ROBERT KOCH INSTITUT

Bundesministerium für Gesundheit

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

Berlin, November 22-23, 2010

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15.30 – 17.30 **1.** Auditorium **2.** Library **3.** Gallery	**Group work on:** - Group 1: Which evidence do we need for the development of evidence-based vaccination recommendations? - Group 2: Which methodologies are suitable for the development of evidence-based vaccination recommendations? - Group 3: Overall need and processes for international collaboration in developing evidence-based vaccination recommendations	Facilitator/Rapporteur: Frode Forland Yngve Falck-Ytter Faruque Ahmed Philippe Duclos Kamel Senouci Piotr Kramarz
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11.30 – 13.00	Presentations and Plenary Discussion - Group 1, 2 & 3	Rapporteur Group 1, 2 & 3
13.00 – 13.30	Résumé and closing discussions to identify main key messages and further conceivable procedures	Gérard Krause
13.30 Closing Lunch		

2. Background and Objectives

Objectives:	-	To review current procedures and experiences of National Immunization Technical Advisory Groups (NITAG's) in developing a framework for evidence-based vaccination recommendations
	-	To discuss the applicability of methods like GRADE
	-	To discuss potential benefits of and terms of references for international working groups to facilitate the development of evidence-based recommendations for NITAG's
Outcomes:	-	Identification of appropriate procedures to develop a framework for evidence-based vaccination recommendations
	-	Publication of an edited, peer-reviewed meeting report in a scientific journal

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4. Abstracts of Scientific Programme

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4.1 Introduction: The need for a framework for evidence-based recommendations for immunization

Ole Wichmann, Immunization Unit, Robert Koch Institute, Berlin, Germany

In recent years, several new vaccines have been marketed, and even more vaccines are currently in the development pipeline with the potential to be licensed in the near future. New vaccines often come with advanced technologies or product profile, but also with higher costs. Some protect against diseases that cause a considerable disease burden but only low mortality, depending on the settings. In light of these complexities, but also considering limited financial resources and public acceptance of an increasing number of recommended vaccines, governments must make decisions as to which vaccinations based on likely benefits on the one hand and downsides (e.g. costs, potential side-effects) on the other should be included in public immunization programs.

Transparent criteria are needed for the decisions to include vaccinations in public programs, and the standardization of a comprehensive methodology for evaluating available data underlying these decisions has become increasingly crucial. A systematic approach helps to improve the quality and reliability of the decision-making process by minimizing bias and increasing transparency, thereby facilitating critical appraisal of ensuing recommendations. This serves to build awareness and trust, thus contributing to the acceptance of the recommendation in the professional community as well as in the public.

Many countries have established National Immunization Technical Advisory Groups (NITAG) to provide guidance regarding immunization policies and to give recommendations related to the national immunization program (e.g. on introduction of new vaccines, vaccination schedules, or target groups). Several NITAG, e.g. in Canada or the Netherlands, have published analytical frameworks for comprehensive and systematic evaluation of factors to be considered before making vaccine-introduction decisions. Epidemiology and clinical characteristics of the disease, vaccine characteristics (effectiveness and safety, duration of immunity), feasibility of the program, public acceptance of the vaccination and economic issues (e.g. cost-effectiveness) are examples of factors frequently considered. There is currently debate as to whether more structured approaches, such as grading the quality of underlying evidence and the strength of recommendations are necessary and practical to enhance the evidence-based decision-making process in NITAG.

During the international workshop “Procedures for the Development of Evidence-based Recommendations for Immunization” to be held in Berlin on November 22/23, current procedures and experiences of NITAG in developing a framework for evidence-based vaccination recommendations will be reviewed and the applicability of methods that use criteria for the grading of evidence will be discussed.

