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National Advisory Groups and their role in immunization policy-making processes in European countries

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Abstract

During the twenty-first century, the development of national immunization programmes (NIP) has matured into robust processes where evidence-based methodologies and frameworks have increasingly been adopted. A key role in the decision-making and recommending processes is played by National Immunization Technical Advisory Groups (NITAGs). In a survey performed among European Union member states, Norway and Iceland, in February 2013, 85% of the 27 responding countries reported having established a NITAG, and of these, 45% have formal frameworks in place for the systematic development of vaccination recommendations. Independent of whether a formal framework is in place, common key factors are addressed by all NITAGs and also in countries without NITAGs. The four main factors addressed by all were: disease burden in the country, severity of the disease, vaccine effectiveness or efficacy, and vaccine safety at population level. Mathematical modelling and cost-effectiveness analyses are still not common tools. Differences in the relative weighting of these key factors, differences in data or assumptions on country-specific key factors, and differences in existing vaccination systems and financing, are likely to be reasons for differences in NITAG recommendations, and eventually NIPs, across Europe. Even if harmonization of NIPs is presently not a reasonable aim, systematic reviews and the development of mathematical/economic models could be performed at supranational level, thus sharing resources and easing the present work-load of NITAGs. Nevertheless, it has been argued that harmonization would ease central purchase of vaccines, thus reducing the price and increasing access to new vaccines.

Keywords: Decision-making, Europe, evidence, immunization programme, recommendations, vaccination

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Introduction

In Europe, licensure of vaccines and indications for their clinical use are regulated by the European Medicines Agency and national regulatory authorities. Before licensure, a candidate vaccine undergoes extensive immunogenicity and safety evaluations, and usually also evaluation of efficacy under ideal conditions in the intended main indication target group(s). Once a vaccine is licensed and available on the market, qualified medical personnel can prescribe and administer the vaccine to individual subjects. Off-label use is discouraged, but at times indications or schedules may be altered from those on the label, based on an individual benefit–risk assessment or on population risk–benefit or cost-effectiveness assessments.

How widely the commercially available vaccines are eventually used in a population depends largely on the delivery and

financing system of the national immunization programme (NIP). The adoption of a vaccine in a NIP is usually linked to its funding through public sources. In contrast to the treatment of sick patients, vaccines as a preventive measure do not only confer a benefit on the vaccinated individual, but often also on the total population in which the vaccine has been introduced. The public health benefits of large-scale vaccination in a population can include overall disease burden reduction; for several diseases, the protection of vulnerable (potentially unvaccinated) individuals by reducing disease transmission (herd protection); the complete elimination of a disease in a geographic region; and/or cost-savings in the healthcare system. To make the most efficient use of a vaccine and to maximize its benefits, specific strategies can be implemented within a NIP, e.g. by targeting either the total population or only specific age cohorts or other population subgroups with an increased risk of acquiring the disease or of developing more severe disease once infected.

Since the birth of the Expanded Programme on Immunization after successful eradication of smallpox in the 1970s, there has been a steady drift away from thinking that one programme can fit all countries. Therefore, the WHO has recommended and the Global Vaccine Action Plan has recently endorsed as a strategic goal, that countries should establish or strengthen formal and, if possible, independent technical expert committees to guide country immunization policies and aid national decision-making for NIPs [1,2]. The underlying thinking is that national decision-making and recommendation on the use of vaccines at population level should be based as much as possible not only on universally applicable best-available scientific evidence, but also on local disease burden, and country-specific cost-effectiveness [2]. Taking these into account would then be the core tasks of a National Immunization Technical Advisory Group (NITAG), together with ensuring that the process of adopting a vaccine in a NIP is less likely to depend on commercial or other vested interests.

Frameworks and Key Factors Considered by NITAGs

A NITAG is a technical resource providing evidence-based guidance to national authorities and policy-makers [1]. Such a resource is particularly important in view of the complex and vast bodies of evidence, as well as a dynamic vaccine market, with new products targeting a variety of age groups and specific at-risk populations [1].

