ROBERT KOCH INSTITUT

Bundesministerium für Gesundheit

Second International Workshop on Procedures for the Development of Evidence-based Recommendations for Immunization

Berlin, September 15-16, 2011

Tryp Hotel Mitte
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10115 Berlin

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Bundesministerium für Gesundheit

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1. Background and Objectives

Background:	In November 2010 a first international workshop was held in Berlin to review current procedures and experiences of National Technical Advisory Groups (NITAGs) in developing evidence-based vaccination recommendations.
Objectives of the second international workshop:	To continue the dialogue and to provide an update on recent experiences and procedures in developing evidence-based vaccination recommendations To further discuss the applicability of GRADE for the development of evidence-based vaccination recommendations To discuss challenges of developing vaccination recommendations at the country-level and possibilities for providing international support to NITAGs.

2. Agenda

Thursday 15 September 2011		
9.00 – 9.30	Registration	
9.30 – 9.45	Welcome	MOH, RKI
9.45 – 10.00	Introduction and background	Ole Wichmann, RKI
10.00 – 10.30	Evidence-based methodologies for public health. Report from a working group at ECDC	Frode Forland, ECDC
10.30 – 11.00	Which criteria are used by National Technical Advisory Groups for making recommendations? – Results from a Survey in 2011	Guillaume Dedet, Kamel Senouci, SIVAC
11.00 – 11.30	Using GRADE to develop recommendations for immunization: recent advances	Holger Schünemann, GRADE Working Group
11.30 – 12.00 Coffee Break		
12.00 – 12.30	WHO's Strategic Advisory Group of Experts (SAGE): Update on the SAGE approach to develop evidence-based vaccination recommendations	Philippe Duclos, WHO
12.30 – 13.00	Country experience: The US Advisory Committee on Immunization Practices (ACIP) and the application of GRADE	Faruque Ahmed, CDC, United States
13.00 – 13.30	What to do when country-specific data are lacking? Minimum requirements and procedures when developing vaccination recommendations in Finland	Hanna Nohynek THL, Finland
13.30 – 14.30 Lunch Break		
14.30 – 17.00	**Group work on:** - Group 1: The GRADE approach and immunisation recommendations. Challenges and possible solutions - Group 2: Challenges to develop country-level immunisation recommendations. How can international support be provided to NITAGs	Facilitators: Doug Campos-Outcalt ACIP, United States Matthias Perleth The Federal Joint Committee, Germany Kamel Senouci SIVAC Piotr Kramarz ECDC
18.30 Welcome reception and dinner		

Friday 16 September 2011		
9.00 - 9.30 Warm up Coffee		
9.30 – 12. 30	**Group work (contd.)** Continue discussion Summarize group discussions, refine key messages and recommendations, and prepare 10 min presentation	
12.30 – 13.30 Lunch		
13.30 – 14.30	**Plenary discussions** Presentations of Group 1& 2	Rapporteur Group 1 & 2
14.30 – 15.00	Résumé and closing discussions to identify main key messages and further conceivable procedures	Gérard Krause, RKI
15.00 End of the Workshop		

3. List of participants

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What to do when country-specific data are lacking? Minimum requirements and procedures when developing vaccination recommendations in Finland

4.1 Introduction and background to the Workshop

Ole Wichmann, MD
Head of Immunization Unit, Robert Koch Institute, Berlin, Germany