4.2 Introduction to the development of evidence-based public health decisions (including GRADE)

Yngve Falck-Ytter, GRADE Working Group, Case Western Reserve University, School of Medicine, Director of Hepatology, VA Medical Center Cleveland, USA

Developing recommendations for public health decisions follows a common pathway of weighing desirable consequences (such as preventing disease) against undesirable consequences (such as harms, inconvenience and cost) based on the best available evidence and taking into account peoples' values and preferences. Empirical evidence has shown that guideline recommendations may suffer from a series of problems, such as statements that are not actionable or statements of facts rather than recommendations and more often than not strength of recommendations are absent or inaccurate.

However, well done evidence-based guidelines will have a number of advantages that facilitates not only standardizing and strengthening the underlying methodology, but also improves transparency of the process. The original evidence hierarchy – introduced by the Canadian Task Force on the periodic Health examination in 1979 – has led to the creation of numerous similar systems created in the last 40 years. However, one of the main drawbacks of those systems resulted from the use of a variety of lettering and numbering schemes causing confusion. In addition, because the application of most of those evidence hierarchies required implicit steps to be taken, empirical evidence has shown arbitrary down- and upgrading of evidence categories to be common.

When selecting methodological rigorous evidence grading system for developing public health recommendations, a number of essential issues need to be considered:

1. Creating structured questions and defining the suitability and importance of outcomes
2. Understanding the importance of an outcomes-centric system of rating the body of evidence rather than solely assessing study level data
3. Extending the concept of risk of bias to include additional categories that influences the quality of evidence, such as inconsistency of effect, indirectness of evidence, imprecision and publication bias, as well as magnitude of effect and dose-response gradient.
4. Guidance on how the rating of the overall quality of evidence across outcomes in regards to a management decision needs to reconcile possible differences in quality for benefits as well as harms
5. Avoiding the pitfall of confusing quality of evidence with strength of recommendation by clearly separating those issues and recognizing that other factors beyond the quality of evidence influences our confidence that adherence to a recommendation causes more benefits than harm
6. Recognizing that balancing the benefits and downsides of a recommendation requires understanding the baseline risk, the relative and absolute effects of the intervention and the importance of creating standardized evidence summaries that make those judgments transparent
7. Understanding the importance of recognizing the variability (or uncertainty) of people's values and preferences and how this may influence the implications of strong and conditional recommendations

4.3 Current methodological procedures of the German Standing Committee on Vaccination (STIKO) to develop vaccination recommendations

Thomas Mertens, Institute of Virology, Ulm University Hospital, Ulm, Germany

Today the STIKO assembles 16 unsalaried specialists in vaccinology, immunology, bacteriology, virology, epidemiology, evidence based medicine, tropical medicine, public health, paediatric diseases, general medicine as well as two representatives from public health assurance and regional hygiene and preventive medicine. Nine permanent guests represent federal administrations and institutions. The work of the STIKO is supported by the general management office located at the Robert Koch Institute, Berlin.

The STIKO has to provide advice on vaccinations, vaccination policy and other measures for specific prophylaxis against transmissible diseases in humans, provided that these been approved in Germany. The STIKO may deal with vaccines that are in the process of being approved, if all available unpublished data are accessible to the commission. The STIKO generally meets twice yearly, however, sometimes, more meetings are necessary.

Every vaccination recommendation is preceded by answering 13 standardized questions: 1. aim of a vaccination, 2. morbidity of the preventable disease, 3. population based effects of the vaccination, 4. availability of suitable vaccines, 5. further achievable positive strategic effects of a vaccination campaign, 6. expected individual adverse effects and availability of complete or sufficient safety data, 7. relevant adverse population based effects that may be expected after implementation of the general vaccination. 8. vaccination coverage necessary for a positive epidemiological effect, 9. overall epidemiological judgement on the relation between advantages and disadvantages of the vaccine, 10. cost-effectiveness relation in comparison to other specific measures, 11. practicability of a recommendation 12. requirements of data monitoring after implementation of the vaccination campaign 13. public interest in the vaccination campaign.

The STIKO installs subcommittees to elaborate specific questions and may invite additional specialists.