To systematically assess and weigh the available evidence, to minimize bias, to improve transparency, and to enable a structured evaluation, different evidence-grading systems have been developed and applied, especially for clinical practices [3]. However, the public health domain has been slow in adopting such approaches [4]. Nevertheless, in recent years, the approach of the Grading of Recommendations' Assessment, Development and Evaluation (GRADE) Working Group has increasingly been proposed and used as a tool for the development of evidence-based recommendations, also in the field of immunization [5,6]. The GRADE system has the advantage that it does not only grade the quality of evidence related to the efficacy and safety of an intervention; it also takes into account that other factors beyond the quality of evidence (e.g. preferences, values and resource implications) influence our confidence that adherence to a recommendation causes more benefit than harm [7]. Another advantage of GRADE is that the quality of evidence derived from observational studies, which in most evidence-grading systems are considered *a priori* to provide lower quality of evidence, can be up-rated under specific conditions. This is of particular importance in the field of immunization, because some aspects (e.g. very rare adverse events or population-level effects such as herd protection) are difficult to assess in randomized controlled vaccine trials [8].

Even without a methodologically rigorous system like GRADE, most NITAGs have a framework in place to consider various key factors when developing a recommendation [9]. These key factors are evaluated either informally or formally. Often, decision-making tools are used, such as health technology assessment, in combination with epidemiological, ethical and behavioural analyses; such analyses can include mathematical modelling to predict population level and long-term impacts in a given population, depending on different vaccination strategies, and health-economic evaluations of strategies. In the Netherlands, for example, the factors that determine a vaccine's suitability for inclusion in the NIP have been translated into seven selection criteria, grouped under five thematic headings: seriousness and extent of the disease burden, effectiveness and safety of the vaccination, acceptability of the vaccination, efficiency of the vaccination, and priority of the vaccination [10]. In Canada, the analytical framework proposed included 58 criteria classified into 13 categories [11]. As in other systems, the National Advisory Committee on Immunization in Canada has three broad stages in the preparation of a recommendation statement: (i) knowledge synthesis (based on individual studies); (ii) synthesis of the body of evidence on benefits and harms, considering the quality of the evidence and the magnitude of effects observed; and (iii) translation of evidence into a recommendation [12]. Other frameworks have been established elsewhere; we describe these briefly for Finland, Germany and Italy in the Supplementary material, Appendix S1 [13,14].

A global survey of NITAGs was conducted by the WHO in 2008. Of the 193 eligible countries, 147 participated, including 47 of the 53 European countries [9]. In Europe, 34 (72%) responding countries stated that they had a NITAG. In the 88 countries with NITAGs, key factors that are considered when a NITAG makes recommendations were: vaccine safety (100%), disease burden in the home country (99%), disease epidemiology (95%), financial aspects (91%) and public perception of the disease (59%) [9].

Information on NITAG composition, ways of working, and decisions made, as well as indicators to assess NITAGs [15], can be found online from several national sites as well as via web portals. The WHO holds a resource website of NITAGs (www.who.int/immunization/sage/national_advisory_ commit tees/en/). Also, the SIVAC (Supporting National Independent Immunization and Vaccine Advisory Committees; www.sivac.org/about-sivac) initiative established in 2008, holds a NITAG observatory, where links to 43 NITAGs around the world, including 11 European countries, can be found (www.nitag-resource.org/en/observatory/dashboard.php).

2013 Survey on NITAGs in the European Union, Iceland and Norway

Expressly for this review, we conducted, in February 2013, a web-based survey (www.surveymonkey.com) on NITAG qualities and processes among the gatekeepers of the project 'Vaccine European New Integrated Collaboration Effort' (VENICE; http://venice.cineca.org). Country contact points working with national vaccination programmes in 27 European Union (EU) Member States, Norway and Iceland, were approached and requested to fill in the questionnaire.

If the gatekeepers were not the key holders of the requested information, they were asked to identify a competent expert instead, who would then fill in the questionnaire. Furthermore, in addition to filling in the structured survey forms, a brief description of the process of inclusion of a vaccine in the NIP and the main factors considered for the decision were requested from all, including countries without a NITAG.

