LITERATURE REVIEW ON NITAGS

1. Introduction

National Immunization Technical Advisory Groups (NITAGs) have become a topic of high importance within the international immunization community over the last decade, and the presence of a functional NITAG is an indicator (Strategic objective 1) in the Global Vaccine Action Plan (GVAP). We conducted a broad literature review on this topic, in preparation of the NITAG session at the WHO SAGE meeting, April 25-27 2017 so as to make a review of how NITAGs were addressed in the scientific literature.

The objectives of this literature review are to:

- Make a list of articles with NITAGs as the main (or one of the main) topic
- Present an overview of the types of articles and their contents
- Identify recurring NITAG issues, topics and challenges described in the literature
- Identify insufficiently addressed or unaddressed topics in the literature.

2. Methods

We conducted two literature searches, one on PubMed and one on Science Direct databases.

- On Science Direct, we used the following search: “Search with (National Immunization Technical Advisory Group) or (NITAG) in key words”

We also included one article that was accepted for publication and that we were aware of.

3. Results

3.1. Articles retrieved

The search conducted on PubMed retrieved 468 articles, 245 of which were published on the last fifteen years (2002-2017). Articles published before 2002 were not considered for the literature review. The search
conducted on Science Direct retrieved 65 articles, including 58 of them also being retrieved through the PubMed search. Total result of the search is 475 articles, 252 of them being published over the 2002-2017 period.

Many articles dealt with specific NITAG recommendations and were not included. We have neither included articles that only mentioned briefly the existence of NITAG in papers dealing with broader policy-making or vaccine introduction considerations.

We finally included 54 articles, published between 2009 and 2016\(^1\), and one article accepted for publication. Years of publication of these articles are:

<table>
<thead>
<tr>
<th>Year of publication</th>
<th>Number of articles</th>
</tr>
</thead>
<tbody>
<tr>
<td>2009</td>
<td>4</td>
</tr>
<tr>
<td>2010</td>
<td>20(^2)</td>
</tr>
<tr>
<td>2011</td>
<td>3</td>
</tr>
<tr>
<td>2012</td>
<td>6</td>
</tr>
<tr>
<td>2013</td>
<td>4</td>
</tr>
<tr>
<td>2014</td>
<td>4</td>
</tr>
<tr>
<td>2015</td>
<td>7</td>
</tr>
<tr>
<td>2016</td>
<td>5</td>
</tr>
<tr>
<td>2017</td>
<td>1(^3)</td>
</tr>
</tbody>
</table>

### 3.2. Types of articles

Articles were grouped into 8 categories, based on the main purpose of the article:

- Description of a particular NITAG (n=27)
- Review / comparison of a sample of NITAGs (from 2 to 30 NITAGs) (n=9)
- Global view on NITAGs (n=7)
- Guidance/ description of tool for NITAGs (n=4)
- Presentation of the work and lessons learned from initiatives supporting NITAGs (n=4)
- Proposition of implementation of collaboration between NITAGs (n=1)
- Other: position of one funding partner on country-owned decision-making (n=1)
- Other: study case on the role of NITAGs (n=1)

Most of the topics that we will discuss in section 3.3 (e.g. collaboration amongst NITAGs, processes to issue recommendations) are addressed in articles of different types.

---

1. We wanted to include another article published in 2002 on the Indian NITAG [1] that was referenced on PubMed but it was not existing

2. All of them in the Vaccine supplement “The Role of National Advisory Committees in Supporting Evidence-Based Decision Making for National Immunization Programs” (Volume 28, Supplement 1)

3. Accepted for publication

March 2017
3.2.1. Articles describing a particular NITAG

27 articles [2-28] describe a specific NITAG. The table below presents the number of articles per region and per country, and the focus of the article.

