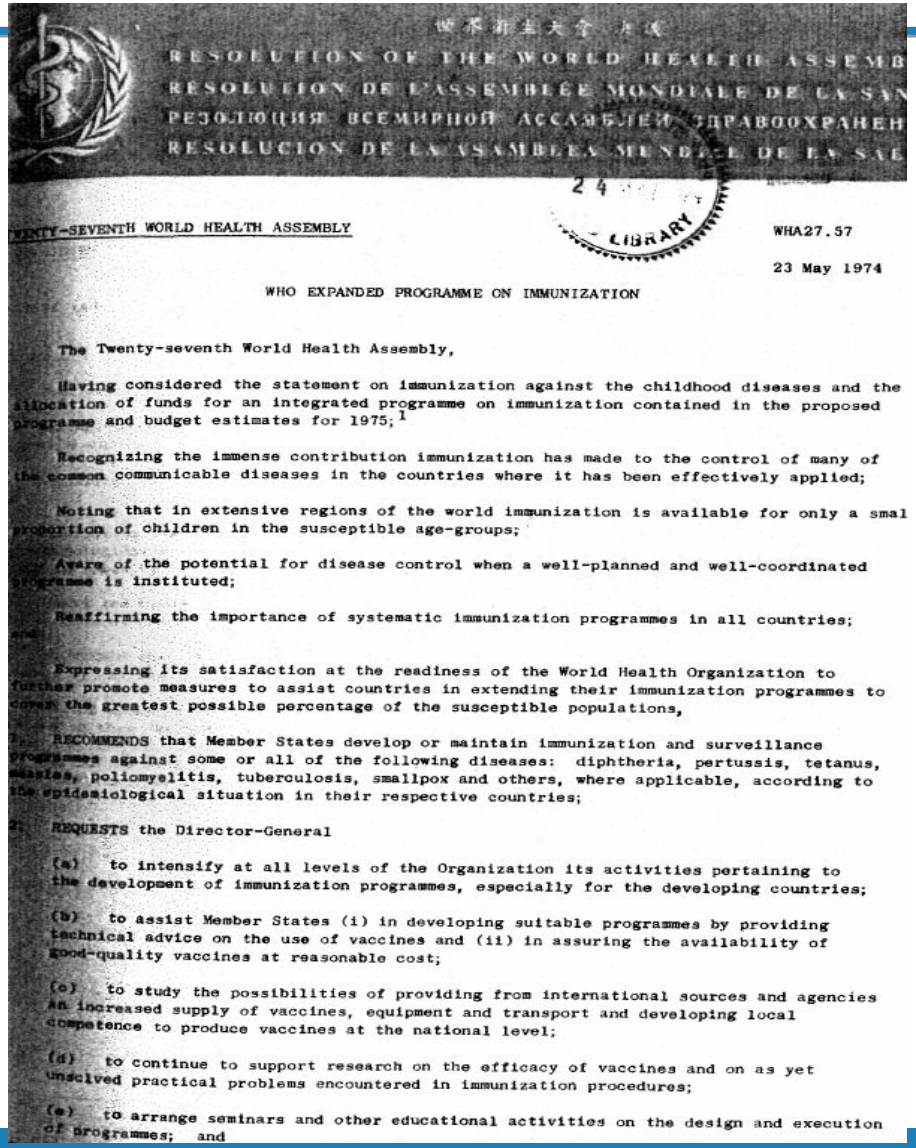
WHO's Strategic Advisory group of Experts (SAGE) on immunization: approach to international evidence-based recommendations

Philippe Duclos, WHO

WHA Resolution on WHO Expanded Programme on Immunization (EPI)



RESOLUTION OF THE WORLD HEALTH ASSEMB
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TWENTY-SEVENTH WORLD HEALTH ASSEMBLY

WHA27.57

23 May 1974

WHO EXPANDED PROGRAMME ON IMMUNIZATION

The Twenty-seventh World Health Assembly,

Having considered the statement on immunization against the childhood diseases and the allocation of funds for an integrated programme on immunization contained in the proposed programme and budget estimates for 1975;[1]

Recognizing the immense contribution immunization has made to the control of many of the common communicable diseases in the countries where it has been effectively applied;

