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

Philippe Duclos, WHO

Immunization Policy Advisory Framework

- Safety
- Standards
- Practice
- Burden assessment/ modelling

Other WHO Technical Advisory Committees ⟷ **Strategic Advisory Group of Experts (SAGE)**

- Global policy recommendations & strategies
- Support regional/national challenges

Regional Technical Advisory Group

- Regional policies & strategies
- Identify & set regional priorities
- Monitor regional progress

- National Policies & Strategies
- Prioritize problems & define optimal solutions
- Implement national programme & monitor impact

Countries ⟷ **National Technical Advisory Group on Immunization**

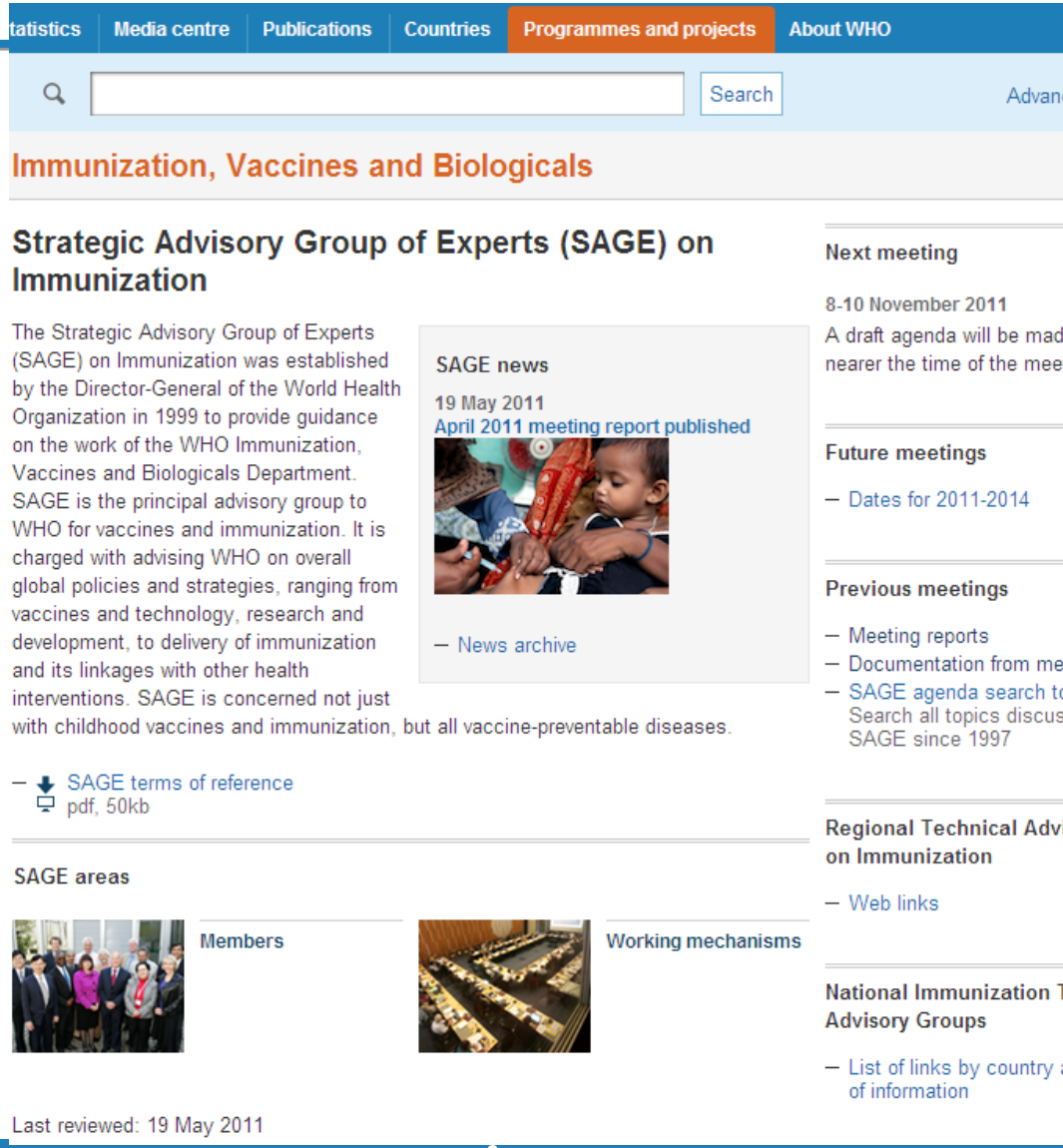
Strategic Advisory Group of Experts (SAGE) on Immunization

