systematic review management software (DistillerSR. Version 2.35. DistillerSR Inc.; 2023). To assist with the volume of literature returned from the search strategy, the DistillerSR Artificial Intelligence System (DAISY) was leveraged. DAISY is a natural language processor which can build a Text Classification model by using the response sets completed by reviewers. The classifier was trained using a training set of 1,300 citations (approximately 300 included citations), which had previously been manually reviewed by the team. The performance of DAISY was validated prior to implementation, with an accuracy $>$ 95 %. Additionally, prior to implementation, a two-week test period was used, where DAISY was run in parallel with manual, human review on a set of approximately 850 citations. Approximately 95 % of citations were correctly predicted by the classifier, and this was considered to be highly acceptable accuracy for an emergency system (recall sore of 0.94 +/- 0.06). In addition, the classifier was also able to identify potentially relevant citations that were missed by human review (approximately ≈3% of references). At the time of writing, the classifier has correctly predicted 98 % of 21,729 citations which have undergone human review to date.

The literature search was deduplicated by the ESG prior to receipt by EXTRA. Citations obtained from L·OVE and ESG were imported to DistillerSR and the classifier was run. Titles and abstracts deemed potentially relevant by the classifier, typically ranging from 10 to 15 % of the imported citations, then underwent rapid title screening by a single human reviewer. Abstracts were consulted when a decision regarding eligibility could not be made from the title alone. Following this process, potentially relevant citations were exported from DistillerSR to Zotero

Table 1
Eligibility criteria of items collected by the EXTRA COVID-19 vaccine scan.

	Inclusion	Exclusion
Population	No restriction	
Interventions/ exposures	• Any COVID-19 vaccine (including variant-specific vaccines, primary series or booster doses) • Monoclonal antibody therapies for prophylactic use • Convalescent plasma, antibody-based therapy (included only if comparator group received a COVID-19 vaccine)	• Monoclonal antibodies for therapeutic useIndirect evidence from other vaccines (e.g., BCG, influenza)[1] • Natural infection only[1]
Outcomes	• Safety (including allergies) • Immunogenicity • Efficacy/effectiveness	• Ethics, equity, feasibility, acceptability • Cost-benefit
Study designs	• Primary studies (e.g., clinical trials, case-control studies, cohort studies; includes studies reporting *ex vivo* data from human participants) • Systematic reviews • Rapid reviews • Position/guideline statement with primary data	• Preclinical studies[2] • *In vitro* or *in silico* studies • Non-systematic reviews • Commentaries or editorials not containing primary data • Modelling studies

[1] Initially included but later excluded as studies of COVID-19 vaccines became available.
[2] Preclinical studies of new COVID-19 vaccine formulations authorized in Canada (i.e., bivalent mRNA BA.4/5 COVID-19 vaccines) were included prior to the availability of clinical data.

for full-text screening by a single human reviewer. Citations not meeting eligibility criteria described in Table 1 were removed from the Zotero repository and archived in a separate folder. Potentially relevant citations identified from the other sources of interest (i.e., social media, GPHIN, news media), were also added directly to the Zotero library for full-text review by a human reviewer after title and abstract screening. Due to the overlap of titles found between different sources, a manual check for duplicates was conducted by a human reviewer after potentially eligible citations were uploaded to Zotero. Bibliographic details (i.e., title and DOI) of potential duplicates were compared and if articles were determined to be exact duplicates, one copy of the duplicate reference was removed. Updated preprint versions of previously included preprint articles were considered duplicates, and the original was deleted from the repository unless there were changes to the title, sequence of authors, or preprint server. Upon publication in a peer-reviewed journal, preprint versions were retained in the repository for completeness and linked to the published version using the "related" feature in Zotero.

Table 2
List of active tags.