Noting that in extensive regions of the world immunization is available for only a small proportion of children in the susceptible age-groups;

Aware of the potential for disease control when a well-planned and well-coordinated programme is instituted;

Reaffirming the importance of systematic immunization programmes in all countries;

Expressing its satisfaction at the readiness of the World Health Organization to further promote measures to assist countries in extending their immunization programmes to cover the greatest possible percentage of the susceptible populations,

1. RECOMMENDS that Member States develop or maintain immunization and surveillance programmes against some or all of the following diseases: diphtheria, pertussis, tetanus, measles, poliomyelitis, tuberculosis, smallpox and others, where applicable, according to the epidemiological situation in their respective countries;

2. REQUESTS the Director-General

(a) to intensify at all levels of the Organization its activities pertaining to the development of immunization programmes, especially for the developing countries;

(b) to assist Member States (i) in developing suitable programmes by providing technical advice on the use of vaccines and (ii) in assuring the availability of good-quality vaccines at reasonable cost;

(c) to study the possibilities of providing from international sources and agencies an increased supply of vaccines, equipment and transport and developing local competence to produce vaccines at the national level;

(d) to continue to support research on the efficacy of vaccines and on as yet unsolved practical problems encountered in immunization procedures;

(e) to arrange seminars and other educational activities on the design and execution of programmes; and

- The twenty-seventh World Health Assembly
  - Recognizing immense contribution of immunization…
  - …

1. Recommends

   that Member States develop or maintain immunization and surveillance programmes.. according to the epidemiological situation in their respective countries

2. Requests the WHO DG
   - **To assist member states (i) in developing suitable programmes by providing technical advice on the use of vaccines and (ii)** in assuring availability of good quality vaccinesat reasonable costs

WHA27.57, Fourteen Plenary meeting – 23 May 1974

World Health Organization

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**

What is needed?

1. Best evidence-based recommendations

2. Impact
   - usefulness
   - communication and access
   - credibility

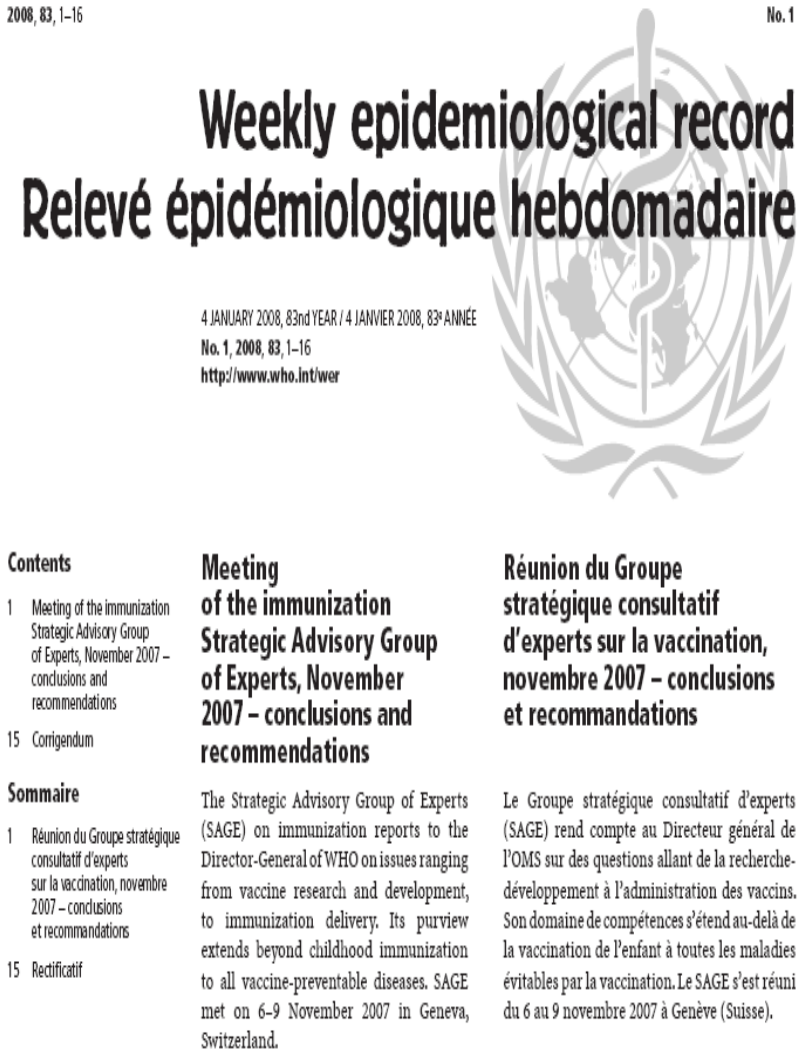
→Continuous enhancement of processes as a result of feed-back and external reviews