- **Principal advisory group to WHO for vaccines and immunization → reports directly to DG and involves all relevant WHO departments**

- **Membership -15 members**
  - Individual capacity and broad range of expertise
  - Balance of professional affiliation, geographic representation
  - Declarations of interest
  - Appointed by WHO DG upon recommendation of external selection panel - Public call for nominations

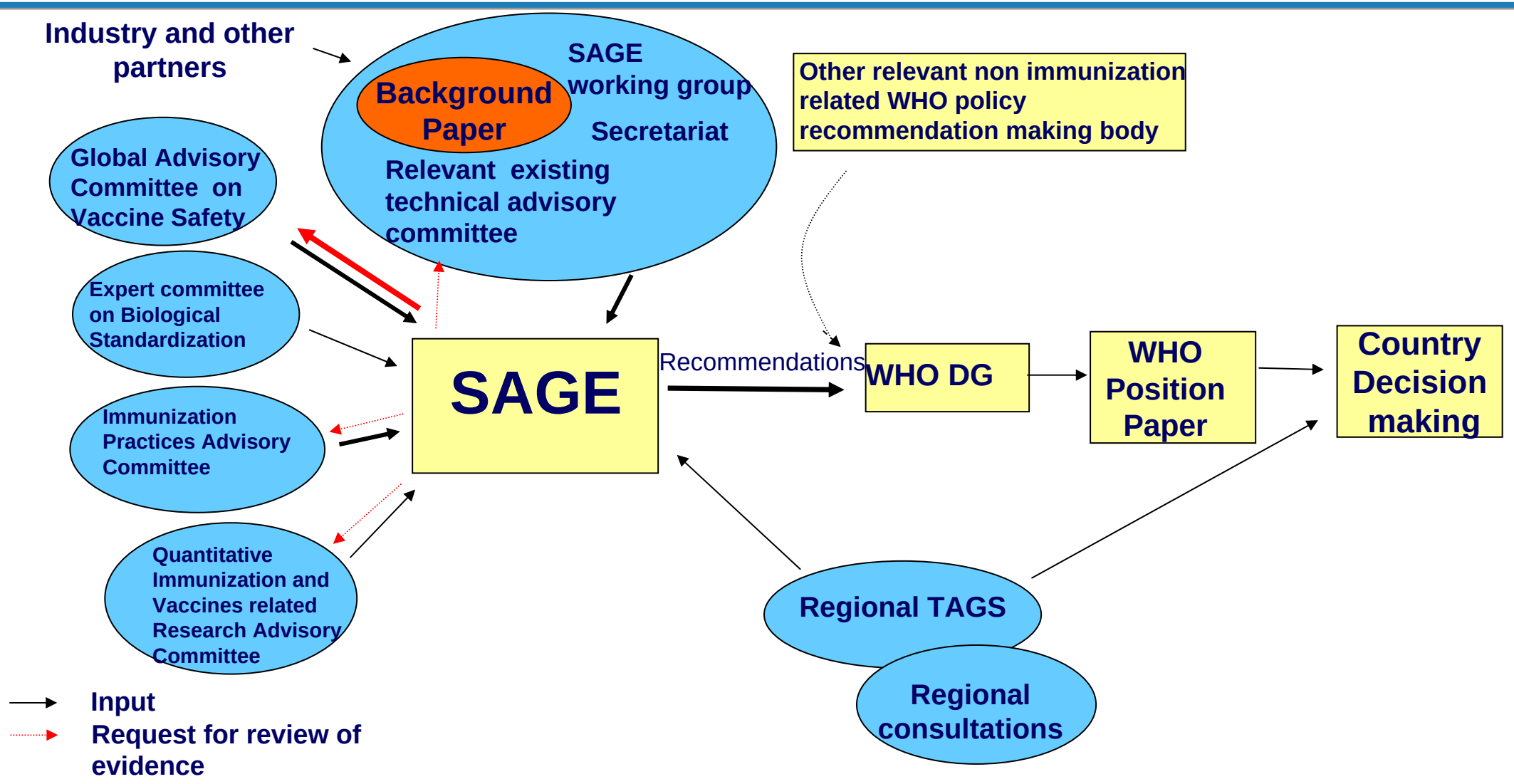
- **Meetings and operational procedures**
  - Two meetings a year (April and Nov)
  - Only plenary sessions – transparent process
  - Extensive representation from key partner organizations
  - Experts invited as needed
  - Evidence-based
  - Working groups

