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Developing evidence-based immunization recommendations and GRADE☆

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ABSTRACT

The Strategic Group of Advisory Experts (SAGE) on immunization is an independent advisory committee with a mandate to advise the World Health Organization (WHO) on the development of vaccine and immunization related policies. SAGE working groups are established on a time-limited basis to review and provide evidence-based recommendations, together with their implications, for open deliberation and decision-making by SAGE. In making its recommendations, SAGE takes into consideration: the epidemiologic and clinical characteristics of the disease; vaccine and immunization characteristics; economic analysis; health system considerations; the existence of and interaction with other intervention and control strategies; costing and social impacts; and legal and ethical concerns. Since 1998, WHO has produced evidence-based vaccine position papers for use primarily by national public health officials and immunization programme managers. Since April 2006 all new or updated position papers have been based on SAGE recommendations. The Grading of Recommendations Assessment, Development and Evaluation (GRADE) approach has been adopted by WHO and, since 2008, GRADE tables that rate the quality of evidence have been produced in support of key recommendations. SAGE previously expressed concern that GRADE was not ideally suited to many immunization-specific issues such as the vaccine population level effect and the inclusion of surveillance system data, particularly for vaccine safety. Extensive productive interactions with various advisory groups including the US Advisory Committee on Immunization Practices, the European Centres for Disease Control, the German Standing Committee on Vaccination (STIKO), WHO's Global Advisory Committee on Vaccine Safety and the GRADE working group resulted in key enhancements to accommodate vaccine-relevant evidence. This facilitated integration and acceptability of the GRADE approach in the development of immunization related SAGE and WHO recommendations. Ongoing utilisation should result in further fine-tuning of the approach to ensure that recommendations are based on the full range of appropriate evidence.

Abbreviations: GRADE, Grading of Recommendations Assessment Development and Evaluation; PICO, population/intervention/comparator/outcome; RCTs, randomized controlled trials; SAGE, Strategic Advisory Group of Experts on immunization; WHO, World Health Organization; WG, working group.

☆ One of the authors is a World Health Organization staff member. The opinions expressed in this article are those of the authors and do not necessarily represent the decisions, official policy or opinions of the World Health Organization.

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1. Introduction

Millions of lives have been saved and disabilities averted due to the widespread availability and use of vaccines. However, availability of vaccines does not ensure their appropriate use. The World Health Organization (WHO) is tasked to provide leadership in global health; shape research agendas; provide guidance and standards for public-health practice; and support country programmes [1]. Since 1998, the WHO has published vaccine position papers [2] with recommendations for vaccine use. The Strategic Group of Advisory Experts (SAGE) on immunization is an independent advisory committee with a mandate to advise the WHO on the development of policy related to vaccines and immunization [3,4]. These recommendations are captured in SAGE meeting reports published in the Weekly Epidemiological Record. All reports, meeting presentations and background documents are publicly available online [5].

Since 2006, SAGE has provided systematic oversight of WHO vaccine position papers. SAGE working groups (WGs) review all relevant available evidence relating to the specific vaccine position paper and develop recommendations for SAGE consideration. After deliberation, SAGE makes recommendations to the WHO on the use of vaccines, which are then incorporated into the position papers.

The evidence review is extensive with a focus on assessing impact in different epidemiological settings, risk benefit considerations, health system considerations, other consequences, generalizability, and utilizing the best available evidence while taking account of social values and preferences. While the evidence reviewed is the result of scientific endeavours, evaluating the quality of the evidence and making recommendations are activities that require expert interpretation and judgement in addition to rigorous scientific review. The process of public-health decision-making is often stepwise, multifaceted and complex. Decision-making under uncertainty is an unavoidable part of public health practice. To inform policy-makers and the public honestly, it is necessary to deal with uncertainty explicitly and transparently.