Strategic Advisory Group of Experts (SAGE)

- Principal advisory group to WHO for vaccines and immunization (from research to delivery of immunization and linkages with other health interventions - all vaccines, all ages) → reports directly to DG and involves all relevant WHO departments
- Clear terms of reference and standard operating practices
- Membership -15 members
  - Nomination process
  - Declaration of interests and public disclosure

Strategic Advisory Group of Experts (SAGE)

- Meetings and operational procedures
  - Two meetings a year (April and Nov)
  - Only plenary sessions – **transparent process**
  - Extensive representation from partner organizations
  - Experts invited as needed
  - Evidence-based
  - Working groups
- Neutral forum
- Strong links with Regional and other key Technical Advisory Groups
- Report and communications



2008, 83, 1–16 No. 1

Weekly epidemiological record
Relevé épidémiologique hebdomadaire

4 JANUARY 2008, 83rd YEAR / 4 JANVIER 2008, 83e ANNÉE
No. 1, 2008, 83, 1–16
http://www.who.int/wer

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Sommaire

Meeting of the immunization Strategic Advisory Group of Experts, November 2007 – conclusions and recommendations

The Strategic Advisory Group of Experts (SAGE) on immunization reports to the Director-General of WHO on issues ranging from vaccine research and development, to immunization delivery. Its purview extends beyond childhood immunization to all vaccine-preventable diseases. SAGE met on 6–9 November 2007 in Geneva, Switzerland.

Réunion du Groupe stratégique consultatif d'experts sur la vaccination, novembre 2007 – conclusions et recommandations

Le Groupe stratégique consultatif d'experts (SAGE) rend compte au Directeur général de l'OMS sur des questions allant de la recherche-développement à l'administration des vaccins. Son domaine de compétences s'étend au-delà de la vaccination de l'enfant à toutes les maladies évitables par la vaccination. Le SAGE s'est réuni du 6 au 9 novembre 2007 à Genève (Suisse).

http://www.who.int/immunization/sage/en/index.html

World Health Organization

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*

Issues taken into consideration by SAGE

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; and changes in epidemiology over time

