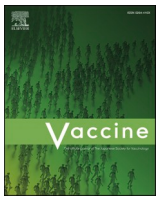
Vaccine 62 (2025) 127581

Contents lists available at ScienceDirect

Vaccine

journal homepage: www.elsevier.com/locate/vaccine



Exploring off-label vaccine use: a survey of the global national immunization technical advisory group network

Candace Roberts [a], Karina A. Top [b], Louise Henaff [c], Matthew Tunis [a], Awnish Singh [d], Judith van Holten [c], Simona Ruta [e], Shalini Desai [a,*]

[a] Public Health Agency of Canada, 130 Colonnade Rd S, Nepean, Ontario K2E 1B6, Canada
[b] Department of Pediatrics, Faculty of Medicine and Dentistry and School of Public Health, University of Alberta, 11405-87 Avenue, Edmonton, Alberta T6G 1C9, Canada
[c] World Health Organization, Immunization, Vaccines and Biologicals Department, Avenue Appia 20, 1211, Geneva 27, Switzerland
[d] Department of Epidemiology, University of Michigan, 1415 Washington Heights, Ann Arbor, MI, United States of America
[e] Carol Davila University of Medicine and Pharmacy and Stefan S. Nicolau Institute of Virology, 285 Mihai Bravu, Bucharest 030304, Romania

ARTICLE INFO

Keywords:
Off-label vaccines
Vaccination
Immunization
Vaccine policy
National Immunization Technical Advisory Group

ABSTRACT

Background: National Immunization Technical Advisory Groups (NITAGs) are crucial for enhancing vaccine use in immunization programs, particularly through off-label recommendations. This study sought to assess the adoption and trends of off-label vaccine recommendations made by NITAGs across low-, middle-, and high-income countries since the COVID-19 pandemic.

Methods: An online survey was distributed to NITAG representatives in World Health Organization (WHO) member states, asking questions related to off-label use of vaccines including policies, procedures, legislation, and regulations for NITAGs in participants' countries. Respondents across all six WHO regions were invited to participate.

Results: Respondents from 76 countries participated in the survey (55 %) were NITAG representatives, and 45 % were immunization program managers or from the NITAG secretariat). Most respondents 52 (68 %) reported their NITAG makes off-label recommendations, 18 (24 %) indicated their NITAG does not make off-label recommendations, and 6 (8 %) were unsure of their NITAG's role. There was a noticeable shift relating to off-label vaccine recommendations observed pre, during, and post-pandemic period. Prior to 2022, 25 (48 %) respondents indicated their country recommended off-label vaccines, 11 (21 %) specified off-label recommendations were limited to emergencies as temporary or conditional expansions, and 6 (12 %) were unsure. After 2022, 30 (58 %) respondents indicated their country recommended off-label vaccines, 4 (8 %) specified off-label recommendations were limited to emergencies as temporary or conditional expansions, 18 (35 %) selected no, and 0 (0%) were unsure. While most countries make off-label recommendations, few (15 %) have policies and procedures to support implementation.

Conclusions: Although WHO broadly provides guidance on the mandate and core functions of NITAGs, globally, they have differing mandates and operational capacities related to off-label vaccine use. These findings suggest the need for increased awareness of off-label vaccine recommendations and strengthened dialogue around implementation of off-label recommendations.

1. Background

National Immunization Technical Advisory Groups (NITAGs) play a vital role in optimizing vaccine use within immunization programs to maximize public health benefits and minimize risks. Once vaccines are licensed, NITAGs play a key role in reviewing scientific evidence, including vaccine safety, immunogenicity, effectiveness, and disease epidemiology for program introduction and as needed for program updates [1–3]. Based on emerging evidence or public health needs (i.e. outbreaks), NITAGs may consider a change in the recommendation of vaccine use for particular age groups, populations, or schedules. NITAGs may reevaluate the risk-benefit analysis of immunization in outbreak

* Corresponding author.
E-mail address: shalini.desai@phac-aspc.gc.ca (S. Desai).

https://doi.org/10.1016/j.vaccine.2025.127581
Received 6 June 2025; Received in revised form 28 July 2025; Accepted 31 July 2025
Available online 12 August 2025

and pandemic situations, such as the COVID-19 [4] pandemic, in vaccine shortages (i.e. inactivated polio vaccine) [5], and for specific subgroups [6]. Additionally, they may explore alternative dosing schedules (i.e. HPV vaccine) [7,8], fractional doses (i.e. yellow fever vaccine) [9], and the interchangeability of different vaccines.

When specific use cases are not listed in the approved product labelling information, they are called "off-label." There has been variability in how off-label vaccines are defined. For example, Health Canada uses "when a drug is used in a treatment regime or patient population that is not included in the Notice of Compliance (NOC), and a drug is used for an indication other than those specifically included in the NOC" [10]. The European Medicines Agency defines off-label vaccination as "use of a medicine for an unapproved indication or in an unapproved age group, dosage, or route of administration" [11]," while the US Food and Drug Administration defines it as "when a marketed drug is prescribed to treat a patient for an unlabelled indication" [12]. In some areas of therapeutic medicine, particularly pediatrics, [13–16] off-label use is exceedingly common in clinical practice. Recognizing that therapeutic use is different than preventive use, pediatric prescriptions are provided off-label for therapeutic use at varying rates in most clinical settings, and 50 % or more in specific clinical settings in some countries [13,15–17].

Numerous reasons exist for making off-label recommendations for vaccines. These reasons may include specific age groups or subpopulations that may be at heightened risk for complications arising from the disease [18], such as administering influenza vaccinations to immunocompromised patients and pregnant women who were not included in pre-licensure clinical trials, and therefore may not be listed in the product labelling information. Additionally, there may be variations in the recommended immunization schedule, exemplified by recommendations for a one-dose schedule for the human papillomavirus (HPV) vaccine [7,8]. Beyond the considerations for specialized groups and immunization schedules, NITAGs may also issue off-label recommendations to facilitate the integration of new vaccines into the existing immunization schedule, thereby promoting greater vaccine uptake and reducing costs. The ability of NITAGs to issue recommendations differs among countries, primarily as a result of legal constraints, and concerns regarding liability [19].