By April 2013, 27 (93%) countries had completed the survey. Only Hungary and Portugal did not respond. Twenty-three (85%) countries reported having a NITAG (Table 1). Cyprus, Italy, Norway and Sweden reported that they did not have a NITAG. Sweden mentioned, however, that the Swedish National Board of Health has, as a national authority, responsibilities similar to a NITAG. Most NITAGs had been active for many years: the oldest, since 1902. Five NITAGs were established in 2006 or later. The number of NITAG-members ranged from seven to 35 (median 14). In 17

TABLE 1. Description of 23 National Immunization Technical Advisory Groups (NITAGs) based on a survey conducted during February–April 2013 among the VENICE gatekeepers.

Country	Year NITAG was established	Number of NITAG members	Permanent guests without voting rights (e.g. representatives from the MoH, regulatory authority, professional societies)	External experts temporarily invited for specific topics	Pharmaceutical industry as occasional external experts	Meeting is always open to the public	Declaration of conflict of interest	Meetings per year	Minutes published online	Framework in place for the systematic development of vaccination recommendations	Results from economic evaluations routinely considered for NITAG's recommendations
Austria	1991	9	No	Yes	No	No	Yes	3–5	No	No	No[a]
Belgium	1991	35	Yes	Yes	No	No	Yes	>5	No	No	No[a]
Bulgaria	2002	13	Yes	Yes	Yes	No	No	3–5	No	No	Yes
Czech Republic	2010	11	Yes	Yes	No	No	Yes	3–5	Yes	No	Yes
Germany	1972	12–18	Yes	Yes	No	No	Yes	≥2	Yes, since 2013	Yes	No
Denmark	At least from 1980	14	No	Yes	No	No	Yes	0–2	Yes	Yes	Yes
Estonia	2006	15	Yes	Yes	Yes	No	Yes	3–5	No	Yes	Yes
Finland	2001	13	No	Yes	Yes	No	Yes	3–5	Yes, since 2013	Yes	Yes
France	1985	17	Yes	Yes	Yes	No	Yes	>5	No	No	Yes
Greece	1991	11	No	Yes	No	No	No	3–5	No	No	No
Ireland	1996	18	Yes	Yes	No	No	Yes	>5	No	No	Yes
Iceland	1998	7	Yes	Yes	Yes	No	No	3–5	No	No	Yes
Lithuania	1999	11	Yes	Yes	Yes	No	Yes	3–5	No	No	No
Luxembourg	1963	14	Yes	Yes	No	No	Yes	>5	No	Yes	Yes
Latvia	2000	15	No	Yes	Yes	Yes	No	≥2	Yes	No	No
Malta	2007	8	Yes	Yes	No	No	Yes	≥5	No	Yes	Yes
Netherlands	1902	about 20	Yes	Yes	No	No	Yes	>5	No	Yes	Yes
Poland	2003	17 + 10	Yes	Yes	No	No	N.A.	3–5	No	Yes	Yes
Romania	2008	15	Yes	Yes	No	No	Yes	3–5	No	No	Yes
Spain	1991	19 + 4	Yes	Yes	No	No	No	≥2	No	Yes	Yes
Slovakia	2006	9	No	Yes	No	No	Yes	3–5	No	Yes	Yes
Slovenia	2011	10	Yes	Yes	No	Sometimes	Yes	3–5	Yes	Yes	Yes
United Kingdom	1963	18–20	Yes	Yes	No	No	Yes	>5	Yes	No	Yes

[a]Health-economic evaluations are not considered when developing the NITAG recommendation, but constitute a second (independent) step in the decision-making process for adopting a new vaccination in the national programmes.
NA, not available.

TABLE 2. Professional expertise represented among National Immunization Technical Advisory Group (NITAG) members in 22 countries with NITAGs ([a]).