The Grading of Recommendations Assessment, Development and Evaluation (GRADE) approach has been incorporated into SAGE and the development of WHO recommendations on immunization. GRADE [6,7], which is one of several frameworks developed over the years to assess the quality of evidence, has been adopted by WHO and over 50 other organizations. The use of the GRADE methodology to rate the quality of evidence supporting key recommendations included in WHO vaccine position papers was introduced in 2008 [8]. A hallmark of GRADE is its aim to improve transparency in decision-making. Although GRADE remains subject to individual interpretation, interested parties are able to follow the logic and processes that led to a given conclusion, recommendation and/or guideline. The process also promotes useful dialogue and opportunities to reassess the evidence as required.

The evidence for all critical recommendations for interventions is rated using the GRADE framework to assess the quality of related evidence. Based on this rating, and additional important factors (e.g. balance between benefits and risks, social values and preferences, and cost and resources), recommendations are made. A strong recommendation can still occur with low or very low quality evidence—it is the net result of all relevant factors that is important.

We briefly describe the SAGE process for reviewing evidence in the development of recommendations and the integration of GRADE in this process. More detailed information about this process can be accessed at: http://www.who.int/immunization/sage/Guidelines_development_recommendations.pdf.

2. SAGE process for reviewing evidence

The initial review of evidence occurs in SAGE WGs [9] although in some instances, it builds on specific reviews of the data performed by other technical advisory group (e.g. The Global Advisory Committee on Vaccine Safety for vaccine risk assessment and the Quantitative Immunization and Vaccine Research Advisory Committee for disease burden and cost-effectiveness data) [4].

The key steps involved in preparing evidence-based SAGE recommendations are:

a. Defining the questions to inform recommendations.
b. Identifying the critical questions and outcomes for which an in-depth review of evidence is needed.
c. Conducting a review of the literature with or without meta-analysis and, where necessary, commissioning research to address gaps in evidence.
d. Reviewing the quality of the evidence, in particular through assessment of the risk of bias and confounding.
e. Rating the quality of the evidence (using the GRADE approach for data on safety and effectiveness).
f. Developing proposed recommendations.
g. Presenting proposed recommendations, along with their supporting evidence to the entire SAGE membership at SAGE meetings.
h. SAGE discussion, deliberation and decision regarding the proposed recommendations to WHO.

The guiding principles of this process are that careful review and consideration of the evidence precede the development of recommendations. The entire process should be transparent, robust and reproducible.

2.1. Defining the questions to inform the recommendations and for which a rating of the quality of evidence should be applied

A well-accepted methodology for framing questions mandates carefully specifying the target population, the intervention of interest, the comparator group and the clinical outcomes of interest. The PICO (population/intervention/comparative intervention/outcome) approach leading to focused SAGE recommendations can be illustrated with the example of rotavirus vaccines—Population: healthy infants 2–6 months, or HIV-infected or immunocompromized children; Intervention: two different vaccines, two or three doses; Comparator: absence of vaccination, standard prevention procedures (hygiene), oral rehydration; Outcome: morbidity, hospitalization, consultations, parental work loss, mortality, nosocomial infections, minor or serious adverse events including fever, diarrhoea, and intussusception [10]. Outcomes of interest selected should be important to the target population and the broader community. If surrogate outcomes are used they will frequently require downgrading of the evidence quality rating due to indirectness. An initial rating of the importance of outcomes should precede the review of evidence with all potential patient-important outcomes identified and a preliminary outcome classification made using the following categories: those that are critical; those that are important but not critical; and those that are of limited importance. Evidence regarding the first two outcome types will or may have bearing on the recommendations, while evidence regarding the third outcome type will not. For pragmatic reasons, the rating proposed in step e above is generally only applied to critical outcomes including safety outcomes.

The framing of questions relating to vaccine safety focuses on potential serious and specific adverse events (e.g. the occurrence of intussusception after vaccination with a rotavirus vaccine) [11]. However, as variation in vaccine reactogenicity, with minor