<table>
<thead>
<tr>
<th>Region</th>
<th>Country</th>
<th>General</th>
<th>Focus on History</th>
<th>Focus on Methods</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td>AMR</td>
<td>Argentina</td>
<td>1</td>
<td></td>
<td></td>
<td>1</td>
</tr>
<tr>
<td></td>
<td>Canada</td>
<td>1</td>
<td></td>
<td></td>
<td>1</td>
</tr>
<tr>
<td></td>
<td>Honduras</td>
<td>1</td>
<td></td>
<td></td>
<td>1</td>
</tr>
<tr>
<td></td>
<td>USA</td>
<td>4</td>
<td>3</td>
<td>3</td>
<td>10</td>
</tr>
<tr>
<td></td>
<td>Total AMR</td>
<td>7</td>
<td>3</td>
<td>3</td>
<td>13</td>
</tr>
<tr>
<td>SEAR</td>
<td>India</td>
<td>1</td>
<td></td>
<td></td>
<td>1</td>
</tr>
<tr>
<td></td>
<td>South Korea</td>
<td>2</td>
<td></td>
<td></td>
<td>2</td>
</tr>
<tr>
<td></td>
<td>Sri Lanka</td>
<td>1</td>
<td></td>
<td></td>
<td>1</td>
</tr>
<tr>
<td></td>
<td>Thailand</td>
<td>1</td>
<td></td>
<td></td>
<td>1</td>
</tr>
<tr>
<td></td>
<td>Total SEAR</td>
<td>5</td>
<td></td>
<td></td>
<td>5</td>
</tr>
<tr>
<td>EUR</td>
<td>France</td>
<td>1</td>
<td></td>
<td></td>
<td>1</td>
</tr>
<tr>
<td></td>
<td>Switzerland</td>
<td>1</td>
<td></td>
<td></td>
<td>1</td>
</tr>
<tr>
<td></td>
<td>UK</td>
<td>1</td>
<td></td>
<td></td>
<td>1</td>
</tr>
<tr>
<td></td>
<td>Total EUR</td>
<td>3</td>
<td></td>
<td></td>
<td>3</td>
</tr>
<tr>
<td>EMR</td>
<td>Iran</td>
<td>1</td>
<td></td>
<td></td>
<td>1</td>
</tr>
<tr>
<td></td>
<td>Oman</td>
<td>1</td>
<td></td>
<td></td>
<td>1</td>
</tr>
<tr>
<td></td>
<td>Total EMR</td>
<td>2</td>
<td></td>
<td></td>
<td>2</td>
</tr>
<tr>
<td>WPR</td>
<td>Australia</td>
<td>1</td>
<td></td>
<td></td>
<td>1</td>
</tr>
<tr>
<td></td>
<td>China</td>
<td>1</td>
<td></td>
<td></td>
<td>1</td>
</tr>
<tr>
<td></td>
<td>Total WPR</td>
<td>2</td>
<td></td>
<td></td>
<td>2</td>
</tr>
<tr>
<td>AFR</td>
<td>South Africa</td>
<td>2</td>
<td></td>
<td></td>
<td>2</td>
</tr>
<tr>
<td></td>
<td>Total AFR</td>
<td>2</td>
<td></td>
<td></td>
<td>2</td>
</tr>
<tr>
<td></td>
<td>Total</td>
<td>21</td>
<td>3</td>
<td>3</td>
<td>27</td>
</tr>
</tbody>
</table>

The retrieved articles describe 16 NITAGs, in the 5 WHO regions: 4 NITAGs in the Americas and South-East Asia regions, 3 NITAGs in the European region, 2 NITAGs in the Eastern Mediterranean and the Western Pacific Region, and one NITAG in the African region. For most of these NITAGs (n=13) there is only one article. Two articles are about the South Korean NITAG, and two articles are about the South-African NITAG, one of which is about the whole decision-making process, more specifically about the introduction of new vaccines in the NIP. There are 10 articles on the US Advisory Committee on Immunization Practices (ACIP) [2-6,8,17,24,26,28].

All articles but two [24,26], were authored by nationals, mostly NITAG members.

Most of the articles (n=21) present an overview of the NITAG, including (generally all of the following) its history and/or its terms of reference and/or its membership and/or its principles for functioning and/or its methodology to issue recommendations and/or its role in the decision-making process. Some of the articles also describe NITAG specific activities, NITAG production, and challenges.