Category	Terms
Category: 1. Publication Type	Journal publication, News report/press release, Position statement, Poster/conference abstract, Preprint/non-peer reviewed, Regulatory/NITAG/government report
Category: 2. Study Design	Case report, Clinical trial, Preclinical studies, Real-world observational study, Systematic review/*meta*-analysis (SR/MA)
Category: 3. Intervention [Vaccine]	Any vaccine, APA vaccine[1], Non-APA vaccine
Category: 4. Intervention [Vaccine platform]	DNA vaccine, Live-attenuated vaccine, Inactivated vaccine, mRNA vaccine, Mucosal vaccine, Multivalent, Protein subunit (including VLP), Variant vaccines, Viral vector vaccine, XBB.1.5 vaccine
Category: 5. Intervention [Vaccine manufacturer]	**APA Vaccines:** AstraZeneca/Covishield, Janssen/J&J, Medicago, Moderna, Novavax, Pfizer/BioNTech, Sanofi **Non-APA Vaccines:** Bharat Biotech, CanSino, CureVac, Gamaleya Research Institute, Medigen, Sinovac, Sinopharm, Unspecified COVID-19 vaccine
Category: 6. Intervention [Vaccine administration and dose issues][2]	Booster/Additional dose, Concurrent administration, Correlate of protection, Dose 1 outcome, Dose 2 outcome, Dose 3 outcome, Dose 4 outcome, Dose 5 outcome, Dose 6 outcome, Dose 7 outcome, Dose number not specified, Dosing errors, Extended interval, Fractional dose, Greater dose, Mixed schedule, Vaccine administration
Category: 7. Population[3]	Autoimmune, Breastfeeding, Children, Children under 12, Immunocompromised, Long COVID, Long-term care, Multi-system inflammatory syndrome (MIS)[4], Older adults, Pregnancy, Seropositive
Category: 8. Outcome *(Only applied when study reports results on the associated clinical outcome)*	**Allergy/AEFI Outcome Tags:** Allergy/AEFI, Anaphylaxis, Bell's palsy, Capillary leak syndrome, Fertility, Guillain-Barré syndrome, History of allergy, Immune thrombocytopenia, MIS (Multisystem inflammatory syndrome in children (MIS-C) or adults (MIS)), Myocarditis, Thrombotic thrombocytopenic purpura, Vasculitis, VITT **Other outcome tags:** Breakthrough infection, Efficacy/effectiveness, Immunogenicity, Mechanism, Reinfection, Transmission/asymptomatic infection outcome, Viral load, Variant Outcome Tags, Delta, Omicron
Category: 9. Other intervention/policy issue	Cross-reactivity, Drug interaction, Medication to prevent side effects, Prophylactic mAbs

[1] *APA: advanced purchase agreement. COVID-19 vaccine manufacturers with which Canada had an advanced purchase agreement include: Pfizer, Moderna, AstraZeneca, Janssen, Novavax, Medicago, and Sanofi.*

[2] *Only applied when study includes vaccinated individuals who received one of these vaccine administration methods/dose issues and reports outcomes in these individuals.*

[3] *Only applied when study includes vaccinated individuals who fall into one of the population groups and reports on the outcome of vaccine in these individuals.*

[4] *Includes MIS as an outcome in children (MIS-C) or adults (MIS-A), or studies where the population of interest already has MIS-C or MIS-A.*

2.5. Tagging and categorization of literature

To optimize efficient use of the Zotero repository and enhance searchability, custom tags were devised from controlled vocabulary developed by EXTRA. Custom tags allow for detailed characterization of each record and easy retrieval by keywords of interest and are organized into eight categories: publication type, study design, vaccine platform, manufacturer, special populations, vaccine outcome, and miscellaneous. The full list of active tags is outlined in Table 2. Similar to the eligibility criteria, the list of tags was dynamic allowing for the addition and removal of tags as the evidence base and internal information priorities evolved. For example, with the emergence of clinical evidence on bivalent COVID-19 vaccines in the beginning of 2022 [15], the tag *multivalent vaccines* was added to the list in January of 2022.

2.6. Dissemination to end users

Along with updating the Zotero repository, a comprehensive list of curated literature (titles and abstracts) was shared at regular intervals via email with NACI members, PHAC staff, and external groups (e.g., provincial public health organizations), for situational awareness of parties involved in decision-making. At the height of the COVID-19 vaccine response starting in March 2021, the circulation of the email occurred daily. The distribution frequency was reduced to twice weekly in April 2022 and then once weekly as of March 2023. Key studies of interest were highlighted at the top of the email. Fig. 1 outlines the entirety of EXTRA's COVID-19 literature curation process.

2.7. Analysis

To characterize the Zotero repository and to analyze trends, Microsoft Power BI data visualization software was used to analyze the frequency of recorded tags. The bibliographic data, including publication date, date added, categories of articles and associated tags, were exported into an Excel document from the EXTRA Zotero repository using the software export function. Two macros were developed and modified by EXTRA members in Microsoft Excel to extract the necessary data and to separate each tag into separate columns. This file was imported into Microsoft Power BI to create visual representations to record the trends and patterns in COVID-19 vaccine scientific literature.