In November 2010, the first “Workshop on Procedures for the Development of Evidence-based Recommendations for Immunization” was held in Berlin. More than 40 international experts attended the workshop to review current procedures and experiences of National Immunization Technical Advisory Groups (NITAGs) in developing evidence-based vaccination recommendations. It was concluded that “Grading of Recommendations Assessment, Development and Evaluation” (GRADE) or a modification of this methodology can be applied for the grading of quality of evidence related to vaccine effectiveness and safety. Furthermore, there was consensus that international cooperation would be beneficial to develop common framework methodologies for the development of national immunization recommendations and to avoid duplication of effort.
This second Workshop has been organized by the German Ministry of Health and the Robert Koch Institute to continue the fruitful dialogue that was initiated in 2010. Updates will be presented from the Advisory Committee on Immunization Practices (ACIP) of the United States, the Strategic Advisory Group of Experts on Immunization (SAGE) at WHO, the GRADE Working Group, and the European Centre for Disease Prevention and Control. In Germany, the Standing Committee on Vaccination (STIKO) decided to test the applicability of GRADE when developing the next vaccination recommendation. New “Standard Operating Procedures” have been developed by the STIKO methods working group, which will be proposed to the STIKO during the next meeting and which are currently already tested in cooperation with the STIKO rotavirus working group. Based on the experiences made so far by various NITAGs and international expert groups, the second Workshop will provide a forum where challenges will be discussed when applying GRADE to the development of vaccination recommendations.
A second objective of the Workshop is to further discuss, how international support can be provided to NITAG to develop country-level vaccination recommendations. It was general consensus during the first Workshop, that the development of evidence-based vaccination requires considerable resources, but still tremendous duplications do occur e.g. when each NITAG individually reviews the existing literature related to a vaccine-specific question. During the second Workshop further questions will be discussed: What challenges do NITAGs commonly face, what are their needs, and what components should be part of guidance documents developed by international organizations such as WHO or ECDC? As an introductory to this topics, experiences from Finland will be presented and results from a survey on NITAG needs that was performed by the “Supporting Independent Immunization and Vaccine Advisory Committees” (SIVAC) initiative in 2011.

NOTE

4.2 Evidence-based methodologies for public health. Report from a working group at ECDC

Frode Forland, Senior Expert ECDC

The objective of the working group was to explore how methods of evidence-based medicine (EBM) can be applied in the field of public health infectious diseases. Members were from EBM organisations, public health institutions and from ECDC.
Evidence-based public health could be defined as integrating the best available evidence with the knowledge and considered judgements from stakeholders and experts to benefit the needs of a population. Data from observational studies, surveillance and modelling play an important role as evidence base in public health. Since information about outbreaks can only be gathered while an outbreak is ongoing, it is important to perform and report outbreak investigations better. Uncertainties can arise at all stages of public health decision-making. Uncertainties should be handled explicitly and be communicated to policymakers.
A variety of methods for reporting, assessing and grading evidence are identified and the applicability of these tools to public health is discussed. Special attention has been given to the GRADE instrument, which has been adopted by many influential organisations. A table with a list of issues concerning the applicability of GRADE in public health is presented.
Many tools required to produce evidence-based advice already exist, but there is a need to further develop instruments and checklists for some of the study designs relevant to public health.
We evaluated the guideline evaluation instrument “AGREE II” for the purpose of infectious diseases guidelines. The importance of the different domains and items is discussed and some additional criteria for communicable diseases guidelines are proposed. Consensus methods can be applied by members of a guidance development group to decide on disagreements in the interpretation of the evidence and on judgements of benefits and harms.
Prioritised areas for future work should be:

- to develop better templates for reporting and checklists for assessing the quality of outbreak reports;
- to explore how evidence-based grading systems could integrate and possibly upgrade the value of evidence from observational research in situations where only such evidence is attainable;
- to develop better retrieval and search systems for observational studies to find the best available evidence under time constraints; and
- to assess how to more explicitly express uncertainties from the scientific evidence and the judgements of it.

NOTE

4.3 Which criteria are used by National Technical Advisory Groups for making recommendations? Results from a Survey in 2011

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Introduction: Based on the successful role of worldwide National Immunization Technical Advisory Groups (NITAGs) in setting immunization policies and programs, countries have requested support from WHO and its technical partners (SIVAC, US-CDC…) in strengthening "national capacity for making evidence-based policy decisions to adopt new vaccines". Once a NITAG is established, it should make recommendations following a clearly defined and transparent evidence-based methodology according to international standards.
Today, very little is known about the criteria used by NITAGs worldwide to issue recommendations. We decided to conduct a survey on some NITAGs in order to learn more about the basis of their recommendations.
Methods: Several NITAGs were selected with the help of WHO regional offices within the 6 WHO regions. Selection criteria included geographic representativeness and level of economical development. The target interviewee was the committee's chairperson or the executive secretariat. Four categories of variables were considered: variables characterizing the respondent, variables characterizing the NITAG, variables characterizing the process for decision making, and variables characterizing the criteria used to formulate recommendations. The questionnaires were completed during phone interviews.
Results: Out of the 21 pre-selected committees, 14 completed the questionnaire (1 in AFRO, 2 in EMRO, 5 in EURO, 3 in PAHO, 2 in SEARO and 1 in WPRO). Eight of the interviewees were chairmen or members of the committee, 6 were members of the executive secretariat.
Regarding the ranking of evidence, 50% of the committees reported that they didn't use a formal ranking system. Furthermore 65% declared that they used a formal framework to elaborate their recommendations, but less than half indicated that this was available for external consultation. The three most important criteria being used were: vaccine characteristics, epidemiologic features of the disease and economic considerations.
Discussion: Although this survey has many limitations, it illustrates interesting information regarding the criteria used by NITAGs to issue recommendations. No committee interviewed reported socio-cultural issues as an important criterion to consider when making a recommendation. It would be interesting to see if the criteria taken into consideration depend on the welfare of the nation or on its geographic localization.