Off-label recommendations require a careful assessment of potential benefits and risks, with an emphasis on populations with the greatest medical need or aimed at optimizing programmatic use through streamlined immunization schedules. For example, during the COVID-19 pandemic, many NITAGs extended the time between doses of the primary series to accommodate supply related issues [4], but later maintained an extended interval period when data showed better immune responses and lower risk of adverse events, such as myocarditis or pericarditis, with a longer duration between doses [20]. NITAGs often review and update recommendations as new observational and clinical trial data emerge [21]. In contrast, product labelling information is not revised proactively unless the vaccine company/manufacturer submits new data and requests a change in indications through their regulatory body.

The practices of countries worldwide regarding off-label vaccine use are not well understood. A previous study of functional NITAGs reported that several are empowered to issue off-label recommendations [22], and these off-label recommendations are made for several different reasons, including burden of disease in specific populations (immunocompromised populations), cost, simplification of schedules, among others [23]. Accordingly, the Global NITAG Network (GNN) has identified off-label vaccine use as an issue for further study, [24] considering its potential broad implications for policy, ethics, program delivery, and legal considerations.

The present study aimed to examine the adoption and trends in off-label vaccine recommendations by NITAGs in low-, middle-, and high-income countries, with a specific focus on changes observed since the COVID-19 pandemic. Furthermore, the study sought to identify the evidence requirements, legal implications, enabling factors, and policy frameworks that support the integration of off-label vaccine use into immunization programs.

2. Methods

An online survey was conducted to review the existing policies, procedures, legislation, and regulations governing the use of off-label vaccines by NITAGs. WHO member states with a NITAG were invited to participate.

The survey tool was developed using Top et al.'s [22] survey instrument as a guide. Given the change in context and new literature since the original instrument was designed, additional questions were added to capture change in practices before, during and after the COVID-19 pandemic. The survey was entered into the Microsoft Forms for distribution in three languages: English, French, and Spanish.

Invitation emails containing an embedded personalized link to the survey was sent to the current chair and secretariat of NITAGs that had provided their contact information to WHO. The email was sent from the GNN secretariat which resides within WHO. The survey was open for a total of 3 weeks. Only one reply per country was requested. After the initial email, two additional reminder emails were sent one week apart. Participants indicated their consent by clicking on the consent form to proceed to the survey.

The online survey consisted of questions regarding existing policies, procedures, legislation and regulation governing the use of off-label vaccines by NITAGs in the participants' countries. Participants were asked about the types of evidence and enablers NITAGs consider when recommending an off-label use of vaccines, and if and how post-implementation reviews regarding off-label vaccine use are conducted. In addition, participants were asked about policies and procedures to support the implementation of off-label recommendations and whether there are legal concerns surrounding off-label use in their countries, as well as their position, years in current role, and country (see Appendix B).

This study was reviewed by the WHO and PHAC research ethics boards and determined to be exempt from full review.

2.1. Analysis

Survey data was downloaded from Microsoft forms and uploaded into MS Excel. Data cleaning was completed to ensure that skip patterns were enforced. Analysis of survey responses included quantitative and qualitative components. Quantitative analysis used descriptive statistics to stratify responses by WHO regions and World Bank national income status categories [25]. Further analysis was conducted to analyze off-label use pre (before 2020), during (2020−2022),and post (after 2022)-the COVID-19 pandemic and if vaccines were used as an emergency measure or part of routine programs. In addition, evidentiary requirements, policies, legislation and practices gathered from survey respondents were reviewed and assessed for commonalities and differences. Qualitative analysis was conducted to identify themes in free-text questions. Given the limited free-text questions, qualitative analysis was done in Microsoft Excel.

3. Results

3.1. Demographic data

Of the 173 countries with NITAGs, contact details were available for 120 (69 %). The 120 countries were contacted and 76 responses were received, resulting in a response rate of 63 %. The demographic characteristics of survey respondents are presented in Table 1. Countries responded from all 6 WHO regions, and from low-, middle-, and high-income countries (see Fig. 1). Responses received were from NITAG representatives 42 (55 %) and Immunization Program Manager or the

