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Governing off-label vaccine use: An environmental scan of the Global National Immunization Technical Advisory Group Network

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ABSTRACT

Background: National Regulatory Authorities approve the indications for vaccine use in the product information. Occasionally, National Immunization Technical Advisory Groups (NITAGs) make off-label recommendations for use in different age groups, populations, and dosing schedules from the product information. We sought to determine the rationale, policies and procedures for NITAG off-label recommendations.

Methods: We conducted an environmental scan of Global NITAG Network members, immunization program managers and regulators in 38 high-, middle- and low-income countries. Participants completed an online survey regarding policies, procedures, and legislation governing development of off-label recommendations. A sub-sample of respondents met for a focus group and interviews which were analyzed qualitatively.

Results: Thirty-four people responded from 26/38 (68%) countries surveyed; 76% of respondents were NITAG members or immunization program managers. Recommendations for off-label vaccine use were made in 14/26 (54%) countries; the NITAG made those recommendations in 8/14 (57%) countries. Reasons for off-label vaccine recommendations included response to disease outbreaks or vaccine shortages. Only one country had standard operating procedures for developing off-label recommendations while 6/14 (43%) countries had policies for implementing off-label recommendations. Nine respondents from 8 countries agreed to participate in a focus group (n = 6) or individual interviews (n = 3). Barriers to off-label recommendations included legal concerns, lack of standard definition for off-label use, and manufacturer reluctance to update product information. Facilitators included confidence in the decision-making process, and transparency of open communication among stakeholders.

Conclusions: Best practice guidelines are needed that define off-label use and outline a transparent, evidence-based approach to develop off-label recommendations.

1. Introduction

Indications for use of a new vaccine are provided in the authorised product information following review and approval of the scientific evidence for the vaccine's safety, efficacy and quality by the country's National Regulatory Authority (NRA). Recommendations for incorporating the vaccine into the immunization program are then made by the National Immunization Technical Advisory Group (NITAG) following expert review. NITAG recommendations aim to maximize public health benefit. Following vaccine licensure and introduction into immunization programs, additional scientific evidence is generated predominantly in middle- and high-income countries through clinical trials and observational studies of the safety, immunogenicity and effectiveness of the vaccine in different populations or schedules than those included in pre-licensure trials [1–3]. Based on this new evidence, the NITAG may decide to make recommendations on vaccine use in specific age groups, populations or schedules that are not listed in the original product monograph [4,5]. In addition, disease outbreaks and/or vaccine shortages may compel NITAGs to reassess the risk-benefit balance of immunization in certain subgroups and/or to consider alternate

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dosing schedules even without robust empirical evidence [6–8]. In such cases, NITAG recommendations are termed "off-label".

Off-label use has been variably defined as "*use of drugs (or vaccines) relating to situations where a medicine is intentionally used for a medical purpose not in accordance with the authorised product information*" (European Medicines Agency), "*when a marketed drug is prescribed to treat a patient for an unlabelled indication*" (US Food and Drug Administration), and "*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*" (Health Canada) [9].

Recommendations for off-label use of vaccines may include age groups or sub-populations not included in pre-licensure clinical trials but who may be at increased risk of complications from the disease (e.g., influenza vaccination in immunocompromised patients) [10], or use in a different schedule than what is recommended on the label [e.g., 2 instead of 3 doses of human papillomavirus vaccine (HPV)] [4,5]. In response to a shortage of yellow fever vaccine (YFV) during a large outbreak, the World Health Organization (WHO) recommended fractional dosing of YFV [8]. Fractional dosing of inactivated polio vaccine (IPV) has also been suggested to reduce costs and stretch the limited vaccine supply [11]. Finally, NITAGs may make off-label recommendations to facilitate incorporation of a new vaccine into the existing immunization schedule. NITAGs review and update recommendations regularly as new observational and clinical trial data emerge [12]. In contrast, NRAs do not require regular updates to product information except where new safety concerns arise or the company submits new data to request a change in indications [9].