Field	Countries	Proportion (%)
Clinical medicine	22	100
Epidemiology	21	96
Paediatrics	20	91
Public health	18	82
Microbiology (incl. Virology)	17	77
Immunology	16	73
Vaccinology	16	73
Health economics	5	23
General practice	5	23
Regulatory Authority on Medicines	5	23
Ministry of Health	2	9
Social sciences	2	9
'Well-baby clinics'	2	9
University faculty	1	5
Ethics	1	5
Health insurance system	1	5
Lay members	1	5
Occupational health	1	5
Non-governmental organizations	1	5
School Health Medicine	1	5
Travel medicine	1	5

[a]Spain is not included because the composition of NITAGs varies by Region.

of 22 NITAGs, members are requested to declare their potential conflicts of interest. In Table 2, the professional expertise of NITAG members is described. Clinicians, epidemiologists and paediatricians are the most frequently represented professional groups in NITAGs.

Besides regular members, permanent guests without voting rights can attend NITAG meetings in 17 countries. In 23 countries, external experts are temporarily invited for specific topics. In eight NITAGs, representatives of the pharmaceutical industry are occasionally invited as external experts. In one country, the NITAG meetings are public, unless a decision to the contrary has been made; in another country, NITAG meetings are sometimes public. Minutes are published online by seven NITAGs, while another six provide minutes upon request.

Ten of the 22 countries with NITAGs stated that their NITAG had a framework for the formal process when recommending a vaccine for the NIP. Currently, two countries apply the GRADE methodology (Germany and France). In four out of 23 countries, the NITAG can give different degrees of strength to its recommendation. Table 3 summarizes the key factors of NITAG decision-making: disease burden in the country, severity of the disease, vaccine effectiveness or efficacy, and vaccine safety at population level were the four common factors shared by the NITAGs of all responding countries.

In all 23 countries that have a NITAG and that provided a response to this question, a separate governmental or health insurance structure entity makes the final decision on NIP inclusion or reimbursement of vaccination. In 16 of these 23 countries, NITAGs provide information directly to the national entity that takes this final decision. In the remaining seven NITAGs, the decision needs to be validated by another entity before final decision-making (e.g. a National Board or Intra-territorial Council or a National Public Health Institute, or Public Health Authorities).

Reasons for Differences in NITAG Recommendations and NIP Schedules

Despite similar key criteria considered by NITAGs in Europe, substantial differences in vaccination schedules (http://vaccine-schedule.ecdc.europa.eu/Pages/Scheduler.aspx) and policies exist [16,17]. Besides historical reasons, these differences can partially be explained by differences in the vaccination

TABLE 3. Key factors considered in the decision-making process of adopting vaccines in the national immunization programme of surveyed countries (n = 21 with and n = 5 without a National Immunization Technical Advisory Group (NITAG)

Factor	Number of countries that consider this a key factor (n)	Number of responding countries (n)	Proportion (%)
Disease burden in home country	25	25	100
Severity of disease	25	25	100
Vaccine efficacy/effectiveness	25	25	100
Vaccine safety at population level	25	25	100
Vaccine safety at individual level	23	25	92
Feasibility of recommendation	23	25	92
Guidance document from WHO	22	25	88
Priority among other vaccine-preventable diseases	21	25	84
Results from economic evaluations	20	25	80
Guidance document from ECDC	20	25	80
Recommendations of other countries	18	24	75
Method of vaccine administration	14	24	58
Priority of vaccination compared with all other possible health interventions	12	24	50
Results from mathematical modelling	11	24	46
Public perception about the disease	10	24	44
Disease burden in neighbouring country	7	24	29
Feasibility of local vaccine production	1	24	4

systems, including funding schemes and the role of responsible authorities in decision-making regarding inclusion of a vaccine in a NIP. The UK, the Netherlands and Finland are examples of centralized systems with government-funded vaccination programmes and central vaccine procurement (see country examples in the Supplementary material, Appendix S1). In contrast, Germany is an example of a decentralized, private vaccination system, where vaccinations are reimbursed by statutory health insurances, and vaccines are usually administered by a private physician who can freely choose among vaccine brands available on the market. Italy, on the other hand, has a decentralized public health system with government-funded vaccination programmes and 21 regions free to decide on schedules, brand of vaccines and the organization of regional immunization activity. This explains why some key factors play a more dominant role in some NITAGs than in others, for example: health-economic evaluations in countries with a centralized system.