3. Results

3.1. Characteristics of COVID-19 vaccine literature

3.1.1. General characteristics

As of December 31, 2023, with the assistance of DistillerSR's AI function, EXTRA processed 581,469 citations, of which 64,302 titles were screened manually. Of these, 19,050 records were eligible for inclusion and were added to the Zotero library. Here, we describe the characteristics and research themes of the 19,050 articles identified and fully tagged up to December 31, 2023. From March 2021 to December 31, 2023, a monthly median of 606 articles were included in the repository (Fig. 2); this estimate is inclusive of articles identified prior to March 03, 2021, which were retroactively added to the repository. The

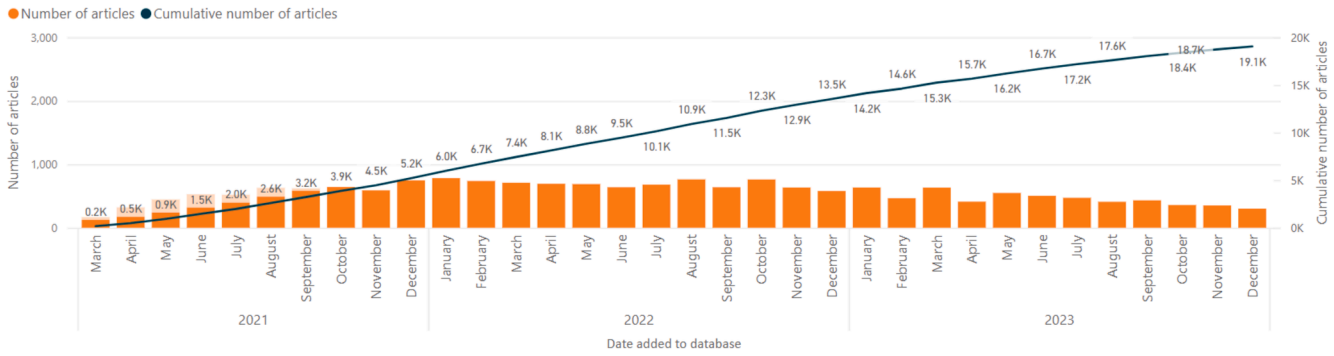

Fig. 2.

majority of relevant articles (63.9 %) were identified between August 2021 and January 2023, with an average of 20 articles added to the repository daily during this period. Change in volume of literature correlated with the evolution of COVID-19 pandemic and vaccine related events. For instance, a notable increase in volume occurred in late 2021, corresponding with the emergence of the Omicron variant. Another increase was observed in August and October 2022, which may have been associated with approvals and use of bivalent mRNA COVID-19 vaccines [16,17]. While the volume of evidence has remained relatively stable thereafter, a small but steady decline began in May 2023. Out of the articles found, 18 % (n = 3,436) were preprint articles (Supplementary Figure 1); approximately 45 % (n = 1,549) of these were later published in a journal. For study design, real-world observational studies comprised the bulk of articles (62.4 %; n = 11,890), followed by case reports (19.7 %; n = 3,760), systematic reviews (3.7 %; n = 713) and clinical trials (2.9 %; n = 566) (Supplementary Figure 2).

3.1.2. *Vaccine characteristics*

The majority of articles reported on mRNA vaccines (n = 13,910), followed by viral vector vaccines (n = 6,975), inactivated vaccines (n = 3,541), protein subunit vaccines (n = 648), and DNA vaccines (n = 26). Nearly two-fold more articles reported on Pfizer-BioNTech vaccines (n = 12,297) as compared to Moderna (n = 6,650); of these, 5,654 articles reported on vaccines from both manufacturers. Fewer articles reported on COVID-19 vaccines from AstraZeneca/Covishield (n = 5,291), Janssen (n = 2,342), Sinovac (n = 2,072), Sinopharm (n = 1,308), Gamaleya Research Institute (n = 613), Bharat Biotech (n = 433), Novavax (n = 287) and other manufacturers (i.e., Sanofi, Medicago, Medigen, CanSino, CureVac) (n = 314). Supplementary Figure 3 shows the volume of literature over time according to vaccine manufacturer.