In 2017, 131 high-, middle-, and low-income countries reported having NITAGs in place to make immunization recommendations and provide guidance to national policy-makers and program managers to enable evidence-based immunization program decision-making, including off-label use [13]. Off-label use of vaccines may have broad implications for policy, ethics, program delivery and the law, yet country-specific practices regarding off-label vaccine use are not well known. Uncovering the similarities and differences in how these issues are approached and the evidence required across different countries will help to identify best practices for off-label vaccine recommendations and policies that can guide future policy and programmatic decisions. The Global NITAG Network has flagged off-label use as an issue for further study [14].

This study sought to describe the processes NITAGs in low-, middle- and high-income countries use to make recommendations for off-label use of vaccines, and identify barriers and facilitators to making off-label recommendations.

2. Methods

2.1. Study design and participants

We conducted an environmental scan in low-, middle- and high-income countries that were members of the Global NITAG Network. We included NITAG members, immunization program managers and drug and/or vaccine regulators working in countries with NITAGs that met the six basic WHO criteria for a functional NITAG based on the WHO/UNICEF joint reporting process and/or were members of the Global NITAG Network Steering Committee [15]. Eligible participants were contacted via email and asked to complete an online survey regarding existing policies, procedures, legislation and regulation governing the development and implementation of off-label recommendations for vaccine use. Survey respondents who provided their contact information were invited to participate in a focus group or interview to provide further details of barriers and facilitators to developing off-label recommendations in their country.

2.2. Ethics

All participants provided informed consent. The study was approved by the IWK Health Centre Research Ethics Board.

2.3. Survey development

The 20-item questionnaire was developed by the investigators, reviewed for content validity, and piloted among 4 experts in public health, drug or vaccine regulation and vaccinology, including a former NITAG member. Questions were in multiple choice and free-text format and captured demographics (country of work, role in vaccine policy and decision-making), the existence of standard operating procedures (SOPs), legislation and/or regulation concerning the development, communication and implementation of off-label vaccine recommendations, and the ethical and legal issues considered in developing the off-label recommendation (Supplemental Content 1). The survey was professionally translated into French and Spanish, back translated to verify accuracy, and distributed using Opinio survey software on a server hosted in Halifax, NS, Canada. Participants indicated their consent by clicking on the consent form to proceed to the survey.

2.4. Focus groups and informant interviews

To gather in-depth information on the development and implementation of off-label recommendations for vaccine use, survey respondents were invited to participate in a 45 min focus group held in conjunction with the Global NITAG Network meeting in Ottawa, Canada on December 6–7, 2018 or in informant interviews (30–45 min). The focus group and interviews were conducted in English and recorded and transcribed verbatim. They probed for past experience with developing, implementing and/or regulating off-label vaccine use; concerns raised, strategies used, policies developed, communication plans implemented, and legislation addressing this area. Interview participants were given the opportunity to review their interview transcript for accuracy and confidentiality.

2.5. Data analysis

Survey data were downloaded from Opinio into SAS® and narrative comments were downloaded into MS Excel for analysis. Analysis was performed by country. Where multiple responses were received from the same country, responses were combined. Where there were discrepancies, the response from the NITAG member was given priority. Quantitative analysis was descriptive and used SAS® statistical software version 9.4 (SAS Institute, Cary, NC).

Qualitative analysis of interview and focus group data was conducted using the process of thematic analysis [16,17]. Following transcription, two researchers individually coded the data using NVivo11™ software (QSR International, Burlington, MA). Both researchers read all transcripts to generate an initial set of codes. The initial codes were then collated into potential themes by constant comparison of all relevant data. The researchers met regularly to review the coding and themes. Disagreements were discussed until consensus was reached. Through ongoing analysis and discussions amongst the study team, the themes were refined and linkages between them were identified.