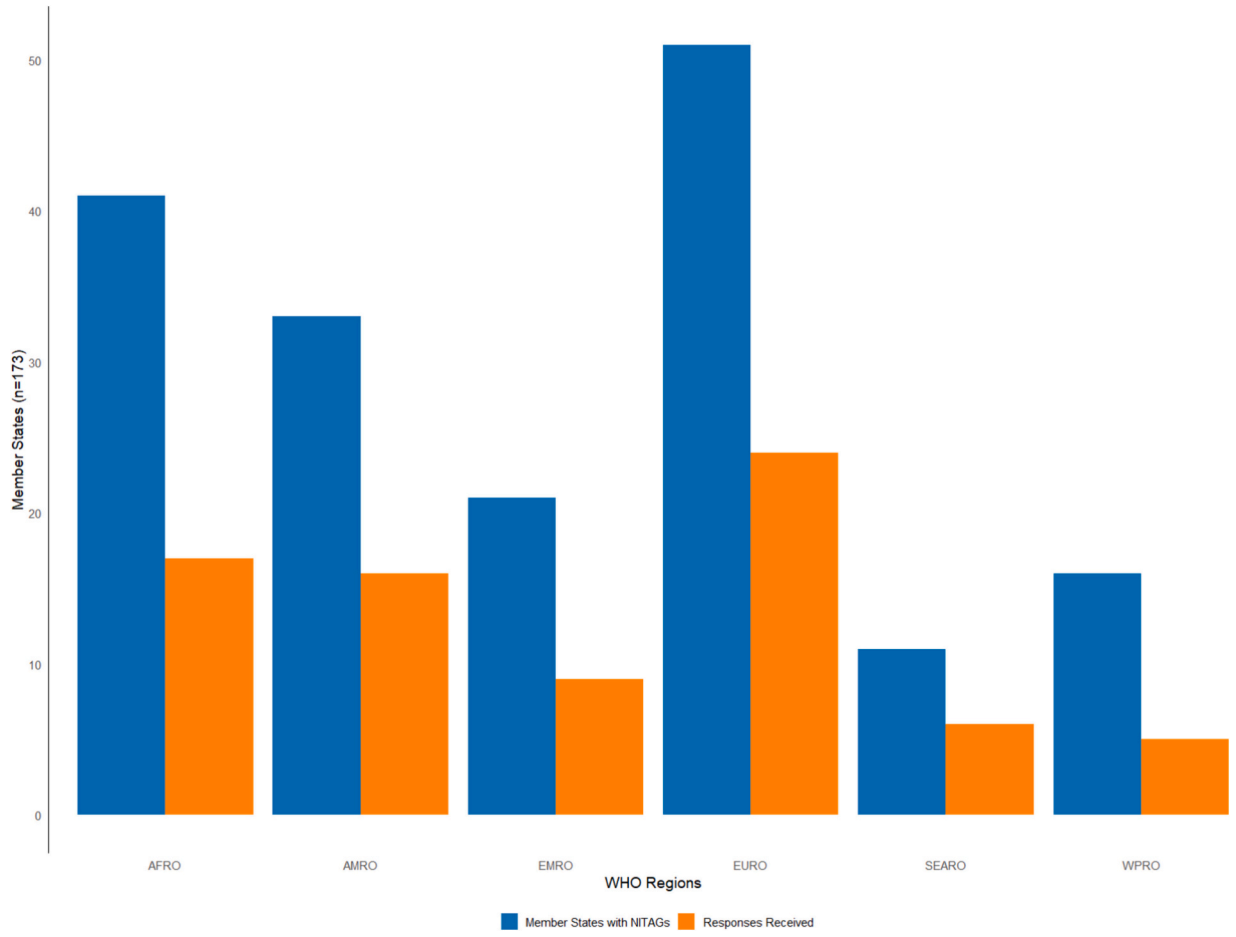


Fig. 1. Responses by region.

NITAG Secretariat 34 (45 %).

3.2. Context for making off-label recommendations

Among the countries surveyed, 52 (68 %) respondents reported that their NITAG had made off-label recommendations at some point, 18 (24 %) indicated that their NITAG did not make off-label recommendations, and 6 (8 %) of respondents were unsure of their NITAG's role in the process of making off-label recommendations. Of the 76 respondents, 54 (71 %) indicated having a definition for off-label use in their country, while 22 (29 %) noted not having a definition. Of those countries who had a definition, the most common definition 48 (89 %) of off-label use was "use of vaccines in age groups, populations, and dosing schedules that are different from the package insert". There were no substantial differences in use off-label recommendations based on WHO region or income level.

When asked if their country's NITAG had a mandate for making off-label recommendations, 33 (43 %) of responding countries indicated that their local NITAG was mandated to make off-label recommendation. Respondents further identified the evidence used and enablers to making recommendations in Table 2. In relation to implementation, 28 (85 %) of the 33 respondents who indicated that their NITAG has a mandate for making off-label recommendations said their recommendation was implemented, 4 (12 %) said the recommendation had not been implemented, and 1 (3 %) were unsure. Nine respondents (12 %) indicated other bodies (i.e. Ministry, ad hoc committee) have a mandate for making off-label recommendations, while 16 respondents (21 %) indicated that they were unsure.

3.3. Pre, during, and post-COVID-19 pandemic

When asked if their country recommended the use of vaccines off-label pre-, during, or post-pandemic, there was a shift from pre-pandemic (before 2020) to post-pandemic (after 2022). Of the 52 countries that responded to this question, in the pre-pandemic period, 25 (48 %) respondents indicated that their country made off-label vaccine recommendations, 11 (21 %) only made off-label recommendations in an emergency as a temporary or conditional expansion of vaccine use, 10 (19 %) selected no, and 6 (12 %) respondents were unsure. Post-pandemic, 30 (58 %) respondents indicated their country recommended off-label vaccines, 4 (8 %) specified off-label recommendations were limited to emergencies as temporary or conditional expansions, 18 (35 %) selected no, and 0 (0%) were unsure, demonstrating a shift away from the "yes, only in an emergency as a temporary or conditional expansion" and "unsure" categories to the "yes", and "no" selections (See Fig. 2).

3.4. Other considerations related to off-label vaccine use

Respondents were asked a series of questions related to additional considerations for off-label vaccine use. Of the 76 respondents, 20 (26 %) reported having a vaccine injury compensation program (VICP). Of the 20 countries who have a VICP, off-label use of vaccine would be eligible for compensation in 11 (55 %) countries. In addition, 27 (35 %) respondents reported having legal concerns regarding off-label use, 24 (32 %) had no legal concerns, and 25 (33 %) were unsure. Respondents' legal concerns are categorized in Table 3. When stratified by WHO region, respondents from the South-East Asia Regional Office (SEARO)

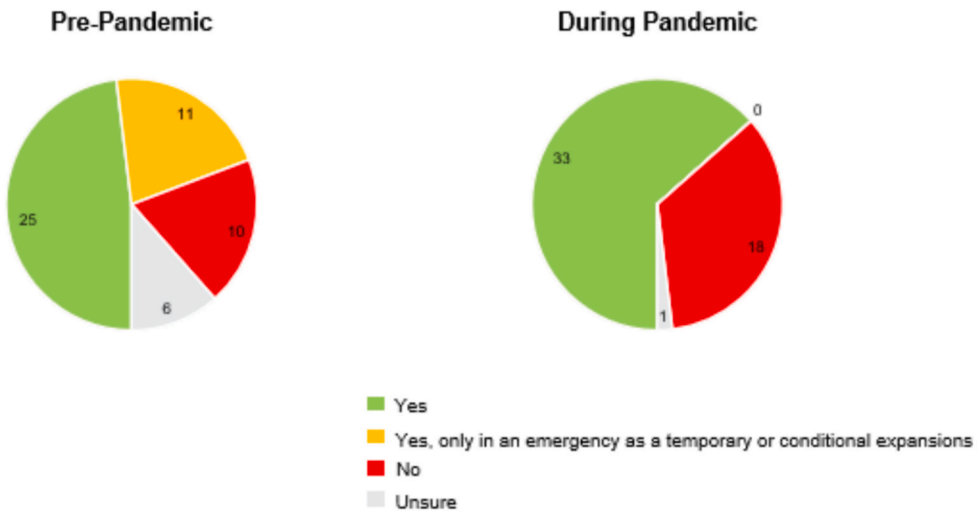


Fig. 2. Pre (before 2020), during (2020–2022), and post-pandemic (after 2022) changes in off-label recommendations.

countries most frequently reported having legal concerns (e.g., healthcare provider liability and litigation of government) when compared to those from other regions (see Table 4 in Appendix A).