3.1.3. *Special populations*

Post-market vaccine studies in special populations are critical to inform guidance development and are often conducted once a vaccine program has been launched, as these individuals are often excluded from pre-licensure clinical trials. In the case of COVID-19, a similar number of articles reported on immunocompromised people (n = 4,113) and adults over 60 years of age (n = 4,045). Just over 1,000 articles (n = 1,092) reported data for children (<18 years) with 35.8 % of those articles (n = 391) reporting data for children under 12 years of age. Data for pregnant and breastfeeding people were reported in 394 and 126 articles, respectively. While the number of articles added to the repository remained relatively stable for each subpopulation over most of the surveillance period, a decline was observed for each group from May to December 31, 2023 (Supplementary Figure 4).

3.1.4. *Outcomes*

Among commonly studied vaccine outcomes, safety outcomes were most frequently reported (n = 8,289) followed by immunogenicity (n = 7,269) and efficacy/effectiveness (n = 3,246) (Supplementary Figure 5). The complete list of tracked outcomes can be found in Category 8 in Table 2. Among the safety outcomes of interest, the most commonly reported were myocarditis/pericarditis (n = 681), VITT (n = 563), and anaphylaxis (n = 251). Articles reporting on anaphylaxis, VITT and myocarditis/pericarditis first emerged in March and April 2021, respectively, with an average of nearly 20, 17, and 7 articles respectively on each outcome archived monthly until December 31, 2023 (Supplementary Figure 6). Other safety outcomes, including Bell's Palsy (n = 118), Guillain-Barré syndrome (n = 241), and vasculitis (n = 279) were less frequently reported on. A total of 2,291 articles specifically examined the occurrence of breakthrough infections as an outcome of interest. Excluded from this estimate are studies that reported breakthrough cases only for the purpose of calculating vaccine effectiveness. Studies reported less frequently on reinfection (n = 281) and transmission or asymptomatic infections (n = 179).

3.1.5. *Dose-optimizing strategies*

During periods of supply scarcity in emergency settings, it is essential to investigate dose-optimizing strategies to extend available resources and increase health equity [13]. For COVID-19 vaccine dose-optimizing

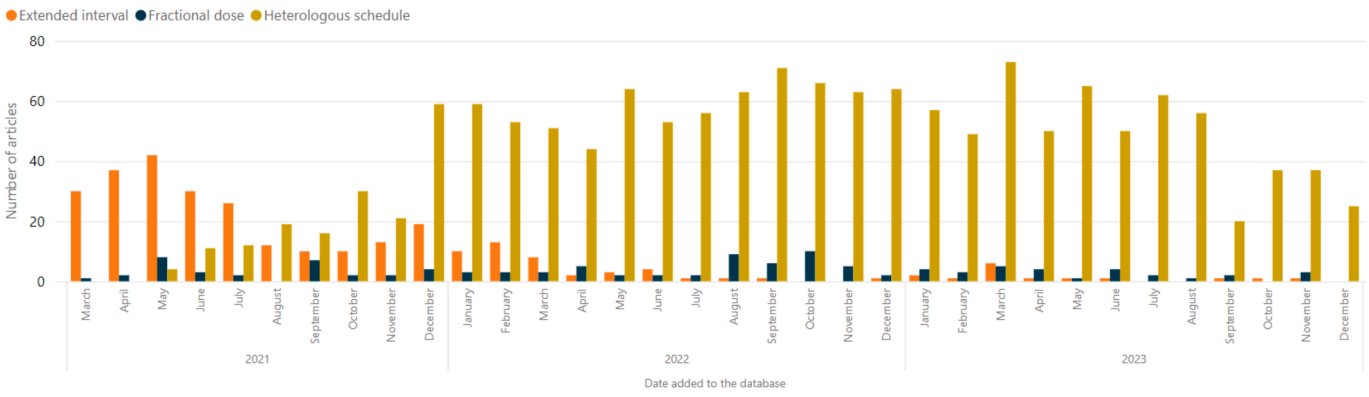

Fig. 3.

strategies, far more articles reported on heterologous schedules (i.e., at least two different vaccines used in the vaccination schedule, n = 1,460) as compared to extended intervals between doses in the primary series (i.e., dosing intervals longer than the authorized indication, n = 288) or fractional dosing (i.e., a dose lower than that of the authorized indication, n = 112) (Fig. 3).