A few articles (all from the USA) focus either on the history and evolution of the NITAG (n=3) [2,3,4] or the methods to issue evidence-based recommendations (n=3) [5,6,28], including one article focusing on managing uncertainty in the recommendation making process.
3.2.2. Review and comparison of a sample of NITAGs

9 articles reviewed and compared a sample of NITAGs with regard to their composition, functioning, process and/or the type of evidence used to issue recommendations and/or their integration in the decision making process:

- 3 articles, including one conference report, present NITAGs’ overview and their processes in Europe [33,34,37]
- 2 articles compare the evidence considered and the policy-making processes in two European countries (France and Netherlands) for the case of seasonal influenza vaccination [29,30]
- 2 articles, including one editorial, analyze and compare NITAG processes in 13 developed countries [35,36]
- 1 article makes an inventory of recommendations issued by 5 European NITAGs, with a focus on the evidence used for similar topics [31]
- 1 article is a review of 15 articles describing particular NITAGs (see 3.2.1) published in a Vaccine supplement [34]

All articles but one, focus solely (n=7) or mostly (n=1) on high-income countries.

3.2.3. Global view on NITAGs

7 articles provide an overview of NITAGs at different levels:

- At the global (n=4) level: 3 articles present the status of NITAG based on data collected through questionnaires, such as Joint Reporting Forms (n=2) [40,41] and 1 article focused on NITAGs is based on a literature review which addresses more broadly the national immunization policy making processes [39].
- At the regional (n=2) level (one in the Americas [42] and one in the WHO European region [43]).
- One abstract [44] compares a sample of NITAGs and their alignment with best practices, but no further information is given; compared components are not clear.

6 out of 7 articles describe the status of NITAGs in the world / region, including presence and key features of NITAGs (such as membership and/or compliance with the 6 WHO processes indicators and/or other). Less description and analysis of NITAG processes is made here.

3.2.4. Description of tool or guidance for NITAG

4 articles provide guidance for NITAG functioning or present tools to support NITAGs in their functioning and operations.

- One article provides guidance for NITAG establishment and strengthening; it provides guidance on most aspects of NITAGs modes of operations, even if not constantly cited in the rest of this review [45]
- One article provides guidance on the interaction between NITAGs and National Regulatory Agencies (NRAs) [46]
- One article presents a set of indicators to assess processes, outputs and outcomes of NITAGs [47]
- One article presents a web platform especially designed for NITAGs, the NITAG Resource Center (NRC) [48]
3.2.5. Presentation of the work and lessons learned from initiatives supporting NITAGs

3 articles describe the work of the SIVAC initiative

- One article describes the overall scope of the initiative [49]
- One article describes the support provided by SIVAC for the establishment of the NITAG in Côte d’Ivoire [50]
- One article presents the lessons learned after 5 years of implementation and recommendations for the future [51]

1 article describes the lessons learned by the ProVac initiative [52], which focused on supporting countries to conduct cost-effectiveness analyses, but that also included support to NITAGs.

3.2.6. Implementing collaboration between NITAGs.

One article is a meeting report on the implementation of collaboration between NITAGs [53].

3.2.7. Partner’s perspective

One article describes the Gavi’s position and support to country-owned policymaking [54].

3.2.8. Study case on the role of NITAGs

One article describes the role of the Indonesian and Ugandan NITAG in the introduction of the inactivated polio vaccine (IPV), and addresses the role of NITAG in the domestication of global recommendations [55].

3.3. Main topics and challenges addressed

The section here above (3.2) presented an overview of the purpose and the content of the NITAG-related articles. Here below, we present a synthesis of recurring topics found in those articles, with a focus on the challenges faced by NITAGs.

3.3.1. Frameworks, processes and evidence to issue recommendations

Most articles on individual NITAGs mention the processes used to issue recommendations. More recent articles, mostly on high-income countries, provide further analysis on the frameworks, processes and evidence used for recommendation making. All information reported below is only based on the experience and analysis of very few NITAGs, and cannot be generalized.

TRANSPARENCY OF PROCESSES, FRAMEWORKS, EVIDENCE

Articles about individual NITAGs, including the 15 articles published in 2010 [9-23] often describe (with various levels of details) the process for recommendation making. The importance of having systematic and
transparent approach is repeated [35,36,37] and is seen as important for the credibility of the NITAG and building trust [35,36].