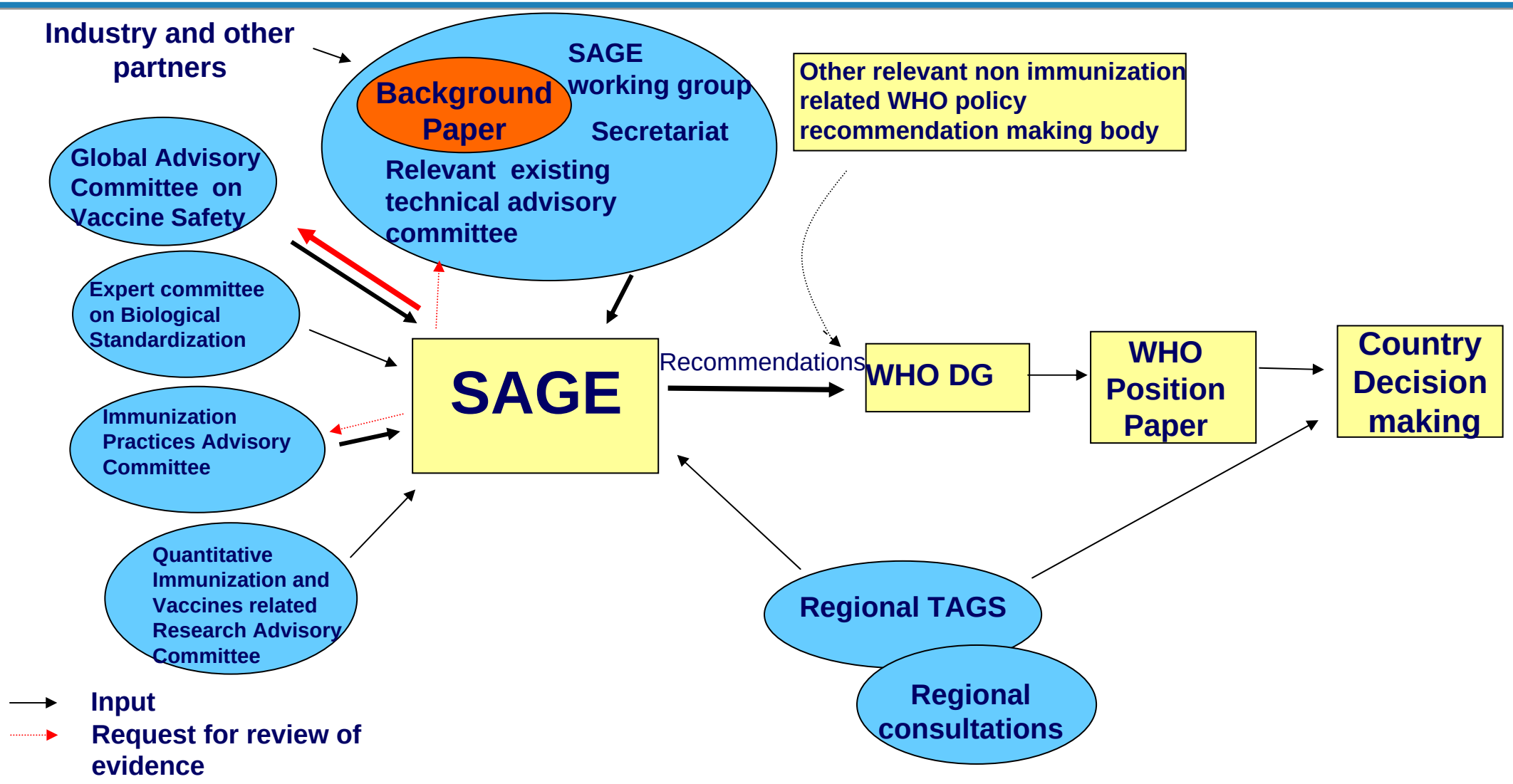
Clinical characteristics

- clinical management of disease, disease severity, primary/secondary/tertiary care implications, long term complications of disease and medical requirements

Issues taken into consideration by SAGE

- **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**

Pathways for WHO recommendations on vaccine use



World Health Organization

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]

World Health Organization

HPV Vaccine Position Paper

- "WHO. . . recommends that routine HPV vaccination should be included in national immunization programmes, . . ."
- "The primary target population is likely to be girls within the age range of 9 or 10 years through to 13 years."

WER 15; 10 April 2009

Footnote

"Moderate quality of scientific evidence to support HPV vaccination of young adolescent girls to prevent cervical cancer later in life."

Question: Is there evidence to support administration of the currently licensed HPV vaccines to young adolescent girls who are naïve to vaccine-related HPV types, to prevent cervical cancer later in life?

Settings: Global

Conclusions: Moderate quality of scientific evidence to support HPV vaccination of young adolescent girls to prevent cervical cancer later in life.

Quality assessment								
No of studies	Design	Limitations	Inconsistency	Indirectness	Imprecision	Other considerations	Quality	Importance
Efficacy of HPV vaccination of young adolescent girls to prevent cervical cancer								
7+ 4[1]	RCTs	no serious	no serious	serious[2]	no serious	none	⊕⊕⊕O MODERATE	CRITICAL
Risk of serious adverse reactions following HPV immunization								
3[3]	RCTs	no serious	no serious	no serious	serious[4]	none	⊕⊕⊕O MODERATE	CRITICAL

[1]7 RCT efficacy studies and 4 immunogenicity studies

The investigation by *SM Garland et al* which involved 5455 women between the ages of 16 and 24 years, studied the protective

Recommendations

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

Perceived challenges to using GRADE when assessing vaccines

- Poor quality of many early studies of existing vaccines (e.g. tetanus)
- Ethical inhibitions to conducting additional RCT's
- Lack of consistency of biological products (e.g. BCG)
- Inability to examine safety vis-à-vis rare AEFI's in RCT's and reliance on post-marketing surveillance
- Difficulty of factoring in indirect effects (e.g. herd immunity)

Perceived challenges to using GRADE when assessing vaccines (cont.)