Responses on whether countries have policies and procedures for off-label use and if post-implementation reviews are conducted are demonstrated by region in Table 5. Out of the 76 countries, 11 countries (15 %) have policies and procedures to support implementation and 16 (21 %) reported conducting post-implementation reviews. The most common types of post-implementation reviews reported by the 16 countries were programmatic evaluation 10 (63 %), followed by serosurveys 8 (50 %), evaluation of immunogenicity in special populations 5 (31 %), evaluation of effectiveness in special populations 5 (31 %), evaluation of economic benefits 2 (13 %), and other 1 (6 %), such as safety assessments (See Table 6 in Appendix A). When asked to select all bodies responsible for conducting the post-implementation studies, most respondents 15 (94 %) selected their government as responsible. In addition to government, 4 respondents (25 %) also selected academic institutions, and one respondent (6 %) indicated that their NITAG was responsible for conducting post-implementation reviews. While most of the responding countries, 9 (56 %), indicated that there has been no change as a result of post implementation studies, 5 (31 %) indicated that their NITAG has been able to strengthen their recommendation, 3 (19 %) reported that the manufacturer used the post implementation studies to update the product labelling information, and finally, 2 (13 %) indicated that they changed back to an on-label recommendation. When stratified by region (see Table 5) and income level (see Table 7 in Appendix A), SEARO and middle-income countries reported conducting post-implementation reviews most frequently.

Table 1
Demographic characteristics.

Demographic Data	Responses (n = 76)	
	No.	% of respondents
Role		
NITAG Representative	42	55
Immunization Program Manager Or NITAG Secretariat	34	45
Years in role		
1–4 yrs	27	36
> 5 years	49	64
Income level		
High	29	38
Middle	38	50
Low	9	12

4. Discussion

This study provides international insights into the definitions, mandates, and operational and legal factors related to off-label use and recommendations during and after the COVID-19 pandemic. Seventy-six countries with NITAGs from all WHO regions reported changes in issuing off-label vaccine recommendations over time. While this study does not provide evidence of causality, further examination of how NITAGs decide on making off-label recommendations would be warranted. In some instances, the reason for off-label recommendations may be mostly related to logistics such as supply issues (COVID-19 vaccines) that occurred during that timeframe [4]. It is possible that activities related to the COVID-19 pandemic have influenced how NITAGs perceive and approach off-label recommendations, resulting in greater acceptance and comfort with this practice. Interestingly, while most

Table 2
Evidence used and enablers to off-label recommendations reported by participants ($n = 33$).[1]

	n	% of respondents
Reported evidence used to make off-label recommendations		
WHO recommendations	30	91
Randomized Control Trials	25	76
Observational studies (e.g., cohort, case-control studies)	22	67
Adverse event and/or disease surveillance data from your country	19	58
Expert opinion	19	58
Adverse event and/or disease surveillance data from another country	18	55
Discussions with other NITAGs	18	55
Information provided by manufacturers	15	45
Discussions with other national regulatory authorities	13	39
Case reports	7	21
Other	2	6
Enablers that facilitate making off-label recommendations		
WHO SAGE recommended off-label use	25	76
Other countries recommended off-label use	20	61
Emergency situation (i.e. outbreak response)	18	55
Need for vaccine use for a specific population	17	52
Response to vaccine shortage	11	33
Possible cost savings	8	24
No concerns about product liability	2	6
Other	2	6

[1] Participants were able to select all that apply.

Table 3
Categories of legal concerns reported by respondents ($n = 27$).[1]

Categories of legal concerns	n	% of respondents
Healthcare providers are liable in event of adverse event following immunization (AEFI) after off-label use	15	56
Government concern about lawsuit in event of adverse event following immunization (indemnity)	14	52
In country rules do not allow for off-label recommendations	7	26
Effect on vaccine purchasing agreements with manufacturers	3	11
Other	3	11

[1] Participants were able to select all that apply.

Table 5
Mechanisms to operationalize off-label recommendations reported by all respondents (n = 76).

	AFRO ($n = 17$)	AMRO (n = 16)	EMRO ($n = 9$)	EURO ($n = 23$)	SEARO ($n = 6$)	WPRO ($n = 5$)
Policies and procedures for implementation						
Yes (n = 11)	2 (12 %)	2 (13 %)	2 (22 %)	3 (13 %)	1 (17 %)	1 (20 %)
No (n = 48)	11 (65 %)	13 (81 %)	4 (44 %)	16 (70 %)	3 (50 %)	1 (20 %)
Unsure (n = 17)	4 (24 %)	1 (6 %)	3 (33 %)	4 (17 %)	2 (33 %)	3 (60 %)
Post-implementation evaluation						
Yes (n = 16)	2 (12 %)	4 (25 %)	3 (33 %)	3 (13 %)	4 (67 %)	0 (0 %)
No (n = 49)	12 (71 %)	11 (69 %)	4 (44 %)	18 (78 %)	1 (17 %)	3 (60 %)
Unsure (n = 11)	3 (18 %)	1 (6 %)	2 (22 %)	2 (9 %)	1 (17 %)	2 (40 %)

countries identified making off-label recommendations, few countries indicated having policies and procedures for implementation and evaluation.

Our study aligns with previous research by Top et al. [22] who reported that 14 (54 %) of the 26 countries surveyed made off-label recommendations. In our study, 52 (68 %) of the 76 countries surveyed reported making off-label vaccine decisions. Though 43 % of countries reported that their local NITAG has a mandate to issue off-label recommendations, not all of those countries had made any such recommendations. This suggests that off-label policy decision making is nuanced by country.