3.2. Utility for vaccine guidance development

As PHAC is heavily depended on by Canadians and provincial/territorial governments to provide vaccination strategies, evidence-based recommendations were required at an unprecedented speed to support the COVID-19 health emergency response. NACI relied extensively on the EXTRA COVID-19 evidence monitoring system to complete rapid COVID-19 vaccine guidance updates for Canada. EXTRA's scan leveraged daily literature searches conducted by the Emerging Sciences Group (ESG) at PHAC, whose work has been previously described [14]. The number of articles identified in this search ranged from 200 to 2,500 citations per day (a median of 700 citations daily during the winter of 2020). It would take a single reviewer nearly a full day to screen and sort this volume of titles manually. In EXTRA's protocol, the AI classifier was the first reviewer, resulting in significant person-hours saved (approximately four to eight hours per day) and importantly allowing for the second review and full-text screening of included articles for tagging purposes to be completed on the same day to facilitate a daily email dissemination of findings. This resulted in a living, searchable, up-to-date repository that could be leveraged to answer research questions within days or weeks. The required turnaround time for some NACI updates and associated evidence reviews during the initial years of COVID-19 vaccine roll-out ranged from days to approximately three to four months. NACI guidance updates on COVID-19 vaccines occurred approximately every one to two weeks throughout 2021–2022, resulting in 51 NACI publications (Supplementary Figure 7) [13]. Notable examples of rapid updates leveraging EXTRA's scanning activities and curated literature repository include the NACI rapid guidance on VITT [18,19], booster doses in individuals and staff in long-term care [20], NACI guidance on myocarditis [21,22] and timing of vaccination in individuals who were previously infected [23], initial guidance on heterologous primary series (Fig. 3) [24], and the off-label additional dose in immunocompromised populations [25].

3.3. Facilitation of rapid reviews

Unlike a gold standard systematic review, the EXTRA model was designed to capture data broadly beyond a single focused clinical question. This breadth was necessary because the system objectives were to support daily vaccine situational awareness, and also to support ad-hoc rapid reviews of evidence on emerging COVID-19 vaccine policy topics to inform new decisions. The accrued volume of literature on COVID-19 vaccines and careful organization by specific topics of interest facilitated the ability to conduct rapid evidence reviews that were used to inform NACI guidance. Fig. 3 demonstrates the evolving nature of the COVID-19 vaccine literature, tailored to topics of interest to public health and governing bodies. There was often a need to develop timely guidance for specific populations for which evidence was not available from initial pre-licensure clinical trials. One such example included individuals with immunocompromising conditions or medications. It became apparent soon after the initial phase of vaccine roll-out in spring 2021 that these individuals had a suboptimal immune response to vaccination with COVID-19 vaccines, and many studies were eventually published including immunocompromised populations (Supplementary Figure 4). The EXTRA repository and tagging system facilitated multiple rapid reviews [26–29] that supported evolving NACI guidance on this topic [26–29], including the development of specific criteria for defining moderately to severely immunocompromised as a clinical status for vaccine recipients [30], which was subsequently implemented in the majority of Canadian provinces and territories.

The EXTRA repository was also leveraged to support NACI guidance on COVID-19 vaccination for individuals who are pregnant or breastfeeding (also populations excluded from clinical trials) [31], on the interchangeability of COVID-19 vaccines [24] and on COVID-19 vaccination for individuals who have been infected with SARS-CoV-2 prior to vaccination (which has gone through several iterations and updates over the past three years) [18,23,32–37]. Similar to vaccination in immunocompromised individuals, these topics were identified as emerging issues soon after vaccine roll-out and NACI and PHAC were able to issue timely guidance in part due to the ability to quickly identify relevant scientific literature from the EXTRA literature scan.

4. Discussion

EXTRA's COVID-19 scientific literature scan and vaccine repository has been integral for PHAC situational awareness. The use of a hybrid (AI and human) curation process enabled the accurate and rapid assessment of the literature needed for the timely development of vaccine guidance. Through observing the trends in COVID-19 vaccine publications over time, we can see that the peak global research efforts occurred over a two-year period from mid-2021 to mid-2023. Recent trends suggest a decline in the production of COVID-19 vaccine literature. It is helpful to observe that the research cycle pertaining to vaccines for a novel pandemic virus (illustrated by SARS-CoV-2 and COVID-19 vaccine research) may include a six-month startup period, a two-year period of intense research outputs, followed by a steady de-escalation. Notably, the EXTRA scan did not include literature on vaccine confidence or non-vaccine related topics such as disease surveillance and clinical disease progression, thus research trends for these topics may be slightly different.