However, several articles point out the scarcity of public information about NITAGs and their processes: if a few NITAGs report to have standardized processes and/or decision analysis frameworks, they are not widely available or published [32, 36]. The review of 15 NITAGs also points that most countries do not report a codified and systematic process for collecting and evaluating data [34]. These processes are described as not always as structured and transparent as processes for other medicines [36].

Similarly, it is difficult to find full documentation on the topics addressed by NITAGs, including the evidence used and whether (and how) it was assessed [31].

**ASSESSMENT OF EVIDENCE**

Literature describes the absence [29,30] or existence of framework / procedures to assess and/or rank evidence. Few NITAGS [3,4,32,36] have adopted the GRADE system and many European NITAGs are reported to see the GRADE approach as appropriate [37].

For selected NITAGs without such procedures, two articles about seasonal influenza vaccination [29, 30] explain that most of NITAG members are aware of the low quality of evidence (or the uncertainty about this quality) and that most of them do not consider that it negatively impacts the recommendation, meaning that expert’s interpretation was of utmost importance in the process.

**VARIABILITY OF PROCESSES**

In addition to the lack of transparency of processes for issuing recommendations, several articles point out the variability of NITAG processes [31, 36, 42].

In particular, despite similarities in key factors considered, there are differences in the relative weight given to each of these factors [33]. Even when similar topics are addressed by NITAGs, the processes for recommendation making can be quite different, and so is the evidence used [31]. One article comparing recommendations on seasonal influenza vaccinations in France and the Netherlands [29] explains that despite the use of similar evidence, the recommendations differ on some aspects.

For authors [36] the disparities in processes and the lack of standardization may explain heterogeneity in immunization programs and delays in introducing new vaccines.

**CONSIDERATION OF ECONOMIC DATA**

Concern about consideration of economic data are often cited, mostly in articles about individual NITAGs. In the review of 15 articles on individual NITAGs published in 2010 [34], the realm of economic data is the most commonly identified area for improvement mentioned by 8 of the NITAGs, including processes to appropriately consider economic data and shortage of experts in the area.

In particular the topic is often mentioned in US ACIP-related articles: ACIP has progressively considered more systematically economic analyses [3], had challenging deliberations on economic analyses [3] and has published a document to providing guidance for the development and presentation of economic data [4]. One
author [2] wonders whether a group mostly made of non-health economists is the best group to undertake such work. If often mentioned that economic should be part of framework analysis at the NITAG level [35, 45], one editorial on NITAG policies in developed countries [35] points that pricing and reimbursement issues should be dealt in another body.

**Consideration of Programmatic Aspects**

One article on the process on new vaccines introduction in South Africa [7] explains that programmatic aspects are not considered at the NITAG level but by the MoH (Department of Health) and calls for a the establishment of an additional committee to take this responsibility. The authors also regret that the NITAG is not fully informed on the budget and funds available for new vaccines.

On the other hand, one article on the experience of NITAGs in the introduction of IPV [55] underlines the consideration of practical aspects by the NITAG.

### 3.3.2. Availability of Expertise and Human Resources

Lack of overall necessary expertise to reach optimal recommendations is the second most commonly identified areas of improvement (mentioned by 5 NITAGs) in the review of 15 articles about NITAG published in 2010 [34]. In addition, the review mentions the challenges of increasing level of work and increasing demands from stakeholders.

Shortage of Human Resources also makes two of the main challenges identified after 5 years of the SIVAC initiative [51]. It includes 1) the scarcity of trained staff for the Secretariat, described as instrumental for NITAG functioning and work, and 2) the lack of national experts.

In regards to Secretariat and preparation of background documents, one article [51] addresses the topic of the institution / organization housing the Secretariat. Also, in addition to articles on individual NITAGs, some elements are provided about ad hoc working groups to prepare the recommendations [29, 45, 51].