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3. Results

The survey was distributed to 85 eligible participants in 38 countries. Responses were received from 34 of 85 (40%) participants in 26 of 38 (68%) countries surveyed. Responses were received from individuals in low-, middle-, and high-income countries and from all 6 WHO regions (Table 1). Participating and non-participating countries did not differ by country income level (p = 0.6) or WHO region (p = 0.8). Most respondents (53%) were NITAG representatives and 68% were health professionals. Nine respondents from 8 countries (2 low-income, 2 middle-income and 4 high-income) participated in a focus group (6) or individual interviews (3).

Respondents from 14/26 (54%) participating countries reported there was no definition for off-label vaccine use in their country, 9 (35%) countries had a definition, and 3 were unsure (11%) (Fig. 1). Respondents from 14 countries (54%) reported that off-label recommendations had been made by the NITAG (8 countries) or another body (6 countries), yet only 1 country had an SOP for making such recommendations. Other bodies responsible for off-label recommendations were the NRA (2), Ministry of Health, a governmental health institute, or the Directorate-General of Health, and 1 respondent was unsure. Six (23%) countries had SOPs for implementing off-label recommendations.

3.1. Context and evidence used for making off-label recommendations

NITAGs made off-label recommendations in a range of situations that included: i) the need for guidelines in specific populations, ii) a response to disease outbreaks or vaccine shortages, iii) to reduce costs, and iv) to facilitate incorporation of the vaccine into the routine schedule (Table 2). Details of country-specific processes for developing off-label recommendations are described in Table 3. Specific examples provided in the survey responses and interviews included implementation of Tdap in every pregnancy during pertussis outbreaks associated with infant deaths, use of MMR in infants 6–11 months of age during measles outbreaks, fractionated IPV dosing in response to a shortage, and reduced dosing schedules (e.g., 2-dose HPV, 2 priming + 1 booster doses of pneumococcal conjugate vaccine (PCV) or meningococcal B vaccination) to improve cost-effectiveness.

To support off-label recommendations, respondents indicated that evidence from observational studies, randomized control trials, disease and adverse event surveillance data, and manufacturer data were reviewed. Informants reported that they frequently reviewed observational and clinical trial data that were published after the product was licensed, noting that product information is not updated regularly. They also considered post-marketing surveillance data on vaccine-preventable disease and adverse events following immunization (AEFIs) from their own countries. A few informants noted that such epidemiologic data may be used to populate mathematical models of vaccine cost-effectiveness, where, for example, "*with the modeling, three-plus-one schedule* [of meningococcal B vaccine] *was not* [found to be] *cost-effective*". One informant noted that their NITAG conducts a formal risk–benefit assessment when considering an off-label recommendation: "*it always boils down to what's reasonable and what's justified in that risk scenario and relying on the risk–benefit analysis*".

3.2. Barriers and facilitators to off-label use

The focus group and interviews further explored barriers and facilitators to off-label use (Table 4). Facilitators included having

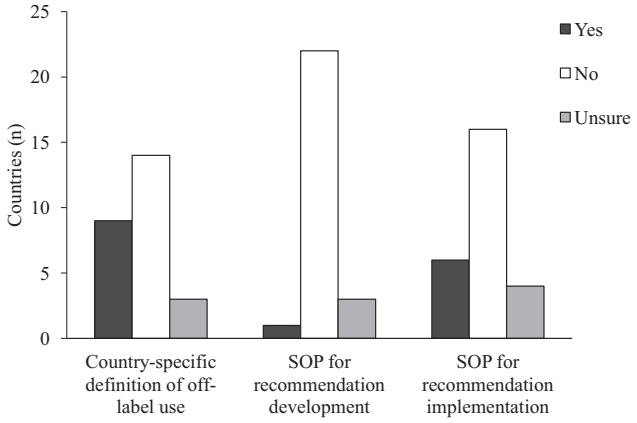

Fig. 1. Presence of definitions for off-label vaccine use and standard operating procedures (SOPs) for development or implementation of off-label recommendations.