During the past years and decades the general attitude towards vaccination recommendations is changing significantly from expert opinion to recommendations based on the best available evidence. The discussion about the applicable methodology for the work of the STIKO is ongoing. Evidence based recommendations obviously require much more data, man power and financial resources. It is undisputable that in many instances data are and will be missing, but nevertheless recommendations may be expected and/or needed. This dilemma cannot be resolved, but urges the necessity to clearly define and publish on exactly what data a recommendation is based on. This is specifically important in Germany where we encounter a public opinion which is traditionally critic towards vaccinations and highly sceptic concerning pharmaceutical companies. Furthermore, there are no legal requirements for vaccinations in Germany and high vaccination coverage can only be achieved by convincing physicians and the public.

4.4 Evidence-based criteria for inclusion of vaccinations in public programmes in the Netherlands

Hans Houweling MD PhD[1], Marcel Verweij PhD[1 2,] Prof. E. Joost Ruitenberg PhD[1,3] on behalf of the National Immunisation Programme Review Committee of the Health Council of the Netherlands

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As more and more new vaccines are developed and brought to the market, governments have to make decisions about which vaccinations to include in public programmes. This paper describes the experience in the Netherlands in developing a framework for assessing whether a vaccination should be included in the National Immunization Programme (NIP). Bearing in mind the public nature, the factors that determine a vaccine's suitability for inclusion in a communal vaccination programme 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. The seven criteria and the explanation of them provide a framework for the systematic examination of arguments for and against the inclusion and prioritisation of particular vaccinations. As an illustration, the vaccinations currently provided in the Netherlands through public programmes as well as twenty-three 'candidate' vaccinations are assessed against the seven criteria. The proposed assessment framework including the selection criteria can take full account of the values and specificities as they may differ between situations and countries; the transparency of the approach may help to clarify which elements of the assessment are pivotal in specific situations. Using the criteria furthers a trustworthy, transparent and accountable process of decision making about inclusion of new vaccinations in public vaccination programmes and may help to retain public confidence.

Keywords: public vaccination programmes; assessment framework; selection criteria; National Immunisation Programme; NIP

4.5 Canada's National Advisory Committee on Immunization (NACI): Current methods and experiences in developing evidence-based recommendations

Joanne M Langley MD, MSc, FRCPC (Chair, NACI, 2007-2011), Professor of Pediatrics and Community Health and Epidemiology Dalhousie University and the Canadian Center for Vaccinology, Canada

Summary: The agency in Canada that addresses one of the World Health Organization's (WHO's) priorities for "national immunization technical advisory committees… as part of the process of ensuring evidence-based decision-making at the country level." is the NACI. NACI is an independent committee composed of volunteers representing a range of expertise relevant to vaccine science. It is charged with providing medical and scientific advice on immunization for Canadians, focusing on scientific evidence to evaluate vaccine safety and efficacy. As a federal state, responsibility for health in Canada is shared by the national and provincial-territorial governments. NACI's recommendations are given to the Chief Public Health Officer of the Public Health Agency of Canada (PHAC). PHAC is the main federal agency responsible for public health and reports to Parliament through the Minister of Health, as well as collaborating closely with all levels of government, and non-governmental organizations.

The planning and delivery of immunization programs in Canada falls under the jurisdiction of each province/territory. A federal/provincial/territorial committee considers programmatic issues (e.g. economics) in the light of NACI statements, and produces recommendations for the Pan-Canadian Public Health Network. The overarching framework for the administration of these committees is the National Immunization Strategy (available at: http://www.phac-aspc.gc.ca/publicat/nis-sni-03/index-eng.php). Ultimately each province has jurisdiction over whether to fund programs for vaccines.