Most NIP vaccines are given in the first 2 years of life, because they protect against highly contagious diseases that affect mainly young children and children in this age-group are most vulnerable. All European countries have recommendations and give vaccines against tetanus, diphtheria, pertussis, polio, *Haemophilus influenzae* type b (Hib), measles, mumps and rubella in their NIP [16]. Even if these vaccines are common, the antigen composition, schedules, co-administration and dosing often differ by country. Partly, this could be a result of different interpretations of the immunological impacts of the varying schedules or of the lack of evidence documenting that one schedule works better than the others in reducing disease incidence in the population.

Issues of Vaccination Systems, Financing Schemes and Pooling Contracts

For the other childhood vaccines, there are even more differences among countries. In addition to the above-mentioned reasons, financial and organizational considerations also play an important role. In some countries, systems are in place to decrease the vaccine dose price to levels comparable to the estimated country-specific threshold price, either through a formal tender system or through negotiations by responsible authorities on the vaccine dose price when integrated into an NIP. Organizational aspects are important, especially when integrating a new vaccine into the existing health systems. The healthcare costs of both the existing NIP and 'well-baby' programmes need to be re-considered, for example by synchronizing the vaccination visits with other growth and development monitoring activities in the well-baby clinics and vaccination centres, which increases the acceptance and attendance rate of parents.

Even within a single country, there may exist differences in baseline disease burden and risk among different population subgroups, depending, for example, on age, gender, underlying chronic disease, access to health care or other socio-demographic parameters. Therefore, the baseline disease burden and risk in different population subgroups must be considered when weighting the benefits and costs of different vaccination strategies. Again, these factors may vary from country to country, and therefore it is a major task of each NITAG to review such data at country-level and suggest the most efficient vaccination strategy accordingly. In addition to group-specific baseline disease risk, other infectious or societal factors might influence a NITAG's decision to target specific population-subgroups.

Yet more country-specific key factors considered by NITAGs may contribute to differences in vaccination schedules and policies across Europe. These include, for example:

- data on local disease incidence, which may or may not be readily available;
- disease-related and vaccination-related costs, which depend on the healthcare system in place. Both impact health economic evaluations, which in turn are dramatically influenced by tendering and negotiation practices for vaccine prices in the country;
- the degree to which a health-economic evaluation is taken into consideration and assumptions made for it (such as indirect costs and discounting); this degree may differ in the decision-making process of a NITAG or other deciding bodies;
- preferences and values (which might be influenced by cultural differences) may or may not play a role; and
- availability of specific vaccines may differ, though local production is nearly non-existent nowadays.

Below, we present five examples on how and why NIPs differ, and we try to elucidate the role of NITAGs in the relevant decisions.

Example 1. Hepatitis B Vaccine for Children

Hepatitis B virus (HBV) vaccines are given universally to children in all European countries except the UK, Denmark, Norway, Sweden, Iceland and Finland (16). Some of these countries state that their HBV disease burden is too low to economically justify universal vaccination, and therefore they have instead chosen to target special risk groups. However, a universal programme might become cost-effective with combination vaccines, if the vaccine price is low enough.

Example 2. Rotavirus Vaccine for Children

As of today, rotavirus vaccine is given universally to infants as part of the NIP only in Austria, Finland and Luxembourg. In Belgium, universal rotavirus vaccination is recommended by the NITAG but is not included in the NIP. However, though the vaccine is only partially reimbursed, a high coverage is reached thanks to the participation of well-baby clinics [18]. In the UK, a decision to include rotavirus vaccine in the NIP has recently been made [19]. In some of these countries, formal cost-effectiveness evaluation has demonstrated that rotavirus vaccination can be justified on reasonable economic grounds [20]. In other countries, the assumed price of the vaccine has mostly been unfavourable in relation to the perceived burden of rotavirus disease to the society.