Table 2
Context and evidence used for making off-label recommendations for vaccine use among 14 countries where off-label vaccine recommendations were made.

	n	%
Context for making off-label recommendations		
Needed guidelines for specific subpopulation	6	43
Vaccine shortage	5	36
Cost-saving measure	3	21
Manage disease outbreak	3	21
Facilitate incorporation of new vaccines into immunization schedule	2	14
Type of evidence used		
Observational studies	6	43
Randomized controlled trials	5	36
Adverse event and/or disease surveillance data from respondent's country	5	36
Adverse event and/or disease surveillance data from another country	5	36
Information provided by manufacturers	5	36
WHO recommendations	4	29
Discussions with other NITAGs or national regulatory authorities	3	21
Case reports	3	21

NITAG, National Immunization Technical Advisory Group; WHO, World Health Organization

Table 1
Characteristics of survey respondents and their countries.

Country and respondent characteristics		n	%
Country income level	Low	5	19
N = 26	Middle	11	42
	High	10	38
Region	Americas	6	23
N = 26	Europe	6	23
	Africa	7	27
	Eastern Mediterranean	3	12
	South East Asia	3	12
	Western Pacific	1	4
Current Role	Immunization Program Manager	11	32
N = 34			
	NITAG Representative	18	53
	National Drug/Vaccine Regulator	6	18
	Other*	2	6
Profession	Epidemiologist only	4	12
N = 34	Pharmacist only	2	6
	Physician only	13	38
	Pharmacist or Physician Epidemiologist	8	24
	Policy analyst	1	3
	Other†	6	18

NITAG, National Immunization Technical Advisory Group.
*Includes pharmacist for immunization program, WHO regional representative for immunization.
†Includes administrator, regulator, scientist, virologist.

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Table 3
Processes for developing off-label recommendations in countries participating in the focus group and interviews.

Country	Context	Data considered	Analyses conducted by NITAG	Frequency of off-label recommendations	Body that makes off-label recommendation
High-income countries					
Canada	• Specific populations	• Clinical trails • Observational studies • Non-specified evidence	• Cost-effectiveness assessment	"*We have in the past, not in the recent past. Measles IVIG is off-label. Also, PCV13, in the old days, was off-label*"	• NACI (NITAG) o Issue off-label recommendations but P/Ts implement them
Finland	• Cost saving measure • Specific populations • Disease outbreak	• Observational studies • Non-specified evidence • Animal studies • Safety data	• Benefit-risk analyses		• National Institute for Health and Welfare (THL) – responsible for off-label recommendations • NITAG is part of THL
Germany				STIKO does not make off-label recommendations – "*In Germany . . . by law, STIKO [is] not allowed to give any recommendation that goes beyond the product information*"	• If pediatrician or GP gives a vaccine off-label, they must tell the patient that it's not a STIKO recommendation and get consent from the patient first.
United Kingdom	• Cost saving measure • Reduced dosage schedule • Incorporation of vaccine into schedule	• Clinical trails • Post-marketing surveillance • Non-specified evidence • Epidemiology • Vaccine effectiveness • Immunogenicity • Safety data	• Cost-effectiveness assessment • Mathematical modelling	"*Numerous off-label recommendations on pneumococcal vaccines, HPV, meningococcal vaccines*"	• JCVI (NITAG) o Make off-label recommendations, which are added to the Green book (National Immunization Guidance)
Low- and Middle-income countries					
Argentina	• Specific populations • Reduced dosage schedule • Vaccine shortage • Disease outbreak	• Post-marketing surveillance • Epidemiology • Vaccine effectiveness • Immunogenicity • Safety data • Efficacy data		*"Hepatitis A, two times in 2005. . .you asked for the last five years. Now, we have Flu in pregnancy in 2011. And then Tdap 2013, HPV 2014 and Hepatitis B, and last year we had one dose of MMR in less than 12 months*"	• NITAG – responsible for off-label recommendations o Recommendations are sent to the Ministry of Health, who has final approval • Implemented by national immunization program
Indonesia	• Specific populations • Reduced dosage schedule • Vaccine shortage • Incorporation of vaccine into schedule	• Post-marketing surveillance		N/A	• NRA responsible for off-label recommendations • NRA will invite NITAG to meet and get their advice on off-label recommendations
Mozambique*	• Specific populations • Cost saving measure • Vaccine shortage	• Randomized controlled trials • Observational studies • WHO recommendations		Twice in past	• Pharmaceutic Department at National Directorate of Pharmacy in Ministry of Health
Nepal	• Cost saving measure • Vaccine shortage	• Non-specified evidence			• NITAG – responsible for off-label recommendations