The methods for NACI statement development are described in two public documents: < http://www.phac-aspc.gc.ca/publicat/ccdr-rmtc/09vol35/acs-1/index-eng.php> and <Vaccine. 2010 Apr 19;28 Suppl 1:A58-63>. Once it is determined that recommendations are needed or need to be revised, a work plan is developed by a Working Group of NACI. A literature search plan is developed, the scope of which is approved by NACI. The broad stages in the preparation of a NACI recommendation statement are: 1) knowledge synthesis (retrieve and summarize individual studies, rank the level and quality of the individual studies, prepare tables which present this information), 2) synthesis of the body of evidence of benefits and harms, considering the information resulting from the knowledge synthesis and the overall direction of the evidence and magnitude of effects and harms, in light of the various factors considered important in an analytic framework for immunization programs in Canada (Erickson and de Wals analytical framework, and 3) translate this evidence (which consists of data on safety, efficacy, immunogenicity, burden of illness etc) and relevant information from the analytic framework into a recommendation that would be considered by the individual care provider and patient or the health policy planner providing a vaccine program to a population. Recommendations are presented with a descriptor (e.g. Fair evidence to recommend against immunization) along with an explanatory note.

4.6 Strategies of the US Advisory Committee on Immunization Practices (ACIP) in developing evidence-based recommendations

Jonathan L. Temte, MD/PhD, Chair – ACIP Evidence-Based Recommendation Work Group, Professor Dept. of Family Medicine University of Wisconsin, School of Medicine and Public, Wisconsin, USA

On October 28, 2010, the U.S. Advisory Committee on Immunization Practices (ACIP) voted to adopt a framework to assist in the incorporation of clinical and public health evidence into vaccine recommendations. The Evidence Based Recommendations Work Group (EBRWG) initially was formed in 2004 and charged with developing a uniform approach to making explicit the evidence base for ACIP recommendations. After initial efforts, this work group became inactive until November, 2007 at which time it was reactivated due to increasing interest by stakeholders to have evidence-based vaccine recommendations. This work group, which has been meeting monthly by teleconference, comprises a diverse array of experts and liaison representatives from stakeholder organizations.

The EBRWG studied past ACIP deliberations and recommendations and found that certain key elements were present in most ACIP recommendations including vaccine safety, vaccine efficacy/effectiveness, and the burden of disease. Economic analyses, such as cost-effectiveness studies, and other elements also had been considered in development of recommendations. The guiding principles for developing an explicit evidence-based framework for use by the ACIP include focus on transparency; use of evidence of varying strengths; consideration of both individual and community health; adoption of an existing system and a commitment to continually strive to improve the process.

In the process, the EBRWG identified and reviewed several existing evidence-based evaluation systems including the Grading of Recommendations Assessment, Development and Evaluation (GRADE), and approaches and systems used by the U.S. Preventive Services Task Force, Guide to Community Preventive Services, American Academy of Pediatrics, and the Canadian National Advisory Committee on Immunization. The EBRWG recommended adoption of the GRADE framework by the ACIP for grading evidence and for moving from evidence to recommendations. The features of GRADE include a clear separation between evidence grade and strength of recommendations; explicit, comprehensive criteria for downgrading and upgrading evidence ratings; a transparent process of moving from evidence to recommendations; explicit acknowledgment of values; and balance between simplicity and methodological rigor. This system was familiar and endorsed by important vaccine stakeholders in the U.S. including the American Academy of Family Physicians (AAFP), the American College of Physicians (ACP), and the Infectious Diseases Society of America (IDSA).

Over the course of three ACIP meeting in 2010, voting members and meeting attendees were provided with succinct reviews of methodological standards for clinical practice guidelines, and approaches used in grading the quality of evidence and synthesizing and presenting recommendations. We invited the organizational perspectives and endorsements of AAFP, ACP and the American Academy of Pediatrics. A detailed review of GRADE was provided along with a presentation on the approach and experience with evidence-based recommendations by the Strategic Advisory Group of Experts of the World Health Organization. In addition, two recently approved ACIP recommendations were subjected to the proposed methods and presented in detail.