- **Report and communications**



World Health Organization

Pathways for WHO Recommendations on Vaccine Use



World Health Organization

Issues taken into consideration by SAGE in developing recommendations

- Epidemiologic features of the disease
- Clinical characteristics
- Vaccine and immunization characteristics
- Economic considerations

Issues taken into consideration by SAGE in developing recommendations

- Health system opportunities and existence of, and interaction with, other existing intervention and control strategies
- Social impacts
- Legal considerations
- Ethical considerations

SAGE working groups

- Establishment and ToRs decided by WHO and SAGE members
- Composition
  - Public call for nominations
  - At least two SAGE members & additional experts
  - Declaration of interests
- To review evidence and address specific issues in great depth and prepare for fruitful discussions at SAGE when issue is complex
- Not allowed to make decisions or speak on behalf of SAGE
- Time limited

SAGE Working Group on influenza vaccines and immunization (established August 2010)

TERMS OF REFERENCE

Objectives of the Working Group:

1. Prepare for a SAGE evidence-based review and updating of WHO recommendations on the use of seasonal influenza vaccine (e.g. priority target groups) with a particular focus on low and middle-income countries and with a view to update the 2005 WHO influenza vaccine position papers.
2. Prepare for a SAGE discussion on coverage goals for seasonal influenza vaccination to be proposed to the WHA to update the coverage goals contained in the 2003 resolution.
3. Identify essential gaps in evidence that may impede SAGE's ability to update the recommendations on the use of influenza vaccines and propose coverage targets.
4. Provide advice about pandemic vaccine preparedness.

COMPOSITION

SAGE Members

- Elizabeth Miller, Chair
- Jon Abramson
- Claire-Anne Siegrist

Experts

- William Kwabena Ampofo, Noguchi Memorial Institute for Medical Research, Ghana
- Joseph Bresee, Centers of Disease Control, United States of America
- Janet Englund, Seattle Children's Hospital, United States of America
- Randeep Guleria, All India Institute of Medical Sciences, India
- Yu Hongjie, Chinese Center for Disease Control and Prevention, People's Republic of China
- Michael Pfleiderer, Paul-Ehrlich-Institut, Germany
- David Salisbury, Department of Health, United Kingdom
- Barry Schoub, National Institute for Communicable Diseases, South Africa

WHO Secretariat

- Marie-Paule Kieny
- Philippe Duclos
- Cuauhtémoc Ruiz-Matus
- Nahoko Shindo

DECLARATION OF INTERESTS FOR WHO EXPERTS

All Working Group members completed a declaration of interests.

Four members reported relevant interests. All interests were assessed not to constitute a conflict of interest. It was concluded that all members could take part in full in all of the discussions. The reported relevant interests are summarized below:

Janet Englund:

- Her department received funding from MedImmune, Novartis, Adamas, ADMA Bio, BioCRYST and Sanofi Pasteur for conducting research in respiratory virology, meningococcal vaccines, influenza therapies, diphtheria-tetanus-pertussis trivalent vaccines and human respiratory syncytial virus immunotherapy. However none of the studies focused on influenza vaccines and immunization which was the subject of the meeting. These interests were assessed as non-personal, non-specific and financially significant*