### 3.3.3. Integration within the National Decision-Making Process

**Recognition by Government**

One identified challenge after 5 years of the SIVAC initiative is that national authorities need to better understand the role of NITAGs [51]. One article on decision making in South Africa calls for the full consideration of the NITAG recommendations by the MoH, with clear communication channels [7]. The review of 15 articles on individual NITAGs also reported as cited areas for improvement the improved coordination between government and NITAG. Other examples describe the good integration of the NITAG in the system [55] and that advice from NITAGs are often considered by ultimate decision makers with minor modifications in high-income countries [30]

**Interaction with Stakeholders**

Some articles on individual NITAGs describe relationships with other immunization stakeholders [4, 34], and some areas of improvement cited include [34] 1) the lack of representation of relevant stakeholders in the...
NITAG 2) the presence of other committees with overlapping agendas 3) the improved interaction with other national committees and 4) the insufficient public recognition of the NITAG role.

One article [46] provides some inputs on the interaction between NITAGs and another type of institutions involved in vaccines decision making, namely NRA.

Relationships both inside the NITAGs and between the NITAG experts and other stakeholders are more extensively described and compared for France and the Netherlands and are reported to differ [30].

One strategic line for strengthening NITAG identified after 5 years of the SIVAC initiative is to reinforce NITAG integration to promote sustainability and credibility [51].

### 3.3.4. Independence of the NITAG and independence of the recommendations

#### INSTITUTIONAL INDEPENDENCE FROM GOVERNMENT

Independence from government is discussed in the literature [45,51], and the ACIP reports to have faced this challenge over its history [2]. A challenge identified after 5 years of SIVAC is that the issue of independence is not well understood by health authorities [51].

#### INDEPENDENCE OF RECOMMENDATIONS

Issue of Conflicts of Interest (CoI), prevention of CoI and independence from vaccines manufacturers is recurring [34,51]. Regarding recommendations on seasonal influenza vaccinations in France and the Netherlands, many members are reported not to be free from CoI, and more stringent rules were implemented after the pandemic episode of influenza in 2009 [30].

### 3.3.5. Collaboration between NITAGs

Several articles insists upon the importance and the wish for enhanced collaboration between NITAGs [32,37].

#### AREAS FOR TECHNICAL COLLABORATION

A prerequisite for future collaboration would be to know what issues other NITAGs are working and planning to work on [31].

Collaboration on technical issues include sharing of already completed documents and joint work to develop common documents [53]. Identified areas for collaboration include collaboration on systematic reviews [32, 53] other background documents for recommendations, mathematical models, health economics evaluations and establishment of common frameworks and methodologies for reviewing and grading evidence [53].

#### IMPLEMENTING COLLABORATION

Collaboration is reported to need a formalized network of NITAGs, that can be built around the NRC [53]. It requires commitment of NITAG to share information and documents [31]. Collaboration is reported to also
involve collaboration among public health and research institutions [31] that are a key source of evidence for NITAGs [31,30]. Barriers for collaboration are also addressed [32].

Both international and regional networks are mentioned [51,53].

**TOOLS FOR COLLABORATION**

Tools for collaboration between NITAGs include the NRC and the technical newsletter [31,48]. The services provided by the NRC are described in a dedicated article [48].

**EXPERIENCE SHARING**

Experience sharing such as visits to other NITAGs is reported as very valuable experience in general, with specific examples of outcomes [51,55]. Three articles specifically mention the positive outputs of delegations visiting ACIP and support from ACIP to develop Standard Operating Procedures [2,27,52].

One of the strategic line to strengthen NITAG (after 5 years of SIVAC experience) is to increase networking and regional collaborations [51].

### 3.3.6. Other topics and challenges

Other topics and challenges found in the literature include the following ones.