GP, general practitioner; HPV, human papillomavirus vaccine; IVIG, intravenous immunoglobulin; JCVI, Joint Committee on Vaccination and Immunisation; MMR, measles-mumps-rubella vaccine; NACI, National Advisory Committee on Immunization; NITAG, National Immunization Technical Advisory Group; NRA, National Regulatory Authority; P/T, provinces/territories; PCV13, 13-valent pneumococcal conjugate vaccine; STIKO, Standing Committee on Vaccination at the Robert Koch Institute; Tdap, tetanus-diphtheria-acellular pertussis vaccine; WHO, World Health Organization.
*Data based partially on survey responses as representative was late joining focus group.

an intermediary between the NITAG and manufacturer to facilitate updates to product information, open communication, transparency, formal collaborations between the NITAG and key stakeholders (e.g., NRA, Ministry of Health, healthcare providers, public, media), and confidence in the decision-making process. One informant described how an intermediary works in Germany: "[NITAG] *was considering immunization of pregnant women – pertussis – and they said, no, it's not. . .in the product information, and . . .these persons from* [the intermediary] *after that, talked to the manufacturer and . . .later, the product information was changed.*"

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Table 4
Barriers and facilitators to off-label recommendations for vaccine use.

Facilitators	
Intermediary between NITAG and manufacturer	"No, the only thing I think, regarding the pertussis during pregnancy. There was an interesting process because one person from the Paul Ehrlich Institute, which is the [inaudible] in Germany, is a guest of STIKO, and two or three years ago, STIKO was considering immunization of pregnant women – pertussis – and they said, no, it's not in the treatment, in the product information, and discussion began, and these persons from the Paul Ehrlich institute after that, talked to the manufacturer and informed them that there's a need and I think, one year later, the product information was changed." – *Germany*
Transparency & Open communication with all stakeholders	"I think for the communication to the providers, is to drop from the Ministry of Health, actually." – *Indonesia* "And of course, we make the communication through scientific societies, scientific meetings, healthcare providers. . .private. . .public so we have a good working communication. In the special case of DTaP, we have very special effort with the obstetric society and gynecology and really, we have a good response from the obstetric and gynecology – very high coverage. It was very successful. So now we have very low levels now of death in these populations. It's very interesting." – *Argentina* "It's communicated to the GPs and to the specialist doctors who care for these patients . . . No, it's announced there's a new paper out where all these new recommendations for patients with HIV, for instance, is in." – *Germany* "JCVI publishes its minutes, they're full and they're detailed. We try and be as transparent as possible. If it's a big issue, we would publish a statement." – *UK* ". . .the recommendation was done, and the training was given to all the health workers who were going to vaccinate." – *Mozambique* "And then we try to make our nuclear messages in a way that the public health nurses who meet with those. . .groups that need to be vaccinated, they have enough facts and dialogue that they can take up in their discussions, should the person question on the difference between the label and the THL recommendation." – *Finland*
Formal interactions and collaboration between stakeholders	"Yes, I think we must sit together – we have a team, because from the NRA they have the authority for the regulations, but also for the users. Users here is the Minister of Health, I think, and NITAG can play a role, as facilitator or coordinator for that. And maybe we need for the company, the vaccine company, to inform in this team." – *Indonesia* "The regulatory authority is represented in the NITAG, so they have a say there, and they did not raise any concern." – *Finland* "In the NITAG, the public health nurses have got a representation, so the consultancy happens from there. Also, the general practitioners are represented, so NITAG is a very well-represented body for those purposes." – *Finland* "And then if we believe that we need wider consultation, then of course that's possible through surveys or discussions. With the pneumococcal vaccines we have used also an open source database commenting possibility, but anybody who is interested in what the recommendations should be can comment. Right now, actually, we have an email address where anybody can give us guidance on how they think that we should recommend the pneumococcal conjugate vaccine for risk groups and elderly." - *Finland*