NOTE

4.4 GRADE for the development of evidence based recommendations for immunization

Holger Schünemann, M.D., Ph.D., M.Sc., FRCP(C),Chair, Department of Clinical Epidemiology & Biostatistics, Michael Gent Chair in Healthcare Research, Professor, Dep'ts. of Clinical Epidemiology & Biostatistics and Medicine, McMaster University Health Sciences Centre, Hamilton, Canada

Grading strength of recommendations and quality of underlying evidence enhances the usefulness of clinical practice guidelines, but the profusion of conflicting grading systems used by different organizations threatens to undermine the value of the grading exercise. This presentation will focus on how the approach of the international Grading Recommendations Assessment, Development and Evaluation (GRADE) group can be applied in the assessment of the quality of evidence and the strength of recommendations in decision about immunization.
Using examples from the immunization literature, the presentation will focus on how the assessment of the quality of evidence based on methodological factors (study design, risk of bias, imprecision, heterogeneity, publication bias, indirectness, dose response effects, large effects, and issues about residual plausible confounding and bias) is related but independent of moving from evidence to recommendations.

NOTE

4.5 WHO's Strategic Advisory Group of Experts (SAGE) on immunization: Update on the SAGE approach to develop evidence-based vaccination recommendations

Philippe Duclos, DVM, PhD
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The Strategic Advisory Group of Experts (SAGE) on immunization is the main WHO advisory group involved with the development of global policy recommendations and strategic advice related to immunization. Its mandate extends to all vaccine-preventable diseases throughout all ages. SAGE working groups are established on a time-limited basis to review and provide evidence based options for recommendations together with their implications for open discussion by SAGE. In making its recommendations, SAGE takes into consideration: the epidemiologic features of the disease, clinical characteristics of the disease, vaccine and immunization characteristics, economic analysis, health system opportunities, existence of and interaction with other existing intervention and control strategies, social impacts, as well as legal and ethical issues.

Since 1998, WHO has produced evidence-based vaccine position papers for use mainly by national public health officials and immunization programme managers. The papers are based on an extensive literature review and are the result of a wide-ranging consultative and review process by various experts and interest groups both inside and outside WHO. Since April 2006, the new or updated position papers have followed the recommendations of SAGE.

The Grading of Recommendations Assessment, Development and Evaluation (GRADE) approach has been adopted by WHO and, since 2008, GRADE tables that score the quality of evidence have been produced in support of key recommendations and are referenced in the vaccine position papers.

SAGE previously found that Grading of Recommendations Assessment, Development and Evaluation (GRADE) was not ideally suited to manage many immunization-specific issues and encouraged a SAGE discussion group on grading to review available evidence to, inter alia, suggest appropriate adjustments to the use of GRADE and develop a paper describing the SAGE approach to reviewing evidence when issuing recommendations.

Extensive and productive interaction took place with various advisory groups including the US Advisory Committee on Immunization Practices, the European CDC, the German national advisory committee on immunization, GACVS and the GRADE working group, particularly with a view to accommodate vaccine population effects, and allow inclusion of surveillance system and vaccine safety data.

In April 2011, the discussion group presented SAGE with a draft guidance document on the process for developing evidence-based recommendations on vaccine use in public health programmes. SAGE indicated that the proposed approach addressed many of its initial concerns, noting that the draft guidelines were a major and timely step forward, and encouraged wider dissemination. SAGE emphasized the need for early identification of the PICO (population, intervention, comparator, outcome) questions for grading early for endorsement by SAGE and the need for training of working group members or to access

expertise on the review of evidence process. Ongoing engagement with current partners by the discussion group was encouraged, particularly to identify challenges to the current GRADE scoring scheme. SAGE noted that for successful evidence review and grading, WHO would need to ensure that adequate resources were available.

An update will be provided on the fine-tuning of GRADE since the 2010 Berlin meeting and remaining challenges will be flagged for discussion.