Example 3. Vaccination of Girls Against Human Papillomavirus

Vaccination programmes against human papillomavirus (HPV) mostly target adolescent girls only [21]. Most countries analysed the cost-effectiveness of various options. Factors considered—in addition to price—for the recommendation are HPV-associated disease burden in the country: most importantly, cervical cancer and the ability of the cancer screening test (Papanicolaou) and HPV-screening systems in place to detect it early. Depending on the main aim of the programme, genital warts and other HPV-associated cancers might also weigh in the decision. As HPV is sexually transmitted and often acquired soon after sexual debut, the vaccine needs to be given before exposure to HPV. Hence, the average age of sexual debut, and probable acceptance of a vaccination against a sexually transmitted disease by the target group and their guardians all play a role [22].

As of November 2012, HPV vaccines have been adopted in the NIP of 21 of 29 surveyed European countries (27 EU Member States plus Iceland and Norway) [21] (Fig. 1). Whereas in most countries the adopted vaccination policy targets only females, both females and males are recommended to be vaccinated in Austria [21]. Adolescents aged 12 years were chosen as the target population for routine vaccination in eight countries, while girls aged 11, 13, 14 years, or an age range including several birth cohorts, were chosen in the other Member States [21].

Example 4. General Adult Vaccination Schedules

Depending on the country, adult vaccine recommendations range from the almost non-existent to the over-abundant. In the 29 EU and European Economic Area (EEA) member states, between four and 16 vaccines are recommended to adults [23]. All countries have recommendations for adults universally or adult subgroups to be vaccinated against seasonal influenza and hepatitis B, followed by recommendations for prophylactic tetanus and diphtheria vaccination, which exist in 76% and 72% countries, respectively [23]. In recent years, with the upsurge of pertussis, acellular pertussis vaccine has also been increasingly viewed as an adult vaccination, and different strategies have been implemented across Europe to combat the re-emergence of pertussis [24]. For example, in the UK, acellular pertussis vaccine has been recommended to all pregnant women since autumn 2012 to avert infant pertussis, while in Germany, a cocoon strategy is in place that targets all household contacts of newborns and so provides an additional

FIG. 1. Countries with human papillomavirus (HPV) vaccine introduced into the national immunization programme (NIP; as of November 2012), in the European Union, Iceland and Norway.

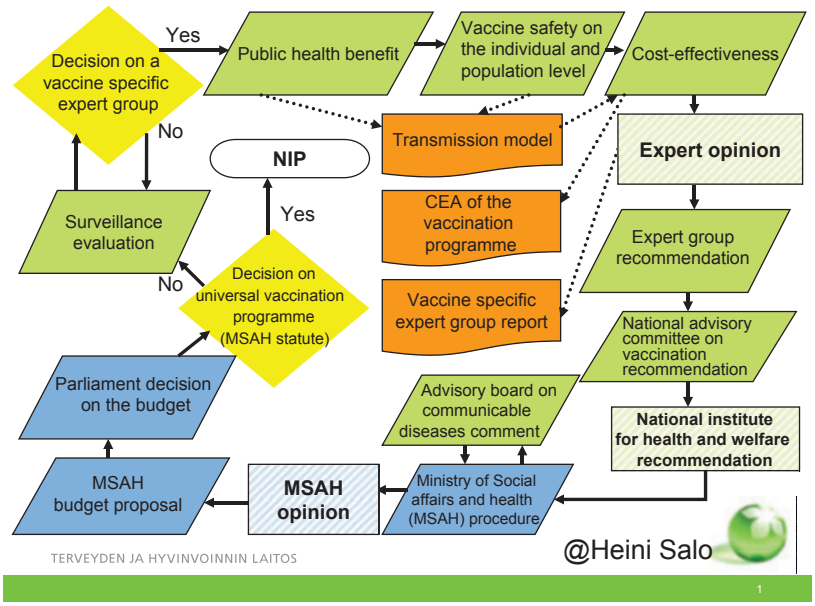

FIG. 2. A schematic description of the decision-making process for recommending the inclusion of a new vaccine in the national immunization programme in Finland. The National Immunization Technical Advisory Group (NITAG) covers the process from decision on the formation of a vaccine-specific expert group to providing a recommendation to the National Institute for Health and Welfare. NIP, national immunization programme; CEA, cost effectiveness analysis; MSAH, ministry of social affairs and health.

booster dose to the German adults who otherwise would receive only one booster dose in their life time [25,26].