Confidence in decision-making process	"What is interesting about the green book, too, because I looked into this to try and understand our Canadian perspective, and we'd done a bit of a scan is that it explicitly states if there is a difference between what is JCVI recommendations vs. the regulator, as a clinician you should go with the NITAG recommendation. That takes precedence. So, it's very clearly stated in the green book." - *Canada* "Yes, it's the EMA labels that says the recommendation of the national authority should be followed." – *Finland*
Barriers	
Lack of standard definition for off-label	". . .there is no true definition for off-label, and I think that's complicated. We've discussed with our legal services about what is this, and they've looked into it and there is nothing and they said probably it's the kind of thing you have a general idea of it, but it would have to be tested in court and you would say what did 9 out of 10 clinicians think is on-label or off-label. It's hard to interpret that at a certain level, or then if we make dedicated recommendations for certain risk groups is that on-label or off-label, it's kind of murky . . .I think, and even for the regulator, not sure that it's totally obvious." – *Canada* "I'm not sure if this is really off-label, but it's not the usual way to do it." – *Argentina*
Lack of SOPs	"No, we have not yet a standard operating procedure. We discuss this change at our NITAG, and this is the way we made it. Maybe we need something like that, I agree with you, but we don't have now a standard operating procedure." – *Argentina* "For drugs, yes, but not for vaccines." – *Indonesia*
Liability	"So, the specific problem in Germany is that by law, STIKO only recommendation, according to the authorized product information. So, they are not allowed to give any recommendation that goes beyond the product information. The main reason for that is, in Germany, the GPs, particularly pediatricians in their own practice, are the ones who are giving the vaccination. So that's the particular thing. So, if they adhere to a STIKO recommendation, they're covered by law, and if anything happens, they cannot be liable. And that's the problem. And therefore, STIKO not allowed to go beyond the product information." – *Germany* "I think that's what we've noted over the years was that the legal aspect of things were actually getting in the way, and you don't speak about it, but the Public Health Agency of Canada was actually told the regulators and PHAC are under the same hat, and so how can one hand say something that the other hand is not agreeing with. That's where we've just backed off for a minute to see how we could keep making off-label recommendations and in which circumstances and how do we deal with this without putting the country in a difficult position." – *Canada* "Regarding off-label recommendations as such, we don't have very strict rules, but as you've already said, the pediatricians while practicing, we are protected by Nepal Pediatric Society. Because even though the government – there is Nepal immunization schedule – but the Nepal Pediatric Society brings out the schedule like these are all the vaccines may be given, although this isn't the national schedule, although this is not there. . . If there's some AEFI, some problem, then the physicians are not liable, because the protection is already there from the Nepal Pediatric Society, immunization schedule of all the vaccines which may be given although it is not in our schedule." – *Nepal*
Reluctance of manufacturers to apply for label changes	"But I think an interesting challenge that's at least been pointed out as a risk from making these off-label recommendations from a legal perspective is, what is there then to incentivize that manufacturer to ever do that? Because it costs them time and money to then submit to the regulator." – *Canada* "And if they already have it for free from the NITAG and is being implemented in practice, then what is the added value? It solves our legal or policy headache, but it doesn't change the fact." – *Canada*
Public concern	"Most of these people who raise these questions are the anti-vaccinists, and often times their reasoning is because this is not in the label, or that because there is data going against what we recommend." – *Finland*