NOTE

4.6 The US Advisory Committee on Immunization Practices (ACIP) and the application of GRADE

Faruque Ahmed, PhD, National Center for Immunization and Respiratory Diseases, Centers for Disease Control and Prevention (CDC), Atlanta, USA

The ACIP has adopted a new framework for developing evidence-based recommendations that is based on the Grading of Recommendations, Assessment, Development and Evaluation (GRADE) approach. Category A recommendations will be made for all persons in an age- or risk-factor-based group, with the exception of persons who have a contraindication. Category B recommendations will be made for individual clinical decision making; category B recommendations do not apply to all members of an age- or risk-factor-based group, but in the context of a clinician-patient interaction, vaccination may be found to be appropriate for a person in an age- or risk-factor-based group. The body of evidence will be categorized into four types: (1) randomized controlled trials (RCTs), or overwhelming evidence from observational studies; (2) RCTs with important limitations, or exceptionally strong evidence from observational studies; (3) observational studies, or RCTs with notable limitations; (4) clinical experience and observations, observational studies with important limitations, or RCTs with several major limitations. Key factors considered in development of recommendations include the balance of benefits and harms, type or quality of evidence, values and preferences of the people affected, and health economic analyses. Category A recommendations can be for or against vaccination; examples would include the ACIP recommendation to routinely vaccinate infants with rotavirus vaccine, and the recommendation against use of the 2010–2011 Afluria influenza vaccine among children aged 6 months through 8 years. An example of a category B recommendation is the recommendation that the 2010–2011 Afluria vaccine may be used, after discussion with the parents or caregivers, for a child aged 5 through 8 years with a medical condition that increases the child's risk for influenza vaccination if no other age-appropriate influenza vaccine is available.

NOTE

4.7 What to do when country-specific data are lacking? Minimum requirements and procedures when developing vaccination recommendations in Finland

Hanna Nohynek, MD PhD, THL Finland

The simple answer is “Go and look for the missing data!” In Finland, the national vaccination programme is financed by the government. No other compensation mechanisms are in place. Partly subsidizing vaccines not included in the national programme (NIP) have been discussed, but so far the response has been against subsidies. The underlying argument for the prudent approach calling for critical evidence base has been that since the vaccines in NIP are paid by the government the programme can be assumed to make a reasonably cost-efficacious impact. Since 2000, Finland has adhered to a so called four-step approach when deciding to introduce a vaccine into the national programme. The elements of this decision making are 1) considerable public health disease burden; 2) demonstrated safety of the vaccine on individual level; 3) demonstrated safety of the vaccine on population level; 4) reasonable cost effectiveness (CEA) of the intervention. The process is quite strict, and missing key data will lead to a situation where the vaccine will not be included. Such was the case of PCV, which has been evaluated twice; in 2001 it did not pass the 4th step and thus was not introduced as there was not sufficiently reliable data on the indirect impact of PCV that Finland could consider using in CEA. With accumulating evidence, in 2008, PCV passed the 4th step, and it was finally included into NPI in September 2010. The other vaccines which have passed the 4 criteria are influenza for children in 2006, rotavirus vaccine in 2009, and in spring 2011 human papilloma virus vaccine. Its inclusion in the programme is pending budget allocation. An example of a limitation of a vaccine to risk group use only undergoing such evaluation is BCG since 2006 (reason = individual safety). The recent cluster of narcolepsy cases among Pandemrix vaccinated children and adolescents in Finland and Sweden is a reminder that even with a prudent use of minimum set of criteria, and while the overall benefit-risk balance may still be on positive side, there is room for improvement in the national vaccine recommendations and procedures.

National programme in Finland in 2011		
Target group	**Age**	**Vaccine antigens**
To all	2 mo	Rota
	3 mo	DTaP-IPV-Hib, PCV10, rota
	5 mo	DTaP-IPV-Hib, PCV10, rota
	6–35 mo	Influenza (2 doses during the 1st vaccination, thereafter once a year), DTaP-IPV-Hib
	12 mo	DTaP-IPV-Hib, PCV
	14–18 mo	MMR (during outbreaks already from 12 mo on)
	4 y	DTaP-IPV
	6 y	MMR
	14–15 y	dtap
	> 65 y	Influenza
To risk groups		BCG-, HBV-, HAV-, influenza-, PCV- and Tick Borne Virus

References: Nohynek H. The Finnish decision-making process to recommend a new vaccine:
From vaccine research to vaccination policy. Eur J Publ Health 2008;16:275-80.