The EBRWG proposed that ACIP adopt a modified GRADE methodology. Two types of recommendations were proposed: Category I recommendations will be for routine (universal) use or for all members of a targeted population; Category II recommendations will be for individual clinical decision making. Significant concerns regarding public perception of the levels of evidence (i.e., grades) were expressed by ACIP members and resulted in three options for the presentation of the evidence level. The ACIP unanimously approved of an approach using an “evidence narrative” statement based directly on the evidence synthesis within GRADE.

Based on this vote, future ACIP recommendations will indicate the category followed by an evidence narrative. A remark section will provide explicit synthesis of benefits, harms, evidence assessment, cost-effectiveness, and values for making the recommendation. CDC and ACIP will begin to implement this process in the coming months.

4.7 WHO's Strategic Advisory Group of Experts (SAGE) on immunization: approach to international evidence-based recommendations

Philippe Duclos, DVM, PhD, Senior Health Adviser and Executive Secretary to the Strategic Advisory Group of Experts (SAGE) on immunization, Immunization, Vaccines and Biologicals,World Health Organization, Geneva, Switzerland

Since 2005, WHO has aimed to strengthen its normative and policy-setting functions for immunization. Necessary adjustments were made to its immunization related advisory committees as a result of external reviews. These changes were particularly focused on evidence-based decision-making and transparency to enhance credibility and impact of global policy recommendations.

The main group involved with the development of global policy recommendations and strategic advice related to immunization is the Strategic Advisory Group of Experts (SAGE), which mandate extends to all vaccine-preventable diseases throughout all ages.

A number of technical advisory committees complement and support the work of SAGE. Such main groups are the Global Advisory Committee on Vaccine Safety; the Expert Committee on Biological Standardization, the Immunization Practice Advisory Committee, and the Quantitative Immunization and Vaccine Research Advisory Committee.

SAGE working groups are established on a time-limited basis to review and provide evidence based information and options for recommendations together with implications of the various options that will then be discussed openly by SAGE.

In making its recommendations, SAGE takes into consideration issues such as disease epidemiology (disease burden including age specific mortality, morbidity, and societal impact; projections for future disease burden; specific risk groups; epidemic potential; disease occurrence over time; serogroup or serotype distribution for serogroup or serotype specific vaccines; and changes in epidemiology over time), clinical characteristics (clinical management of disease, disease severity, primary/secondary/tertiary care implications, long term complications of disease and medical requirements), vaccine and immunization characteristics (efficacy, effectiveness and population impact of vaccine; indirect effects; vaccine safety; cold chain and logistics concerns; vaccine availability; vaccine schedules; schedules acceptability and ability to deliver), economic considerations (disease, vaccine and vaccine delivery costs, perspective for vaccine price reduction, vaccine cost and cost-effectiveness of immunization programmes and affordability of immunization), health system opportunities and existence of and interaction with other existing intervention and control strategies.

Since 1998, WHO produces evidence-based vaccine position papers. These papers include: 1. a section providing information on the respective disease (disease epidemiology, the pathogen, the disease), 2. a section providing information on the available vaccines (composition, safety, immune response, efficacy and effectiveness, cost effectiveness and any other relevant issue), and 3. the WHO position on the optimal vaccine use. The papers are produced for use mainly by national public health officials and immunization programme managers. However, they may also be of interest to international funding agencies, the vaccine manufacturing industry, the medical community and the scientific media. 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.

A SAGE discussion group on grading and review of evidence expressed concern that GRADE was not ideally suited to manage issues specific to immunization, such as assessing positive and negative indirect effects (for example, herd immunity, selection pressure); the duration of protection, taking into account natural boosting; and post marketing experience. SAGE encouraged the discussion group to develop a communication strategy to mitigate any potentially deleterious effects of a narrowly applied GRADE approach and encouraged the group to suggest appropriate adjustments to the process. As a result, work is ongoing to refine the use of the GRADE in collaboration with other immunization advisory committees. Proposed refinements and related guidance will be presented