The COVID-19 literature curation process performed by EXTRA can be considered a form of a living evidence review. A living evidence review is one which utilizes continual updating and the ongoing surveillance of emerging research evidence to provide the most up-to-date evidence-base possible [38]. Several unique challenges in performing these reviews during the COVID-19 pandemic have been discussed [39], including the frequency of required updates, given the rate at which impactful research, which had the ability to impact policy decisions, was being published. Funding and resource constraints often limit the frequency at which updates can be performed, which is why the leveraging of the Distiller AI classifier was so important. In addition, the expedited timelines at which public health guidance was required during the COVID-19 pandemic did not allow for the application of typical evidence review methodology. The use of AI methods to assist with screening in literature reviews continues to spark debate in the evidence synthesis community, however it has shown great promise to date for the reduction in person-hours required to produce high-quality evidence reviews [40,41]. This significant advantage offered by AI-based literature screening methods was of particular importance for EXTRA's work. EXTRA processed over 500,000 citations, a task which would not have been possible without the use of AI-assisted screening methods. While considerable effort was invested in the development, training and refinement of the Distiller AI classifier, the use of this technology ultimately allowed this project to be successful and of great use to the Public Health Agency of Canada and NACI.

During the height of the COVID-19 pandemic, NACI was required to rapidly escalate the pace and output of work in order for PHAC to provide timely guidance on COVID-19 vaccines to Canadians. The number of NACI meetings and publications increased dramatically from three meetings and four publications prior to the pandemic in 2019 to 10, 55 and 24 meetings, and 11, 31 and 20 publications in 2020, 2021 and 2022 respectively (Supplementary Figure 7). Out of the 62 publications released between 2020–2022, 45 publications were on COVID-19. EXTRA's COVID-19 literature curation process was iteratively designed and streamlined to support NACI and the unprecedented pace of work.

The comprehensive search strategy, broad inclusion criteria and timely categorization of the extensive evidence base allowed NACI to base its decisions on the most thorough review of the evidence possible in the given timelines. Otherwise, in an environment where public health advice was often requested just as the supporting data were becoming available, it is possible that public health advice and policy could have been centered around an incomplete evidence base.

EXTRA's COVID-19 literature curation process has outlined a methodology that can be adapted to fit the needs of other research groups and applied to other areas of research, outside of COVID-19. To date, this COVID-19 real-time evidence monitoring process has already been successfully adapted to monitor emerging mpox vaccine literature, allowing PHAC and NACI to quickly respond to the 2022 mpox outbreak [42]; vaccine guidance from NACI was published approximately 21 days after the first reported case in Canada. A similar process has also been adopted by PHAC for an ongoing biweekly scan of scientific literature on influenza vaccines. Going forward, it is well-suited to serve the evidence gathering needs of research teams who are required to respond to future outbreaks of infectious diseases as well as any potential future pandemics. It can also be adapted to serve areas where personnel dedicated to literature surveillance may be lacking. With sufficient investment in both the development of a robust and comprehensive search strategy and the development and training of an AI screening tool, research teams may be able to continuously, actively monitor ongoing literature relevant to a specific topic of interest, without large investments in personnel time. Typically, evidence reviews (including living reviews) are an intensive and time-consuming process, with the article screening process often being the most time-consuming and resource-intensive step [43,44], however AI-assisted screening tools can help to reduce the burden. EXTRA's scan also relied on importing articles to be scanned that were obtained by searches of several databases, which was a time-consuming process and required a significant time investment. This could potentially be reduced by leveraging DistillerSR's LitConnect tool to automatically import newly published literature. DistillerSR's AI classifier can also be used to tag articles, based on information contained in the abstract of imported citations, but not based on information within the full-text articles due to barriers preventing AI applications from automatically accessing full-text content held by publishers. EXTRA did not utilize this feature as application EXTRA's extensive list of tags required full-text review and tags needed to be added in the public-facing Zotero repository. However, this feature could be used for projects with a simpler tagging system and for which access to the library through Distiller alone would satisfy the needs of the project team. Tools to automate additional steps of evidence reviews (such as automating the risk of bias assessments [45]) are available and represent potential next steps in the EXTRA literature curation methodological pathway.