WHO Vaccine Position Papers

- **Position papers = Key reference documents**
  - **Available in all official languages**
  - **Convergence of other WHO documents (International Travel and Health, Essential Drugs List, …)**
- **Developmental and review process (SAGE, extensive peer review, evidence-base, periodic updating)**
- **Format**
  - **Weekly Epidemiological Record**
  - **Current structure (Intro, background** (Disease epidemiology, the pathogen, disease), **info on vaccines** (composition, safety, immune response, efficacy and effectiveness, cost effectiveness and any other relevant issue), **WHO position on vaccine use)**
- **Additional posting of information on the web: GRADing tables, references, summaries (one pager and PowerPoint presentation)**

Immunization, Vaccines and Biologicals

WHO > Programmes and projects > Immunization, Vaccines and Biologicals >

printable version

Vaccine Position Papers

BCG

- Position paper (January 2004) Original English and French versions [pdf 468
- Arabic translation [pdf 174kb]
- Chinese translation [pdf 267kb]
- Russian translation [pdf 289kb]
- Spanish translation [pdf 142kb]
- References [pdf 83kb]

- Revised BCG vaccination guidelines for infants at risk for HIV infection (May
- Chinese translation [pdf 190kb]
- Russian translation [pdf 267kb]
- Spanish translation [pdf 43kb]

CHOLERA

- Position paper (April 2001) Original English and French versions [pdf 159kb]
- Arabic translation [pdf 196kb]
- Chinese translation [pdf 155kb]
- Russian translation [pdf 171kb]
- Spanish translation [pdf 44kb]
- References [pdf 109kb]

DIPHTHERIA

- Position paper (January 2006) Original English and French versions [pdf 214
- Arabic translation [pdf 138kb]
- Chinese translation [pdf 210kb]
- Russian translation [pdf 184kb]
- Spanish translation [pdf 50kb]
- References [pdf 56kb]

Historical perspective

- Since 2008, GRADE tables produced in support of key recommendations in WHO vaccine position papers
- Concern expressed by SAGE working groups
- Very few national advisory groups on immunization using a formal grading process (Canada uses own approach, US considering use of modified GRADE and have seen then adopted its use)
- Limitations for public health interventions and need for adjustments recognized in various fields e.g. CHERG
- SAGE established a discussion group

SAGE - April 2010 meeting: Grading and review of evidence

- SAGE encouraged the discussion group:
  - to develop a communication strategy to mitigate any potentially deleterious effects of a narrowly applied GRADE approach
  - to suggest appropriate adjustments to the process – for example, by applying criteria to increase or decrease the quality-of-evidence score
- SAGE supported development of a paper describing SAGE's approach to reviewing evidence when issuing recommendations
- Partnership between SAGE and other immunization advisory committees was encouraged

SAGE - April 2011
Grading and review of evidence

- Update SAGE on activities since April 2010
- Present a draft paper of the development of evidence-based recommendations on vaccine use - Since April 2010 extensive interaction with other immunization related advisory committees and the Grading of Recommendations Assessment, Development and Evaluation (GRADE) working group which resulted in a number of adjustments to GRADE to accommodate vaccine population effects, and allow inclusion of surveillance system and vaccine safety data.
- Request SAGE feedback on proposed adjustments to scoring of quality of evidence and use of GRADE tables
- Determine if current work sufficiently addresses SAGE's initial concerns
  - vaccine population effects?
  - inclusion of surveillance system data?
  - vaccine safety?
- Has adequate guidance been provided in the background document (web)
- Discuss next steps

GUIDANCE FOR THE DEVELOPMENT OF EVIDENCE-BASED VACCINE-RELATED RECOMMENDATIONS

This guidance applies to the development of recommendations by the Strategic Advisory Group of Experts (SAGE) on Immunization and the development of WHO vaccine position papers. Its aim is to facilitate the work of SAGE, its working groups and the WHO Secretariat. It is also intended to describe the process for the information of the wider readership. The document will be updated as necessary from time-to-time and, in particular, as the GRADE approach evolves.

Comments and suggestions for improvement are welcome, and should be sent to sageexecsec@who.int.