AEFI, adverse event following immunization; DTaP, tetanus-diphtheria-acellular pertussis vaccine; GP, general practitioner; JCVI, Joint Committee on Vaccination and Immunisation; NITAG, National Immunization Technical Advisory Group; NRA, National Regulatory Authority; STIKO, Standing Committee on Vaccination at the Robert Koch Institute.

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The need for open communication and collaboration with stakeholders, as well as transparency surrounding the development and implementation of off-label recommendations were common themes. Formal involvement of the NRA, health professional organizations and even public health nurses in the NITAG were also highlighted as facilitating robust decision-making. One informant described a public consultation process that was being used to help guide recommendations for PCV13 in high-risk adults.

To ensure transparency in decision-making, several participants noted that their NITAGs publish meeting minutes online. Communication was also seen as key to the successful implementation of an off-label recommendation, with one informant noting that "*In the special case of DTaP, we have very special effort with the Obstetric and Gynecology Society and really, we have a good response from the Obstetric and Gynecology* [Society] – *very high coverage. It was very successful.*" Some respondents noted that their NITAGs develop communication and training materials for vaccine providers, and in some cases communicate changes in immunization recommendations via social media or mobile applications.

Evidence for confidence in the NITAG decision-making process was expressed by several European participants when the product information, and in some cases the immunization guidelines, explicitly state that clinicians should follow NITAG recommendations over the product information when there is disagreement.

Barriers to off-label recommendations included liability concerns, lack of standard definition for off-label use, lack of SOPs, and reluctance of manufacturers to apply for label changes. Legal concerns regarding off-label use of vaccines were reported by 8 countries (31%) in the survey. Some respondents expressed concerns about liability for the healthcare provider or manufacturer in case of an AEFI. Respondents also expressed uncertainty whether patients suffering an AEFI after off-label use of a vaccine would be eligible for vaccine injury compensation. Several countries reported that the NRA does not permit off-label use or off-label use is not regulated. One informant noted the legal concern, "*the specific problem. . . is that by law,* [the NITAG]*. . .are not allowed to give any recommendation that goes beyond the product information.*" In another country, the fact that both the NITAG Secretariat and NRA fall under the Ministry of Health presented a challenge, "*The big issues identified for us through our legal services that it's the same minister who governs public health and also the regulator and so it's confusing or conflicting*" [when NITAG recommendations differ from the product information]. In other countries, incorporation of the off-label recommendation into the routine immunization schedule is assumed to provide healthcare providers legal protection.

The lack of a standard definition for off-label use was another barrier that created ambiguity around what types of recommendations were "on-label" versus "off-label". As one informant said, "*then if we make dedicated recommendations for certain risk groups is that on-label or off-label, it's kind of murky . . .I think, and even for the regulator, not sure that it's totally obvious*".

Informants opined the reluctance of manufacturers to seek changes to the product label. Some raised concerns that NITAG off-label recommendations may be a disincentive to such updates, "*it costs* [the manufacturer] *time and money to then submit to the regulator. And if they already have it for free from the NITAG and is being implemented in practice, then what is the added value?*"

4. Discussion

This study of 26 low-, middle-, and high-income countries found that while off-label vaccine recommendations are made in a range of settings and circumstances, few countries use a standard definition of off-label use or have SOPs in place to guide off-label vaccine recommendations. Legal concerns about off-label use included legislation prohibiting such use, physician concerns about liability and the legal implications of disagreement between the NITAG and NRA. Countries that have successfully implemented off-label recommendations identified a rigorous, transparent decision-making process involving key stakeholders, clear communication pathways, and guidance to clinicians to prioritize NITAG recommendations over product information.