Our project is subject to some important limitations. For feasibility, each stage of the literature curation process was conducted by a single reviewer without verification by a second. Title screening by a single reviewer, coupled with solely AI-based exclusion of a vast majority of citations, may have resulted in the inadvertent exclusion of relevant literature. However, the risks remained low, through the mitigation measures put in place by the team (i.e., training of the classifier on a large manually screened dataset, creation of standard operating procedures, training of new team members, regular team meetings, etc.) coupled with the accuracy of the trained Distiller AI classifier (>95 %). Single person review for article tagging may also increase the risk of misclassification resulting in missed studies when utilizing tags for repository mining. However, once again, the team put a number of mitigating measures in place to minimize the impact of these factors including the creation of detailed inclusion/exclusion criteria, extensive training of new personnel over a period of weeks, and the choice to use Zotero to house the literature repository, as its advanced search functions could often compensate for missed tags. EXTRA's screening process, eligibility criteria and indexing terms evolved over the surveillance period to match information needs. Due to the pace of work, efficiency and rapid identification and categorization of the latest scientific literature were prioritized, which may limit the use of the repository for other purposes. Achieving a high level of specificity with respect to identifying literature within the repository on specific topics is precluded by the tagging structure. For example, when data for multiple populations are reported in an article, it is difficult to attribute a reported outcome to a specific population of interest, therefore all applicable tags are used. For example, selecting the tag "Efficacy" and "Older adults" may result in an overinclusive yield, with all articles reporting on the efficacy, and reporting on outcomes in older adults, but not necessarily efficacy *in* older adults (i.e., efficacy estimates may not have been stratified by age). While these limitations have implications on the utility of the repository, they should be interpreted in the context of a public health emergency requiring access to evidence in a timely manner. In particular, while use of level 4 automation (i.e., fully automated decisions regarding eligibility) [10] is not recommended during title and abstract screening for knowledge syntheses products, the repository was not intended to serve as an evidence base for the production of rigorous systematic reviews [12]. Reliance on AI for citation screening was a pragmatic decision necessitated by the volume of emerging evidence and the emergency context.

5. Conclusion

EXTRA's monitoring of COVID-19 vaccine literature and the resulting repository has allowed for the characterization of rapidly emerging evidence during a pandemic. The findings of this system illustrate the trajectory of global research capacity to study and publish on a novel vaccine program, and also demonstrate the inherent time lags between policy needs and available vaccine research. These research time lags are particularly relevant for special populations who are often not included in initial clinical trials, and for dose optimizing strategies which are critical early in the rollout when supply may be limited. Our findings can be used to inform expectations around research volume, type, and rate allowing for the prediction of resourcing needs to prepare for future emergency monitoring activities. Although this hybrid vaccine evidence monitoring system still relied on extensive human resources, there is potential in the future to further automate the process by leveraging more AI capabilities.

CRediT authorship contribution statement

Su Hyun Lim: Writing – review & editing, Writing – original draft, Methodology, Investigation, Formal analysis, Data curation, Conceptualization. **Mona Hersi:** Writing – review & editing, Writing – original draft, Methodology, Formal analysis, Data curation, Conceptualization. **Ramya Krishnan:** Writing – review & editing, Writing – original draft, Methodology, Investigation, Formal analysis, Data curation, Conceptualization. **Joshua Montroy:** Writing – review & editing, Writing – original draft, Methodology, Investigation, Formal analysis, Data curation, Conceptualization. **Bonnie Rook:** Writing – review & editing, Methodology, Investigation, Formal analysis, Data curation. **Kelly Farrah:** Writing – review & editing, Methodology, Formal analysis, Data curation, Conceptualization. **Yung-En Chung:** Writing – review & editing, Methodology, Investigation, Formal analysis, Data curation. **Adrienne Stevens:** Writing – review & editing, Supervision, Methodology, Formal analysis. **Joseline Zafack:** Writing – review & editing, Methodology, Conceptualization. **Eva Wong:** Writing – review & editing, Methodology, Conceptualization. **Nicole Forbes:** Writing – review & editing, Methodology, Conceptualization. **April Killikelly:** Writing – review & editing, Methodology, Conceptualization. **Kelsey Young:** Writing – review & editing, Supervision, Project administration, Methodology, Conceptualization. **Matthew Tunis:** .

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Declaration of competing interest

The authors declare the following financial interests/personal relationships which may be considered as potential competing interests: Matthew Tunis reports financial support was provided by Public Health Agency of Canada. If there are other authors, they declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.jvacx.2024.100575.

Data availability

Data will be made available on request.

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