Version 1
2 August 2011

Guidance for the development of evidence-based vaccine related recommendations: Contents

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Appendices

- 1 **Draft data extraction tool**
- 2 **Checklists for reviewing study quality**
  - 2a Checklist for RCTs
  - 2b Checklist for case-control studies
  - 2c Checklist for cohort studies
  - 2d Checklist for systematic reviews
  - 2e Checklist for controlled before-after studies
  - 2f Checklist for interrupted time series studies
- 3 **Draft summary table for evidence review**
- 4 **Rating the quality of the evidence**
- 5a **Template of a GRADE table used to score the quality of evidence**
- 5b **Example of a completed GRADE table**

References

Additional useful references

GRADE scoring: solutions for vaccines

- Enter observational studies at different levels allowing for a better score of good quality studies e.g. self-controlled case series at 3 and routine surveillance at 1

OR

- Allow for increasing score based on consistency of studies (several studies from different settings, different investigators and different designs) and population level effects
  - Need to define parameters for such upgrading and level of upgrading

Inclusion of disease and post-marketing surveillance data

- Randomised trials → Entry at Level 4
- Observational studies, disease surveillance and post market safety surveillance data → Entry at Level 2

Dose response (population effect)

+1 Evidence of decreased risk with increased vaccine coverage including evidence of reversal at population level (disease returns when vaccine coverage is decreased) population based dose response

+2 Very strong evidence of decreased risk with increased coverage

Antagonistic (mitigated) bias and confounding

+1 All major confounders would have reduced the effect

or (for negative safety studies) +1 Ability of design to control for confounding and avoid biases

+2 If in addition to design, consistency across different settings, different investigators, and possibly different designs

Communicating level of evidence

Level 4: We are very confident that the true effect lies close to that of the estimate of effect on health outcome

Level 3: We are moderately confident in the estimate of effect on health outcome.

Level 2: Our confidence in the estimate of the effect on the health outcome is limited.

Level 1: We have very little confidence in the estimate of the effect on the health outcome.

Quality of evidence	Quality starting factor is first assigned base on Study Design	Quality score is lowered[1] if	Quality score is raised[1] if
We are very confident that the true effect lies close to that of the estimate of effect on health outcome (4)	Randomised trials	**1)Limitation of design:[2]** *-1 Serious* *-2 Very serious* ***2)*Inconsistency:** *-1 Serious* *-2 Very serious* **3)Indirectness:[2]** *-1 Serious* *-2 Very serious* **4)Imprecision:** *-1 Serious* *-2 Very serious* **5)Publication Bias:** *-1 Likely* *-2 Very likely*	**1)Strength of association[1]:** *+1 RR or OR>=2 (or =<0.5)* *+2 RR or OR >=5 (or =<0.2)* **2)Dose response (population based):** *+1 Evidence of decreased risk with increased vaccine coverage including evidence of reversal at population level* *+2 Very strong evidence of decreased risk with increased coverage* ***3)Mitigated bias and confounding:*** *+1 All major confounders would have reduced the effect or increased the effect if no effect was observed.* *or +1 Ability of design to control for confounding and avoid biases* *+2 If in addition to design, consistency across different settings, different investigators, and possibly different designs*
We are moderately confident in the estimate of effect on health outcome. (3)			
Our confidence in the estimate of the effect on the health outcome is limited. (2)	Observational studies including disease surveillance and post market safety surveillance data[2]		
We have very little confidence in the estimate of the effect on the health outcome. (1)			

[1] GRADE refers to it as Large effect

[2] GRADE wording only refers to Observational studie

1=move up or down one grade (for example from high (4) to intermediate (3)),

2= move up or down two grades (for example from low(2) to high(4))2 Should be commensurate with study design.

Table II. Are the currently available TBE vaccines responsible for serious adverse vaccine reactions?