NOTE

5. Key Questions for working groups

Work Group 1: Issues regarding the application of GRADE for the evaluation of vaccinations

Facilitators: Matthias Perleth (The Federal Joint Committee), Doug Campos-Outcalt (ACIP)

General issues

- How to use GRADE for grading the evidence on
  - i. Herd-immunity,
  - ii. Protective effects derived from non-RCTs (efficacy vs. effectiveness)
  - iii. Is it appropriate to handle passive surveillance data same as results from analytical studies (e.g. case-control studies, self-controlled case series)
  - iv. Gradient of effects with scale of population level impact compatible with degree of coverage (all according to Schünemann)
- What is a (very) large magnitude of effect according to vaccines?
- For which questions are meta-analyses (based on systematic reviews) essential?
- Which guidelines or tools are helpful to assess quality of evidence of RCTs or observational studies? Are they helpful on Public Health level?
- How can internal validity of the GRADE methodology be ensured? How can the transparency of individual judgements and interpretation be optimised?
- Re-evaluation of “old” vaccines: different criteria?
- Potential of abuse of GRADE by anti-vaccination activists

Materials:

- WHO: Guidance for the Development of Evidence-Based Vaccine-Related Recommendations. 2. August 2011; Version 1. (http://www.who.int/immunization/sage/Guidelines_development_recommendations.pdf)
- Soares-Weiser K, MacLehose H, Ban-Aharon I, Goldberg E, Pitan F, Cuncliffe N: Vaccines for preventing rotavirus diarrhoea: vaccines in use (Review). Cochrane Library 2010, Issue 6.
- Ahmed F, Temte JL, Campos-Outcalt D, Schünemann H for the ACIP Evidence Based Recommendations Work Group (EBRWG): Methods for developing evidence-based recommendations by the Advisory Committee on Immunization Practices (ACIP) of the U.S. Centers for Disease Control and Prevention (CDC). Vaccine 2011 (in press).
- Rotavirus vaccinations-list of outcomes

Work Group 2: Challenges to develop country-level immunisation recommendations. How can international support be provided to NITAGs?

Facilitators: Kamel Senouci (SIVAC), Piotr Kramarz (ECDC)

Objectives:

A) To summarize experiences and challenges of NITAGs when developing country-level immunization recommendations and applying EBM tools

B) To identify country needs for the support in developing evidence-based immunization recommendations

Agenda:

a) Country experiences and challenges when developing immunization recommendations
   - Opening presentations from selected countries (NITAGs from 4 countries with different economic background. 10 min. per presentation)
   - Discussion

b) Discussion on key questions listed below
c) Summary of discussion and preparation of group presentation

Key questions to be addressed:

Questions addressing objective A:

1) What approach should be taken if there is little or no data for some key indicators / outcomes on a country-level?

2) How shall processes of immunisation recommendation developments be communicated to increase transparency and their acceptance? (General: Standard procedures and methods applied by NITAG. Specific: Single steps in the development of a specific recommendation).

3) Is a differentiation of recommendations into “weak recommendation” and “strong recommendation” as suggested by GRADE helpful (international organization vs. NITAG)?

4) Which tools can be used to evaluate the impact of a vaccination recommendation on a country-level? Procedures when important tools (e.g. a surveillance system) are lacking.

Questions addressing objective B:

5) Are international guidance documents (like WHO position papers or ECDC guidance on specific immunizations) or documents from other NITAGs or other national institutions taken into account when developing national recommendations?

6) Which elements / approaches in international guidance documents on immunisations are the most valuable from the national perspective?

7) How can work / resources be shared (and with whom?) to develop evidence-based vaccination recommendations on a country-level? (including transmission and health economics models)

8) How can international cooperation be improved to better support NITAGs in their decision making processes?

9) How international should international collaboration be (regional, sub-regional?)?

10) How can NITAG-members and staff of the executive secretariat be trained in new EBM methodologies?

References:

- Bryson M, Duclos P, Jolly A, Cakmak N: A global look at national Immunization Technical Advisory Groups. Vaccine 2010; 28S: A13-A17.
- Andreae MC, Switalski K, Abraham L, Freed GL: National Immunization Advisory Committees of the World Health European Region. Vaccine 2009; 27: 3131-3136.
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