- Difficulty of factoring in effects on ecologic niches (e.g. serotype replacement)
- Different measures of effect (immunogenicity with/without surrogates of protection; various clinical endpoints)
- Duration of protection
- Differences in age at vaccination/optimal age for immunization
- Effects of “natural boosting” (e.g. *B. pertussis*)

SAGE - April 2010 meeting: Grading and review of evidence

- Concern that naive use of GRADE scores could lead to undue detrimental rankings for effective public-health programmes
- Encouraged a discussion group to develop a communication strategy to mitigate any potentially deleterious effects of a narrowly applied GRADE approach
- Encouraged appropriate adjustments to the process
  - Focus on clear instruction and minor adjustments (e.g. observational studies, population immunity)
  - Adjusted wording used and proposal for modified format of tables
- Supported the development of a paper describing SAGE's approach to reviewing evidence
- Partnership among SAGE and other immunization advisory committees to enhance the GRADE approach was encouraged

Communicating the level of evidence

- **Level 4:** Further research is unlikely to change the estimated effect on health outcome
- **Level 3:** Further research may change the estimated effect on health outcome
- **Level 2:** Further research is likely to change the estimated effect on health outcome
- **Level 1:** Available data are insufficient to provide a reliable estimate of the effect on the health outcome

Work in progress: Options GRADE scoring with all observational studies entering at level 2 *or with variable entry based on observational study design*

Quality of evidence	Study Design	Lower if	Higher if
Further research is very unlikely to change our confidence in the estimate of effect (4)	Randomised trials	Study limitations:[2] *-1 Serious limitations* *-2 Very serious limitations* Inconsistency: *-1 Important inconsistency of results* Indirectness:[2] *-1 Some uncertainty* *-2 Major uncertainty* Imprecision: *-1 Imprecision* Publication Bias: *-1 High probability of publication bias*	Strong evidence of association with absence of major confounders: *+1 RR>2 (0.5) in 2+ studies* *+2 RR>5 (0.2) 2+ studies* Strong evidence of population effect *+1 Evidence of reversal at population level (disease returns when vaccine coverage is decreased)* Dose-response gradient: *+1 Evidence of dose-response* Direction of major confounders: *+1 All major confounders would have reduced the effect* Consistency across settings: *+1 Consistency across different settings, extended periods of time, different investigators*
Further research is likely to have an important impact on our confidence in the estimate of effect and may change the estimate (3)	*Self-Controlled Case Series studies*		
Further research is very likely to have an important impact on our confidence in the estimate of effect and is likely to change the estimate (2)	Observational studies		
Any estimate of effect is very uncertain (1)	*Uncontrolled studies/passive surveillance*[1]		

[1]Studies without a control/comparison group

[2]Should be commensurate with study design

Potential adjustment of presentation: Example

Evidence of measles effectiveness for preventing measles in young children and adolescents after 1 dose: Observational Studies			
		Rating	Adjustment to score
Quality Assessment	No of Studies/Starting Score	44	2
	Limitations	None serious	-0
	Inconsistency	None serious[1]	-0
	Indirectness	None serious	-0
	Imprecision	None serious	-0
	Publication Bias	None serious	-0
	Strong Evidence of Association	Very strong evidence[2]	+2
	Dose-Response	Not applicable	+0
	Direction of Major Confounders	Not applicable	+0
	Consistency across settings	Strong evidence[3]	+1
	Population Effect	Not applicable[4]	+0
	Final Score[5]		**4**
Summary of Findings	**Quality**		**Further research is very unlikely to change our confidence in the estimate of effect**
	Importance		**Critical**

Study Design	Final Score for Design
RCTs	NA
Observational Controlled Studies	4
Ecological Studies	NA
FINAL SCORE	4

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Thank you

Ackowledgements:

- Kirsten Vanice

- Members of the SAGE discussion group on GRADING:
  - Zulfiqar Bhutta
  - Dave Durrheim
  - Helen Rees
  - Art Reingold

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