When examining additional considerations related to off-label vaccine use, respondents most commonly reported using WHO and SAGE recommendations as evidence and enablers to facilitate making off-label recommendations. Notably, few respondents reported that their NITAGs had policies and procedures for implementation of off-label vaccine recommendations. It is possible that respondents may not be aware of these downstream steps, given that NITAGs are typically not responsible for implementation of vaccine programs. Consequently, few studies or evaluations have been conducted on the post-implementation evaluation of off-label recommendations. Many countries with post-implementation reviews were middle-income countries, more so than high-income countries. In instances where programmatic data is already being collected (e.g., as part of surveillance programs), reporting these findings would be helpful to the overall vaccine landscape and could provide evidence for changes in practice in other countries or to the product labelling information. A small proportion of respondents indicated that the manufacturer used the post implementation studies to update the product labelling information. Future research should explore the motivation, evidence, and enablers used by manufacturers updating product labelling to expand on-label use. A consistent global standard regarding the criteria or situations that merit off-label recommendations would enable NITAGs to adopt similar approaches to off-label vaccine use around the world; however, risk tolerance for off-label advice is a contextual factor and therefore we expect to continue seeing variable approaches based on different country contexts. Given our study identified that the off-label recommendations of peer countries were a strong enabler for each other to pursue off-label use, international information sharing should be encouraged.

In examining legal considerations, many expressed concern about indemnity and liability. These concerns could be mitigated by creating a vaccine injury compensation program that includes compensation for adverse events following off-label use of vaccines as recommended by the NITAG. This, in turn, may encourage off-label use, which could benefit overall immunization program reach.

This study demonstrates that NITAGs continue to be faced with decisions related to off-label vaccine use. While this study offers critical insights, further work is required to better understand the nuances of how off-label recommendations are made and used by countries. Future research could use a case study approach to further investigate how and when NITAGs make off-label vaccine recommendations and what supports are needed to enable NITAGs to make off-label recommendations in line with updated evidence of safety and effectiveness. Case studies in countries that have conducted post-implementation evaluations would also provide a chance to understand how these evaluations were done, how the additional data was brought back to the NITAG and how the results further influenced policy development. In addition, investigation of how NITAG recommendations are communicated to healthcare providers and how providers discuss on-label and off-label use with vaccine recipients could also inform future implementation of NITAG recommendations. For countries where off-label recommendations are not allowed, having additional data generated by academia and others in the public domain could results in a change in product labelling information, allowing these countries to make informed on-label recommendations. Our survey also highlighted the opportunity for further education through GNN activities or as a part of training programs provided for new NITAG members. WHO and SAGE could likewise leverage these findings to support and guide countries in making informed decisions regarding off-label recommendations.

4.1. Limitations

Of the 173 countries that have NITAGs, the authors only had contact details for 120. This may have resulted in a higher proportion of countries who have well established NITAGs responding to the survey. This would likely overestimate the use of off-label vaccine recommendations. It is also possible that in instances where NITAGs are not involved in making off-label recommendations, our survey respondents may not have knowledge of the processes in their country.

The survey was only offered in English, French and Spanish, which may not have been the first language for the respondents who replied on behalf of their country. This may have resulted in respondents not understanding the question in the way it was intended or led to lower response rates from countries where NITAG representatives were not comfortable in any of the available languages. For example, survey respondents were asked about antigen-specific off-label recommendations. However, despite pilot testing the survey tool, inconsistencies in the interpretation by respondents were evident, resulting in the data being excluded from this manuscript. This area requires further investigation in future research to better capture the unique contextual factors within each country.

For numerous questions, “unsure” was selected as the response, as demonstrated in the tables included. It is unclear whether this was a function of respondents being unsure because they are new to their role or if off-label recommendations are not within the scope of their work. This was especially evident in responses related to the pre-pandemic

period. Most respondents (55 %) were new to their roles (1–4 years) and may not be aware of pre-pandemic practices.

5. Conclusion

In conclusion, NITAGs continue to use off-label vaccine recommendations to expand the policies that inform their immunization programs. The definitions, mandates, and factors influencing off-label use varies by country, region, and income level. During the COVID-19 pandemic, there was a notable increase in off-label vaccine recommendations, and more than half of NITAGs have continued to issue off-label advice for vaccines post-pandemic. While numerous factors were identified as influencing off-label recommendations, the notable limited availability of policies, procedures, and post-implementation evaluations available suggest further research is needed regarding the enablers of how countries implement and assess off-label vaccine recommendations.

CRediT authorship contribution statement

Candace Roberts: Data curation, Formal analysis, Methodology, Project administration, Validation, Writing – original draft, Writing – review & editing. **Karina A. Top:** Conceptualization, Data curation, Formal analysis, Investigation, Writing – original draft, Writing – review & editing. **Louise Henaff:** Conceptualization, Data curation, Investigation, Resources, Writing – review & editing. **Matthew Tunis:** Conceptualization, Investigation, Writing – original draft, Writing – review & editing, Formal analysis. **Awnish Singh:** Conceptualization, Formal analysis, Investigation, Writing – review & editing. **Judith van Holten:** Conceptualization, Formal analysis, Investigation, Writing – review & editing. **Simona Ruta:** Conceptualization, Formal analysis, Investigation, Writing – review & editing. **Shalini Desai:** Writing – review & editing, Writing – original draft, Validation, Supervision, Resources, Project administration, Methodology, Investigation, Funding acquisition, Conceptualization.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Acknowledgements

This study was funded by the Public Health Agency of Canada.

Appendix A

Table 4
Legal concerns by WHO region ($n = 76$).

Region	Yes	No	Unsure
AFRO (17/41 countries)	3 (18 %)	5 (29 %)	9 (53 %)
AMRO (16/33 countries)	6 (38 %)	8 (50 %)	2 (13 %)
EMRO (9/21 countries)	5 (56 %)	1 (11 %)	3 (33 %)
EURO (23/51 countries)	7 (30 %)	8 (35 %)	8 (35 %)
SEARO (6/11 countries)	4 (67 %)	1 (17 %)	1 (17 %)
WPRO (5/16 countries)	2 (40 %)	1 (20 %)	2 (40 %)
Total	27 (36 %)	24 (32 %)	25 (33 %)

Table 6
Impact of post implementation reviews ($n = 16$) *participants were able to select all that apply.

	n	% of respondents
Type(s) of post-implementation review		
Programmatic evaluation	10	63
Serosurveys	8	50
Evaluation of immunogenicity data in special populations	5	32
Evaluation of effectiveness in special populations	5	32
Evaluation of economic benefits	2	13
Other	1	6
Who conducts post-implementation review		
Government	15	94
Academic institution	4	25
Other	3	6
Post-implementation studies change recommendation		
No change as a result of post implementation studies	9	56
Their NITAG has been able to strengthen their recommendation	5	31
The manufacturer used the post implementation studies to update the product insert	3	19
They changed back to an on-label recommendation	2	13

Table 7
Post implementation review by income level (n = 76).