4.8 Evidence-based guidance for immunisation. An European perspective of the European Centre for Disease Control (ECDC)

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According to the founding regulation (EC) No 851/2004 of the European Parliament and of the Council, the European Centre for Disease Prevention and Control (ECDC) shall provide independent scientific opinions and scientific and technical assistance. ECDC delivers broadly two types of scientific advice: rapid and non-rapid. Vaccination guidance falls into the latter category. The process of the delivery of non-rapid scientific advice starts with priority setting for topics for potential inclusion in the work plan of the following year. If the work requires utilizing external expertise, the selection of experts is done using various mechanisms with help of the ECDC candidate expert database ECED. The tasks of the scientific panels of the ECDC are to assist the Centre in the production of scientific advice. Scientific panels are set up on an ad hoc basis by the Centre in response to a need for external or internal scientific advice and their remit and the duration of their work are stated in advance of their establishment. The actual work of expert panels is based on an updatable standard procedure defining, among others, the ways to deal with potential conflicts of interest. An important topic for the development of scientific advice is the work on the evidence – based methodology of scientific advice production. Involvement of stakeholders includes consultation of ECDC Advisory Forum which includes public health experts from all Member States, the Commission, the WHO, learned societies, and patient organisations. However, they only advice the Director: no consensus is needed, and the Director does not have to take any views into consideration. A policy on interactions with pharmaceutical industry, including regular update meetings at ECDC premises on a pre-defined topic set up in collaboration with industry umbrella organizations is currently being developed developing. This has no impact on the work of the scientific panels. Delivered scientific advice is usually published online on ECDC Web portal http://www.ecdc.europa.eu/en/publications/guidance/Pages/index.aspx and will be kept in a dedicated database. ECDC has started piloting work on the ways to measure the uptake of scientific advice it delivered. My presentation will include examples of guidance in the area of vaccination ranging from DTP vaccines through public health management of contacts of meningococcal disease cases, to plans to develop annual influenza vaccination guidance.

4.9 GRADE for the development of evidence-based recommendations for immunization

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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. The international Grading Recommendations Assessment, Development and Evaluation (GRADE) group has developed an approach that is useful standardizing the way guideline developers and others making recommendations in healthcare grade the quality of evidence and the strength of recommendations across healthcare interventions.

This presentation will describe how GRADE can be applied to making recommendations about immunization. Using examples 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.

5. Key Questions for working groups

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

Working Group 1: Which evidence do we need for the development of evidence-based vaccination recommendations?

1) Which key indicators/outcomes are essential when developing recommendations for vaccinations?
2) Do we need the same level of evidence and assessment of quality of evidence for each key indicator or outcome?
3) What approach should be taken if there is little or no data for some key indicators/ outcomes?

Facilitators: Frode Forland (ECDC), Yngve Falck-Ytter (GRADE)

Working Group 2: Which methodologies are suitable for the development of evidence-based vaccination recommendations?

1) What are specific requirements for a methodology that can be used to develop evidence-based vaccination recommendations?
2) What are particularities / difficulties when assessing the evidence relevant to the development of vaccination recommendations?
3) What are the advantages/disadvantages of existing systems when applying to vaccination decisions?
    - What are the Pros and Cons of different approaches of summarizing evidence (high, moderate, low, very low, strong, moderate, limited, description of study types
4) What are the advantages/ disadvantages of applying a single methodology for rating evidence for all outcomes as opposed to having different methodologies for different types of outcomes?

Facilitators: Faruque Ahmed (CDC), Philippe Duclos (WHO)

Working Group 3: Overall need and processes for international collaboration in developing evidence-based vaccination recommendations

1) How global should the process of developing vaccination recommendations be?
2) To what extents are international guidelines currently taken into account when working on national recommendations?
3) Do we need an international process of harmonisation on procedures for the development of evidence-based recommendations?
4) Which one of the different stages during development of national immunisation recommendations could be processed in an international context?
5) For which of important key indicators to be assessed could international cooperation play a particular role?
6) How could international cooperation be improved to better support national immunization technical advisory groups in their decision processes?
    - Which elements/ approaches in the international vaccination guidelines are the most valuable from the national perspective?

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

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