			Rating	Adjustment to score
Quality Assessment	No of Studies/Starting Score		5 RCTs[1]	4
	Factors decreasing confidence	Limitation in study design	None serious[2]	0
		Inconsistency	None serious	0
		Indirectness	None serious	0
		Imprecision	Serious[3]	-1
		Publication bias	None serious	0
	Factors increasing confidence	Strength of association	Not applicable	0
		Dose-response	Not applicable	0
		Antagonistic bias and confounding	Not applicable	0
	Final numerical score of quality of evidence			**3**
Summary of Findings	**Statement on quality of evidence**			We are moderately confident in the estimate of effect on the health outcome
	Conclusion			Current TBE vaccines are not causally associated with serious adverse vaccine reactions

VI. As compared to the polysaccharide counterparts, will conjugated MC vaccines more effectively reduce nasopharyngeal carriage of *N. meningitidis* and induce herd protection against meningococcal disease?				
			Rating	Adjustment to score
Quality Assessment	No of Studies/Starting Score		4 Observational Studies (1-4)[a]	2
	Factors decreasing confidence	Limitation in study design	None serious	0
		Inconsistency	None serious	0
		Indirectness	None serious[a]	0
		Imprecision[a]	None serious	0
		Publication bias	None serious	0
	Factors increasing confidence	Large effect	Large effect[1a]	1
		Dose-response	Not applicable	0
		Mitigated bias and confounding	Not applicable	0
	Final numerical score of quality of evidence Score			3
Summary of Findings	Statement on quality of evidence			We are moderately confident that the true effect lies close to that of the estimate of effect on health outcome
	Conclusion			Conjugated MC vaccines reduce nasopharyngeal carriage of *N. meningitidis* and induce herd protection against meningococcal disease more effectively than do the corresponding polysaccharide vaccines

SAGE Recommendations

- No formal scoring
- Weak recommendations are of little value to country immunization programs (different from conditional recommendations)
- Need consistent and clear wording

SAGE: April 2011 meeting

Evidence-based review process & grading of quality of scientific evidence: outcome

- SAGE indicated that the proposed approach addressed many of its initial concerns.
- SAGE indicated that the draft guidelines were a major and timely step forward, and encouraged wider dissemination.
- Suggested improvements focused on stressing the need for quality data, and more explicit guidance on the criteria for scaled upgrading of population-level evidence.
- SAGE emphasised that SAGE working groups should identify the specific questions for grading early for endorsement by SAGE.

SAGE: April 2011 meeting

Evidence-based review process & grading of quality of scientific evidence: outcome (contd.)

- SAGE also noted the need for training of working group members on the review of evidence process.
- SAGE endorsed the preparation of a shorter version of guidelines for peer-reviewed publication after incorporation of their guidance and using a few specific examples such as meningitis C conjugate vaccine.
- Ongoing engagement with current partners and the discussion group was encouraged particularly to identify challenges to the current GRADE scoring scheme. Exploring links with the Campbell collaboration and the Cochrane Effective practice and Organization of Care Group (EPOC) was also recommended.
- SAGE noted that for successful evidence review and grading WHO would need to ensure that adequate resources were available.

Implementation and next steps

- Continue interaction with GRADE WG with a view to refining and further adjusting as necessary
  - Need to actively identify examples where the current GRADE scoring scheme would not be appropriate
  - Participate in review applying GRADE to public health interventions (Cochrane Public Health Group & GRADE WG)
  - Bridge language differences
- Pragmatic approach to GRADing and review of evidence
- Need for "sharing" of information

Conclusion

"All scientific work is incomplete—whether it be observational or experimental. All scientific work is liable to be upset or modified by advancing knowledge.

That does not confer upon us a freedom to ignore the knowledge we already have, or to postpone the action that it appears to demand at a given time.

Who knows, asked Robert Browning, but the world may end tonight? True, but on available evidence most of us make ready to commute on the 8:30 next day." Hill, 1965

Thank you

Acknowledgements:

Members of the SAGE discussion group on GRADING:

- **SAGE members**
  - Zulfiqar Bhutta
  - Dave Durrheim
  - Helen Rees
  - Art Reingold
- **Partners and other experts**
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  - Ole Wichman
  - Frode Forland
  - Ed Asturias
  - Kirsten Vannice
  - John Conly
  - Isabelle Wachsmuth-Huguet
  - Kamel Senouci

World Health Organization