Income (# of respondents)	Yes (% of respondents)	No (% of respondents)	Unsure (% of respondents)
High (29/76 countries)	3 (10 %)	22 (76 %)	4 (14 %)
Middle (38/76 countries)	12 (32 %)	19 (50 %)	7 (18 %)
Low (9/76 countries)	1(11 %)	7 (78 %)	1 (11 %)
Total	16 (21 %)	48 (63 %)	12 (16 %)

Appendix B. Survey Questions

1. In what country do you currently work? (If you work in multiple countries, indicate the country where you are most familiar with immunization policy/regulation)
2. What is your current role in immunization in your country?

a. National Immunization Technical Advisory Group (NITAG) chair or other NITAG member
b. Immunization program manager or NITAG secretariat
c. Other (please specify)

3. How many years have you been in your current role?
   a. < 1 year
   b. 1–4 yrs.
   c. > 5 years
4. How does your NITAG define off-label use of vaccines? Select all that apply.
   a. Use of vaccines outside of the routine EPI program
   b. Use of vaccines in a clinical trial
   c. Use of vaccines in age groups, populations, and dosing schedules that are different from the package insert
   d. Use of vaccines as recommended by a public health body
   e. Other (please specify)
   f. NITAG does not have a definition
5. Does your country recommend any vaccines off label?

a. Yes
b. No
c. Unsure

6. Did your country recommend the use of vaccines off-label pre COVID-19 pandemic (before 2020)?

a. Yes
b. Yes, only in an emergency as a temporary or conditional expansion
c. No
d. Unsure

7. Which vaccines have been recommended off label pre COVID-19 pandemic (before 2020)? Select all that apply.

   a. BCG
   b. Hepatitis (HepA, HepB)
   c. Polio (IPV, OPV)
   d. DTP-containing (Td, DTwP, DTaP, etc.)
   e. Pneumococcal
   f. Rotavirus
   g. Measles-containing (Measles, MR, MMR, MMRV)
   h. HPV
   i. Japanese encephalitis
   j. Yellow fever
   k. Tick-borne encephalitis
   l. Typhoid
   m. Cholera
   n. Meningococcal-containing (MenA, MenB, MenC, MenACWY)
   o. Rabies
   p. Dengue
   q. Malaria
   r. Seasonal Influenza
   s. Varicella
   t. Smallpox/mpox

u. Herpes Zoster

8. How were the vaccines recommended off-label pre COVID-19 pandemic (before 2020)? Select all that apply.

a. Expanded age groups
b. reduced or increased number of doses
c. reduced or extended dosing interval
d. Different route (e.g. ID vs IM)
e. Different dose (fractional dose),
f. Use in special populations not included in package insert (e.g. children, in pregnancy, immunocompromised individuals)
g. Use of indication not in package insert (e.g. post-exposure prophylaxis, different pathogen)
h. Interchangeably between vaccines or mixed schedules

9. Why did your country choose to recommend these vaccines off-label pre COVID-19 pandemic (before 2020)?
   a. Cost issues
   b. Supply issues
   c. Outbreak control
   d. To simplify immunization schedule
   e. To fit our country's epidemiological need
   f. To follow WHO/SAGE recommendations
   g. To promote health equity (i.e. to vaccinate a vulnerable group)
   h. Other (please specify)
10. Did your country recommend the use of COVID-19 vaccines off-label during the pandemic (2020–2022)?

a. Yes
b. No
c. Unsure

11. How were COVID-19 vaccines recommended off-label during the pandemic (2020–2022)? Select all that apply.

a. Expanded age groups
b. reduced or increased number of doses
c. reduced or extended dosing interval
d. Different route (e.g. ID vs IM)
e. Different dose (fractional dose),
f. Use in special populations not included in package insert (e.g. children, in pregnancy, immunocompromised individuals)
g. Interchangeably between vaccines or mixed schedule

12. Why did your country choose to recommend COVID-19 vaccines off-label during the pandemic (2020–2022)?

a. Cost issues
b. Supply issues
c. Outbreak control
d. To simplify immunization schedule
e. To fit our country's epidemiological need
f. To follow WHO/SAGE recommendations
g. To promote health equity (i.e. to vaccinate a vulnerable group)
h. Other (please specify)

13. Did your country recommend the use of vaccines off-label after the pandemic (after 2022)?

a. Yes
b. Yes, only in an emergency as a temporary or conditional expansion
c. No
d. Unsure

14. Which vaccines have been recommended off-label after the pandemic (after 2022)? Select all that apply.

   a. Same as before the COVID-19 pandemic (before 2020)
   b. BCG
   c. Hepatitis (HepA, HepB)
   d. Polio (IPV, OPV)
   e. DTP-containing (Td, DTwP, DTaP, etc.)
   f. Pneumococcal
   g. Rotavirus
   h. Measles-containing (Measles, MR, MMR, MMRV)

i. HPV
j. Japanese encephalitis
k. Yellow fever
l. Tick-borne encephalitis
m. Typhoid
n. Cholera
o. Meningococcal-containing (MenA, MenB, MenC, MenACWY)
p. Rabies
q. Dengue
r. Malaria
s. Seasonal Influenza
t. Varicella
u. Smallpox/mpox
v. COVID-19 vaccines

15. How were COVID-19 vaccines recommended off-label after the pandemic (after 2022)? Select all that apply.

a. Expanded age groups
b. reduced or increased number of doses
c. reduced or extended dosing interval
d. Different route (e.g. ID vs IM)
e. Different dose (fractional dose),
f. Use in special populations not included in package insert (e.g. children, in pregnancy, immunocompromised individuals)
g. Use of indication not in package insert (eg post-exposure prophylaxis, different pathogen)
h. Interchangeably between vaccines or mixed schedules

16. Why did your country choose to recommend vaccines off-label after the pandemic (after 2022)?

a. Cost issues
b. Supply issues
c. Outbreak control
d. To simplify immunization schedule
e. To fit our country's epidemiological need
f. To follow WHO/SAGE recommendations
g. To promote health equity (i.e. to vaccinate a vulnerable group)
h. Other (please specify)