#### Regarding support to NITAGs establishment:
- Importance of step by step and country owned approach to support the establishment and development of NITAGs [49-51]
- The need of a special approach to allow small countries to benefit from advisory groups [41]
- The potential transition from disease specific committees such as polio committees to NITAGs [41]
- International technical agencies and partners and 1) their role in supporting NITAG [40, 45, 51, 52, 54] 2) the lack but nevertheless growing of understanding of NITAGs by offices at local level, which can have hindered their establishment [51]
- Barriers that impede the establishment of NITAG [51]

#### Regarding the development and issuance of recommendations:
- Insufficient data availability [34]
- The GRADE approach [26] that can prevent from making recommendations when there is no robust evidence, for example when the targeted population is too small.
- Building trust in the committee’s recommendations derived from the participation of experts and scientific societies [27]
- Other factors influencing final decisions (by the MoH) that are reported to be [7,29] Gavi, the media, professional groups and activists.
- The opinion of the public (that is the decreasing public trust regarding recommendation) which unconsciously or not influences NITAG discussions [29].
- The need of a format to present recommendations and the availability of committee results [34]

#### Regarding other areas:
The little number of topics addressed commonly by several NITAGs in 5 well-established European NITAGs [31]

- Challenges to accommodate increasing number of vaccines in the recommended child and adolescent immunization schedule [3]
- Lack of funding for NITAG [34]
- The role of the media, seen as a challenge to the NITAG [29]

### 4. Discussion

#### 4.1. Main topics addressed

Literature reports an overall progress in the establishment of NITAGs and the compliance with basic indicators for functioning [40,41]. Challenges and topics often reported include:

- The robustness and transparency of the processes for recommendation making and the assessment of evidence
- The consideration of economic evidence
- The presence of CoI
- The scarcity of Human Resources
- The institutional integration into the decision-making process.

Collaboration between NITAGs is also a recurring topic, especially in the most recent published articles.

#### 4.2. Literature gaps

We identified topics of importance that are not, or only slightly, addressed in the retrieved articles.

**SCARCITY OF LITERATURE ON LOW-INCOME COUNTRIES (LIC) AND LOWER-MIDDLE-INCOME COUNTRIES (LMIC) NITAGS**

Apart the consideration of status of NITAGs at a global or regional level and the articles related to initiatives supporting NITAGs, there is no literature on low-income countries and literature on lower-middle-income countries is limited to the description of 3 NITAGs [16,20,22].

8 out of the 9 articles whom main purpose is the review and/or comparison of a sample of NITAGs (with a further look on processes to issue recommendations) mostly addresses high-income countries and a few upper-middle-income countries.

In the perspective of achieving the GVAP goals, and more broadly to strengthen evidence-based policymaking at national levels, further literature on NITAG in low-income countries and lower-middle-income countries would be welcomed.
IMPACT OF NITAGS

Impact of NITAG is not defined in the literature, and slightly addressed.

- A few articles describing individual NITAGs make a list of the production of the NITAG [4,27,34], underlying the accepted and implemented recommendations, but to which extent it informs about impact can be discussed.
- An example of the very specific added-value of NITAG is detailed for an African country [51] and study case of NITAGs role in IPV introduction is described [55].
- Other elements somehow addressing the issue of impact include 1) one editorial that tends to link the delay in introducing new vaccines after the market authorization with the work of the NITAGs [35], and another article recognizing possible slight delays counterbalances with the benefits of NITAGs involvement in the process [51] 2) one abstract correlates the alignment of NITAG with best practices with proportion of the WHO-recommended and additional vaccines in their NIP [44].

Propositions of definitions of impact and case study discussing impact could be helpful to contribute in the discussions about - and possibly advocacy for support to - NITAG strengthening.

RESULTS OF EVALUATION OF NITAGS

One article mentions the development of indicators to assess NITAGs [47] and another one mentions both some external evaluations of NITAGs and the development of a protocol for evaluation [51]. However there is no further literature on the topic. A bunch of articles presenting evaluation of NITAGs could contribute in clarifying the approach to strengthen NITAGs and optimally use them in the decision making processes.

CAPACITY BUILDING

While need for structured and transparent processes (including assessment of the relevance and quality of the evidence) is repeated, very little is said about building technical capacity on these aspects. Technical capacity building is however mentioned as one of the strategic lines to strengthen NITAG based on SIVAC experience and lessons learned [51].

NITAG FINANCING

Financial sustainability is an identified challenge and the need to investigate innovative mechanisms to sustain funding for NITAGs is raised, but only few is said [51] about such perspectives for financing.
REFERENCES