Example 5. Vaccination Against Seasonal Influenza

For seasonal influenza vaccination, most European countries target population subgroups with an increased risk of developing severe disease, especially individuals with chronic underlying conditions and/or persons above 55 or 60 or 65 years [23,27]. Healthcare workers are also considered as a key target group for influenza vaccination, mainly to reduce work absenteeism and because of their crucial position in caring for those who need the most protection from influenza, but also because they could set a positive example to others. Another special group recently added to the target list is pregnant women. Despite evidence for increased risk of complications of influenza in advancing pregnancy [28] and the lack of adverse events to the offspring when the mother has been vaccinated [29], several European countries are hesitant to follow the advice of the Strategic Advisory Group of WHO to make this recommendation, indicating that evidence is being weighted differently [30,31].

Differences also exist in paediatric or adolescent influenza vaccination policy. As of 2009, only six of 27 (22%) EU/EEA member states recommended influenza vaccination of healthy children aged between 6 months and <18 years [27]. This may suggest knowledge gaps (e.g. evidence related to the occurrence of herd protection), lack of data on the local disease burden, conflicting reports on influenza vaccine efficacy and/or effectiveness in young children, and finally, value differences among NITAGs [27]. Value differences may be the result of various factors, including the ethical dilemma when routinely vaccinating healthy children with non-perfect vaccines, with one of the main goals being to reduce overall disease transmission and thereby (indirectly) also reduce disease incidence in the elderly and more vulnerable population.

NITAG Recommendations and Inclusion of Vaccines in the NIP

Despite obvious disease burden and available intervention options, not all vaccines are included in every country's NIP. The primary role of NITAGs is to develop recommendations to guide national authorities and policy makers. As demonstrated in our survey, in all European countries with NITAGs, there are separate governmental or health insurance authorities that make the final decision of whether to adopt a new vaccine in the NIP, or whether to reimburse the vaccine (Fig. 2). For this reason, in some instances, a NITAG can endorse a

recommendation for a vaccine, but the vaccine is not adopted into the NIP, e.g. for economic reasons. In some countries with more regional autonomy, additional committees or authorities are responsible for decision-making at subnational level. This explains why there are sometimes even different recommendations or programmes within a country.

In many countries, vaccines included in a NIP are free of charge or reimbursed by health insurance. On the contrary, vaccines not included in the NIP but available on the market and administered according to the indications in the licensure are either paid out-of-pocket or only partially reimbursed. This emphasizes the additional role and importance of a NITAG as an advisory body serving clinicians in their decision process for individual patients or patient groups. The situation is complicated when the available scientific evidence is non-existent, weak or contradictory. A recent example is provided by the recommendation of pneumococcal vaccines for adults to prevent invasive and non-invasive pneumococcal diseases. The superiority of the conjugate over the polysaccharide pneumococcal vaccine in prevention of invasive disease is still a subject of academic dispute [32,33]. Laboratory results pointing to the polysaccharide vaccine causing hypo-responsiveness in those vaccinated is challenged by clinical observations [34]. Key clinical opinion leaders may be influenced by the pharmaceutical industry, at the same time that evidence on the impact of the conjugate vaccine on the main outcome from public health perspective, i.e. adult pneumonia, is still lacking.