17. Does the NITAG have a mandate for making recommendations related to off-label use of vaccines?
    a. Yes
    b. No, another body (ie Ministry, ad hoc committee) is responsible.
    c. No, decisions concerning off-label use of vaccines have not been made in my country
    d. Unsure
18. Please specify body (ie Ministry, ad hoc committee) responsible for issuing off-label recommendations
19. Who has submitted requests for recommendations regarding off-label vaccine use to the NITAG?
    a. National Regulatory Authority
    b. Other Public Health Agencies
    c. Organizations within the Ministry of Health
    d. Healthcare professional societies (Physicians, nurses etc)
    e. NITAG members
    f. Other (please specify)
20. What types of evidence does the NITAG in your country use for making recommendations on off-label use of vaccines? (Check all that apply)
    a. Randomized controlled trials
    b. Observational studies (e.g., cohort, case-control studies)
    c. Case reports
    d. Adverse event and/or disease surveillance data from your country
    e. Adverse event and/or disease surveillance data from another country
    f. Information provided by manufacturers
    g. Discussions with other NITAGs
    h. Discussions with national regulatory authorities
    i. WHO recommendations
    j. Expert opinion
    k. Not sure
    l. Other – please specify
21. What were the enablers to make an off label recommendation?
    a. Other countries recommended off-label use
    b. WHO SAGE recommended off-label use

c. Emergency situation (ie outbreak response)
d. Need for vaccine use for a specific population
e. Possible cost savings
f. Response to vaccine shortage
g. No concerns about product liability
h. Other (please specify)

22. Prior to making an off-label recommendation, what other groups does your NITAG speak to?
    a. Ministry of Health
    b. National regulatory authority
    c. Scientific and/or professional organization
    d. Other ministry authority (provinces/states)
    e. Other NITAGs
    f. Other body/organization (specify)
    g. No other bodies are consulted
    h. Unsure
23. Have the off label recommendation made by the NITAG been implemented?

a. Yes
b. No
c. Unsure

24. Please specify below which off-label vaccine recommendations have been implemented in your country:
25. Does your country have a Vaccine injury compensation program (VICP)?

a. Yes
b. No
c. Unsure

26. Are vaccines recommended for off-label use covered by the VICP?

a. Yes
b. No
c. Unsure

27. Vaccines recommended off-label use are covered by the VICP if:
    a. Licensed in our country
    b. Recommended by our NITAG
28. Are there legal concerns (i.e. relating to product liability or indemnification) regarding off-label use of vaccines in your country?

a. Yes
b. No
c. Unsure

29. Please describe the concerns:
    a. Healthcare providers are liable in event of adverse event following immunization (AEFI) after off-label use
    b. Government concern about lawsuit in event of adverse event following immunization (indemnity)
    c. In country rules do not allow for off label recommendations
    d. Effect on vaccine purchasing agreements with manufacturers
    e. Other – please specify
30. How are these concerns addressed?
    a. National Injury compensation program introduction
    b. International Injury compensation program
    c. Change in law
    d. Other (please specify)
31. Are there policies or procedures to support the implementation of off-label recommendations for vaccine use in your country? An example can be found here

a. Yes
b. No
c. Unsure

32. Please describe and send a copy of the policy (and the reference) to: shalini.desai@phac-aspc.gc.ca
33. If your NITAG has made off-label recommendations in the past, does your NITAG conduct post-implementation reviews of these off label recommendations?

a. Yes

b. No
c. Unsure

34. What types of post implementation reviews have you conducted?
    a. Serosurveys
    b. Evaluation of immunogenicity data in special populations
    c. Evaluation of effectiveness in special populations
    d. Evaluation of economic benefits
    e. Programmatic evaluation
    f. Other (please specify)
35. Who conducts the post implementation studies?
    a. Government
    b. Academic Institution
    c. Manufacturers
    d. Other (please specify)
36. Have these post-implementation studies changed the recommendation?

a. No change as a result of post implementation studies
b. Our NITAG has been able to strengthen our recommendation
c. The manufacturer has used the post implementation studies to update the product leaflet
d. We changed back to an on label recommendation
e. Other (please specify)

37. If you have any additional comments on off-label recommendations for vaccine use, please include them below.
38. Can we contact you for more information on off-label recommendations for vaccine use in your country?

a. Yes
b. No

39. If yes to 53, please provide your name, email address and telephone number.
    a. Name _____
    b. Email_____

Data availability

The data that has been used is confidential.

References

[1] Dobson SR, McNeil S, Dionne M, Dawar M, Ogilvie G, Krajden M, et al. Immunogenicity of 2 doses of HPV vaccine in younger adolescents vs 3 doses in young women: a randomized clinical trial. Jama 2013;309(17):1793–802. https://doi.org/10.1001/jama.2013.1625.

[2] Healy CM, Rench MA, Baker CJ. Importance of timing of maternal combined tetanus, diphtheria, and acellular pertussis (Tdap) immunization and protection of young infants. Clin. Infect. Dis. 2013;56(4):539–44. https://doi.org/10.1093/cid/cis923.

[3] Kharbanda EO, Vazquez-Benitez G, Lipkind HS, Klein NP, Cheetham TC, Naleway A, et al. Evaluation of the association of maternal pertussis vaccination with obstetric events and birth outcomes. Jama 2014;312(18):1897–904. https://doi.org/10.1001/jama.2014.14825.

[4] World Health Organization. Interim recommendations for use of the Pfizer–BioNTech COVID-19 vaccine, BNT162b2, under emergency use listing [internet]. Geneva: WHO; 2025. 2021 Jan 8 [accessed 2025 Jul 17]. Available from: https://www.who.int/publications/i/item/WHO-2019-nCoV-vaccines-SAGE_recommendation-BNT162b2-2021.1.

[5] Sutter RW, Cochi SL. Inactivated poliovirus vaccine supply shortage: is there light at the end of the tunnel? J. Infect. Dis. 2019;220(10):1545–6. https://doi.org/10.1093/infdis/jiy739.