Despite the lack of standardized processes, off-label recommendations were made in 54% of countries represented in the survey. Common examples of off-label recommendations included 2-dose HPV or 2 + 1 PCV vaccination, as well as Tdap vaccination of pregnant women, all of which are recommended by the WHO Stategic Advisory Group of Experts (SAGE) [18–20]. Fractional dosing of IPV, also recommended by SAGE was instituted in some low- and middle-income countries in this study [11].

The barriers to off-label recommendations identified in this study are consistent with those discussed by Neels [9]. Definitions of off-label drug use vary between NRAs and other advisory bodies and are not specific to vaccines [9]. Specific definitions for off-label use of vaccines are needed due to differences in review processes and standards of evidence for vaccines and drugs. When the NITAG review occurs concurrently with the regulatory review, discrepancies between NITAG recommendations and the product information may occur simply because the product information was not available to the NITAG [9]. NITAG recommendations are also aimed at maximizing public health benefit, while the regulatory review may focus on benefit-risk to the individual. Gaps in evidence of vaccine safety and effectiveness in specific population groups that may be at higher risk of complications from vaccine-preventable infections, due to their exclusion from pre-licensure trials, often prevents inclusion of specific recommendations for those groups in product information at the time of initial licensure. Further, placing the onus on manufacturers to update their product information, which comes with a cost, as noted by informants in this study, is a barrier to timely information updates. NRAs can act as an intermediary by working with manufacturers to update product information and encouraging manufacturers to conduct additional studies in special populations. Requiring manufacturers to update product information regularly could also reduce the need for off-label recommendations.

The study results show that NITAGs are regularly presented with new challenges from vaccine shortages to disease outbreaks, as well as pressure to maximize cost-effectiveness of publicly funded immunization programs, which require timely action that cannot always wait for new clinical trial evidence, regulatory processes, and/or reluctant manufacturers. Therefore, standard guidance is needed regarding the legal definition of off-label vaccine use, as well as the procedures that should be followed to develop and implement off-label recommendations when required. This guidance should encourage use of country-specific data on disease burden, vaccine safety and effectiveness, and cost-effectiveness where possible to inform off-label recommendations. Discussions and decision-making should be transparent and involve NITAGs, NRAs, ministries of health, and professional organizations. Recommendations and their rationale should be clearly communicated to vaccine providers and the public through multiple media, and training should be provided to vaccine providers when implementing a significant practice change (e.g., intradermal administration of fractional doses). Clarifying that NITAG recommendations should take precedence over labelling information may also facilitate use and reassure clinicians that they are not at legal risk. Such guidance would be of particular benefit to low- and middle-income countries that are already faced with a need to make off-label recommendations while having less developed processes to do so.

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This study had limitations. Respondents may not have had complete knowledge of policies and procedures in their countries. Respondents were recruited from countries with functioning NITAGs and these countries may not be representative of all settings where off-label recommendations are made. Most responses came from high and middle income countries (82%), so the findings may not reflect the situation in low-income countries whose NITAGs may not yet meet all six WHO criteria for functioning NITAGs. Informants from low- and middle-income countries were included in the focus group and interviews.

5. Conclusions

Best practice guidelines for developing and implementing recommendations for off-label vaccine use appropriate to country contexts are needed globally. These guidelines should include standard definitions of off-label vaccine use and outline a multidisciplinary, evidence-based, transparent process to develop and communicate recommendations while encouraging NRAs and manufacturers to develop processes for regularly updating product information to reduce the need for off-label recommendations.

Declaration of Competing Interest

The authors declare the following financial interests/personal relationships which may be considered as potential competing interests: [KAT has received grants from GSK and consultancy fees from Pfizer outside the submitted work. All other authors report no conflicts of interest].

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Appendix A. Supplementary material

Supplementary data to this article can be found online at https://doi.org/10.1016/j.vaccine.2019.11.033.

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