In these instances, NITAGs—in their role of advising national authorities—may decide to await additional evidence from not yet published studies or from the experience of other countries that have already introduced the programme. The GRADE working group suggests that in circumstances in which panels, such as NITAGs, choose not to make a recommendation, they should specify whether this is on the basis of very low confidence in the effect estimates, or because they think the balance between desirable and undesirable consequences is so close that they cannot make a recommendation [7]. In many countries, NITAG recommendations also serve as "best practice guidelines" for physicians, so lacking a recommendation should not obviate physicians from taking a decision whether to vaccinate or not on an individual patient basis. Recommendations from other entities, e.g. professional societies, might be available and support the physician in taking this decision. In the case of pneumococcal vaccines, human immunodeficiency virus experts and lung specialists may want to formulate their own recommendations just as clinicians treating patients with rheumatoid arthritis have formulated recommendations regarding the use of vaccines for patients receiving immuno-modulatory treatments [35].

Future Considerations

The systematic development of evidence-based vaccination recommendations by NITAGs requires a lot of resources, time and effort. If transmission modelling and costing analyses are included, the evaluation easily takes several years to complete. In addition, not all countries have the resources and expertise available to conduct these analyses as a standard procedure when developing vaccination recommendations. Presently, for the majority of European countries, the most resource-consuming, but also most important, part of the decision-making process is the systematic review of the literature and assessment of the quality of available evidence. Often, the same review work is conducted by each NITAG individually. This task offers itself to putative synergies and interaction among countries, which could be facilitated by supranational bodies, such as the European Centre for Disease Prevention and Control or the WHO. Here, the aim should be on reducing the duplication of effort by focusing on common key factors used by NITAGs that are not country-specific, namely the assessment of the quality of evidence related to vaccine effects and vaccination programme effects at population level [36].

While the Paediatric Committee of the European Medicines Agency, vaccine manufacturers, and several authors have called for the harmonization of immunization schedules, arguing that a single, uniform immunization schedule would be ethical, cost-saving, would facilitate mobility of EU residents, improve data collection, and increase vaccination coverage, other authors doubt that these arguments are either quantitatively or qualitatively appropriate [37]. Harmonization might be even ethically problematic, given that, as described above, many factors considered by NITAGs, such as disease burden or cost-effectiveness, are often country-specific. Even though making recommendations and harmonizing vaccination schedules at the European level could save on limited resources and facilitate the research and development of new vaccines, harmonization is also not foreseen as a realistic goal in the light of present policies and the situation of decision-making in Europe. At this stage, therefore, making transparent the path from evaluation to recommendation to final decision of implementation in the NIP would increase understanding and confidence within each country as well as across countries, and ultimately contribute to epidemiologically, immunologically and economically better justified vaccination programmes.

Transparency Declaration

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Appendix 1

VENICE National Gatekeepers: Berthet, Francoise (Luxembourg), Chicin, Gratiana (Romania), Corcoran, Brenda (Ireland), Cotter, Suzanne (Ireland), D'Ancona, Fortunato (Italy), De Melker, Hester (Netherlands), Feiring, Berit (Norway), Floret, Daniel (France), Gill, Denis (Ireland), Gudnason, Thorolfur (Iceland), Hudecova, Helena (Slovakia), Iannazzo, Stefania, (Italy), Kerbo, Natalia (Estonia), Kojouharova, Mira (Bulgaria), Kraigher, Alenka (Slovenia), Kriz, Bohumir (Czech Republic), Limia, Aurora (Spain), Lileikyte, Ausra (Lithuania), Melillo, Tanya (Malta), Nohynek, Hanna (Finland), O'Flanagan, Darina (Ireland), Paradowska-Stankiewicz, Iwona (Poland), Pebody, Richard (United Kingdom), Perevoscikovs, Jurijs (Latvia), Sabbe, Martine (Belgium), Soteriou, Soteroulla (Cyprus), Stavrou, Theodora (Greece), Top, Geert (Belgium), Tegnell, Anders (Sweden), Valentiner-Branth, Palle (Denmark), Van Damme, Pierre (Belgium), Wichmann, Ole (Germany), Wiedermann, Ursula (Austria).

Supporting Information

Additional Supporting Information may be found in the online version of this article:

Appendix S1. Country examples of National Immunization Technical Advisory Groups (NITAGs) and their methodologies in Europe

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