[6] Centers for Disease Control and Prevention (CDC). Updated recommendations for use of tetanus toxoid, reduced diphtheria toxoid, and acellular pertussis vaccine (Tdap) in pregnant women—Advisory Committee on Immunization Practices (ACIP). MMWR Morb Mortal Wkly Rep [Internet]. 2013 Feb 22 [accessed 2025 Jul 17];62(7):131–5. Available from: https://www.cdc.gov/mmwr/preview/mmwrhtml/mm6207a4.htm[1](https://www.cdc.gov/mmwr/preview/mmwrhtml/mm6207a4.htm; 2012.

[7] World Health Organization. Human papillomavirus vaccines: WHO position paper, December 2022. Wkly Epidemiol Rec [Internet]. Dec 16 [accessed 2025 Jul 17];97(50):645–72. Available from: https://www.who.int/publications/i/item/who-wer9750-645-672; 2022.

[8] National Advisory Committee on Immunization (NACI). Update on the recommended human papillomavirus (HPV) vaccine immunization schedule. Ottawa (ON): Public Health Agency of Canada; 2015 [accessed 2025 Jul 17]. Available from: https://www.canada.ca/en/public-health/services/publications/vaccines-immunization/national-advisory-committee-immunization-updated-recommendations-hpv-vaccines.html.

[9] Secretariat WHO. Fractional dose yellow fever vaccine as a dose-sparing option for outbreak response [internet]. Geneva: World Health Organization; 2016 [accessed 2025 Jul 17]. Available from: https://www.who.int/publications/i/item/WHO-YF-SAGE-16-1.

[10] Veterans Affairs Canada. Prescription drugs (POC 10) [internet]. Ottawa: Veterans Affairs Canada; 2025. 2012 May 18 [accessed 2025 Jul 17]. Available from: https://www.veterans.gc.ca/en/about-vac/reports-policies-and-legislation/policies/prescription-drugs-poc-10.

[11] European Medicines Agency. Off-Label use [Internet]. Amsterdam: EMA [accessed 2025 Jul 17]. Available from: https://www.ema.europa.eu/en/glossary-terms/label-use; 2025.

[12] Food and Drug Administration (US). Guidance for clinical investigators, sponsors, and IRBs: Investigational new drug applications (INDs) — Determining whether human research studies can be conducted without an IND [internet]. Maryland: FDA. 2013. Sep [accessed 2025 Jul 17]. Available from:https://www.fda.gov/media/79386/download**[1](https://www.fda.gov/media/79386/download).

[13] Neville KA, DAC Frattarelli, Galinkin JL, Green TP, Johnson TD, Paul IM, et al. Off-label use of drugs in children. Pediatrics 2014;133(3):563–7. https://doi.org/10.1542/peds.2013-4060. COMMITTEE ON DRUGS.

[14] GWT Jong, Eland IA, Sturkenboom MC, van den Anker JN, Stricker BH. Unlicensed and off label prescription of drugs to children: population based cohort study. BMJ 2002;324(7349):1313–4. https://doi.org/10.1136/bmj.324.7349.1313.

[15] Meng M, Ge B, Lei W, et al. Paediatric off-label use of drugs in Gansu, China: a multicentre cross-sectional study. BMJ Open 2024;14:e078126. https://doi.org/10.1136/bmjopen-2023-078126.

[16] Bücheler R, Schwab M, Mörike K, Kalchthaler B, Mohr H, Schröder H, et al. Off label prescribing to children in primary care in Germany: retrospective cohort study. BMJ 2002;324(7349):1311–2. https://doi.org/10.1136/bmj.324.7349.1311.

[17] Schrier L, Hadjipanayis A, Stiris T, et al. Off-label use of medicines in neonates, infants, children, and adolescents: a joint policy statement by the European academy of Paediatrics and the European Society for Developmental Perinatal and Pediatric Pharmacology. Eur. J. Pediatr. 2020;179(6):839–47. https://doi.org/10.1007/s00431-019-03556-9.

[18] National Advisory Committee on immunization (NACI). Canadian immunization guide chapter on influenza and statement on seasonal influenza vaccine for 2016–2017 [internet]. Ottawa (ON): Public Health Agency of Canada [accessed 2025 Jul 17]. Available from: https://www.canada.ca/en/public-health/services/publications/vaccines-immunization/canadian-immunization-guide-statement-seasonal-influenza-vaccine-2022-2023.html; 2016.
[19] Henaff L, Zavadska D, Melgar M, Fihman J, Steffen C, Hombach J. The role of NITAGs in government decisions on vaccine use: insights from the fifth global NITAG network meeting. Lancet Infect. Dis. 2024;24(4):e214–5. https://doi.org/10.1016/S1473-3099(24)00078-1.
[20] Buchan SA, Seo CY, Johnson C, et al. Epidemiology of myocarditis and pericarditis following mRNA vaccination by vaccine product, schedule, and Interdose interval among adolescents and adults in Ontario, Canada. JAMA Netw. Open 2022;5(6):e2218505. https://doi.org/10.1001/jamanetworkopen.2022.18505.
[21] Public Health Agency of Canada. National Advisory Committee on Immunization (NACI): Workplan [Internet]. Ottawa: Government of Canada; [updated 2024; accessed 2025 May 22]. Available from: https://www.canada.ca/en/public-health/services/immunization/national-advisory-committee-on-immunization-naci/workplan.html; 2025.
[22] Top KA, Esteghamati A, Kervin M, Henaff L, Graham JE, MacDonald NE. Governing off-label vaccine use: an environmental scan of the global National Immunization Technical Advisory Group Network. Vaccine 2020;38(5):1089–95. https://doi.org/10.1016/j.vaccine.2019.11.033.
[23] Adams K, Diallo D, Tadount F, Mouajou V, Quach C. Evaluation of the decision-making process underlying the initial off-label use of vaccines: a scoping review. Vaccine 2024;42(23):126246. https://doi.org/10.1016/j.vaccine.2024.126246.
[24] MacDonald NE, Duclos P, Wichmann O, Henaff L, Harnden A, Alshammary A, et al. Moving forward on strengthening and sustaining National Immunization Technical Advisory Groups (NITAGs) globally: recommendations from the 2nd global NITAG network meeting. Vaccine 2017. https://doi.org/10.1016/j.vaccine.2017.10.048.
[25] World Bank. GNI per Capita [accessed 2025 May 12]. Available from: https://data.worldbank.org/indicator/NY.GNP.PCAP.CD?view=chart; 2025.