

Updating World Health Organisation Vaccine Position Papers

Professor David Durrheim
Strategic Advisory Group of Experts (SAGE)
on Immunisation

Outline

- SAGE and global policy making
- Updating Vaccine Position Papers
- GRADE limitations and solutions



Strategic Advisory Group of Experts (SAGE) on Immunization

Principal advisory group to WHO for vaccines and immunization

Membership

Meetings and operational procedures



The screenshot shows the WHO website page for the Strategic Advisory Group of Experts (SAGE) on Immunization. The navigation bar includes links for Statistics, Media centre, Publications, Countries, Programmes and projects, and About WHO. A search bar is located below the navigation. The main heading is "Immunization, Vaccines and Biologicals". The page title is "Strategic Advisory Group of Experts (SAGE) on Immunization". The main text describes the group's establishment in 1999 and its role in providing guidance on immunization work. A "SAGE news" section features a date of 19 May 2011 and a link to the "April 2011 meeting report published", accompanied by a photo of a child. A "Next meeting" section lists dates for 8-10 November 2011. Other sections include "Future meetings", "Previous meetings", "Regional Technical on Immunization", and "SAGE areas" with sub-sections for "Members" and "Working mechanisms".

Statistics Media centre Publications Countries Programmes and projects About WHO

Search

Immunization, Vaccines and Biologicals

Strategic Advisory Group of Experts (SAGE) on Immunization

The Strategic Advisory Group of Experts (SAGE) on Immunization was established by the Director-General of the World Health Organization in 1999 to provide guidance on the work of the WHO Immunization, Vaccines and Biologicals Department. SAGE is the principal advisory group to WHO for vaccines and immunization. It is charged with advising WHO on overall global policies and strategies, ranging from vaccines and technology, research and development, to delivery of immunization and its linkages with other health interventions. SAGE is concerned not just with childhood vaccines and immunization, but all vaccine-preventable diseases.

— [SAGE terms of reference](#)
pdf, 50kb

SAGE news

19 May 2011
[April 2011 meeting report published](#)



— [News archive](#)

Next meeting

8-10 November 2011
A draft agenda will be nearer the time of the

Future meetings

— [Dates for 2011-2012](#)

Previous meetings

— Meeting reports
— Documentation from
— [SAGE agenda search](#)
Search all topics of SAGE since 1997

Regional Technical on Immunization

— [Web links](#)

National Immunization Advisory Groups

— [List of links by country of information](#)

SAGE areas

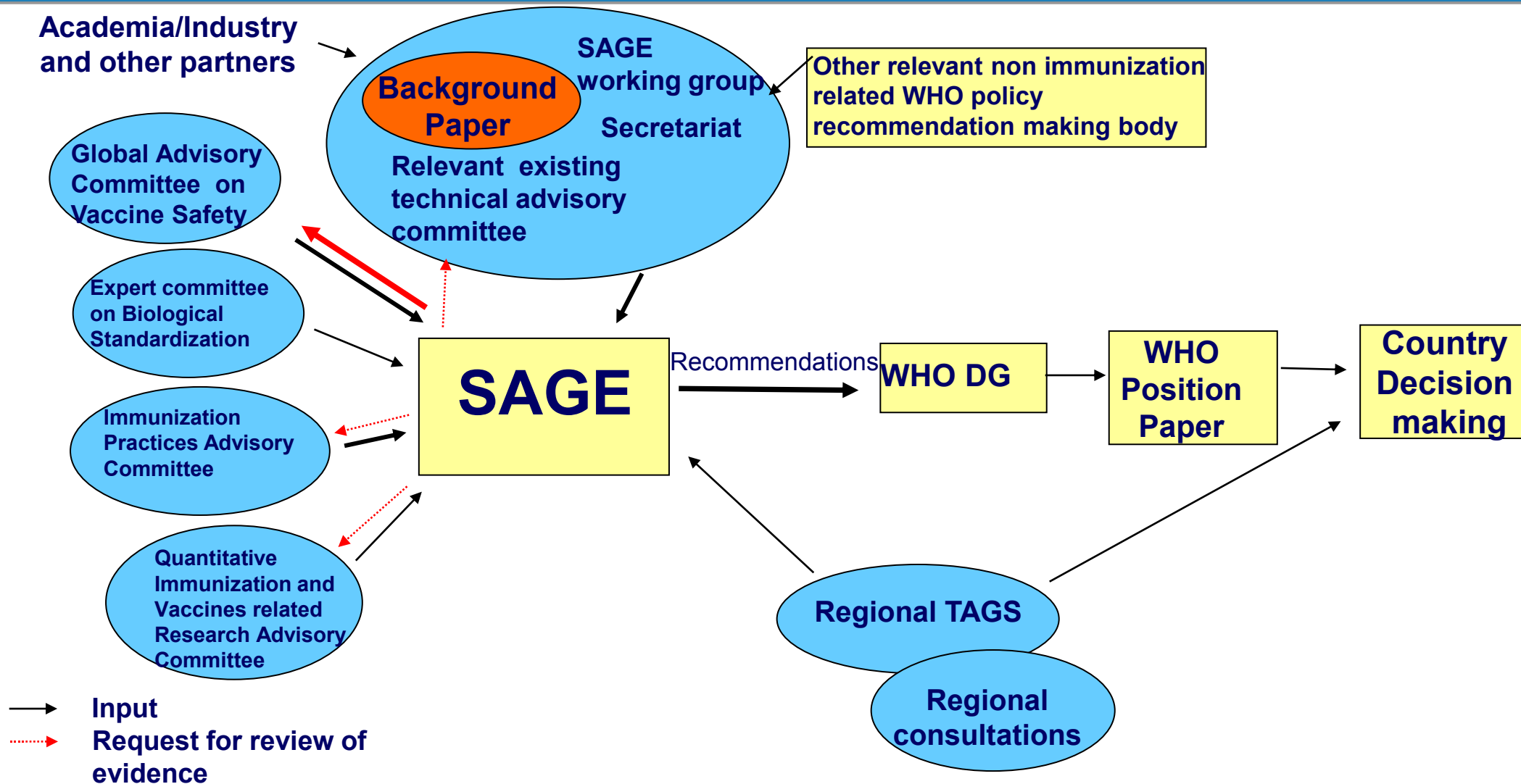
Members



Working mechanisms



Pathways for WHO Recommendations on Vaccine Use



Updating Vaccine Position Papers

- **Position papers = Key reference documents**
- **Developmental and review process**
- **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)**

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 \[pdf 400kb\]](#)
- [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 \(MAY 2006\) Original English and French versions \[pdf 400kb\]](#)
- [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 \[pdf 210kb\]](#)
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- [Chinese translation \[pdf 210kb\]](#)
- [Russian translation \[pdf 184kb\]](#)
- [Spanish translation \[pdf 50kb\]](#)
- [References \[pdf 56kb\]](#)

www.who.int/vaccine



World Health
Organization

Updating Vaccine Position Papers

■ Additional posting of information on the web:

Grading of Recommendations
Assessment, Development and Evaluation
(GRADE) tables, references, summaries
(one pager and PowerPoint presentation)

Immunization, Vaccines and Biologicals

WHO > Programmes and projects > Immunization, Vaccines and Biologicals

 [printable version](#)

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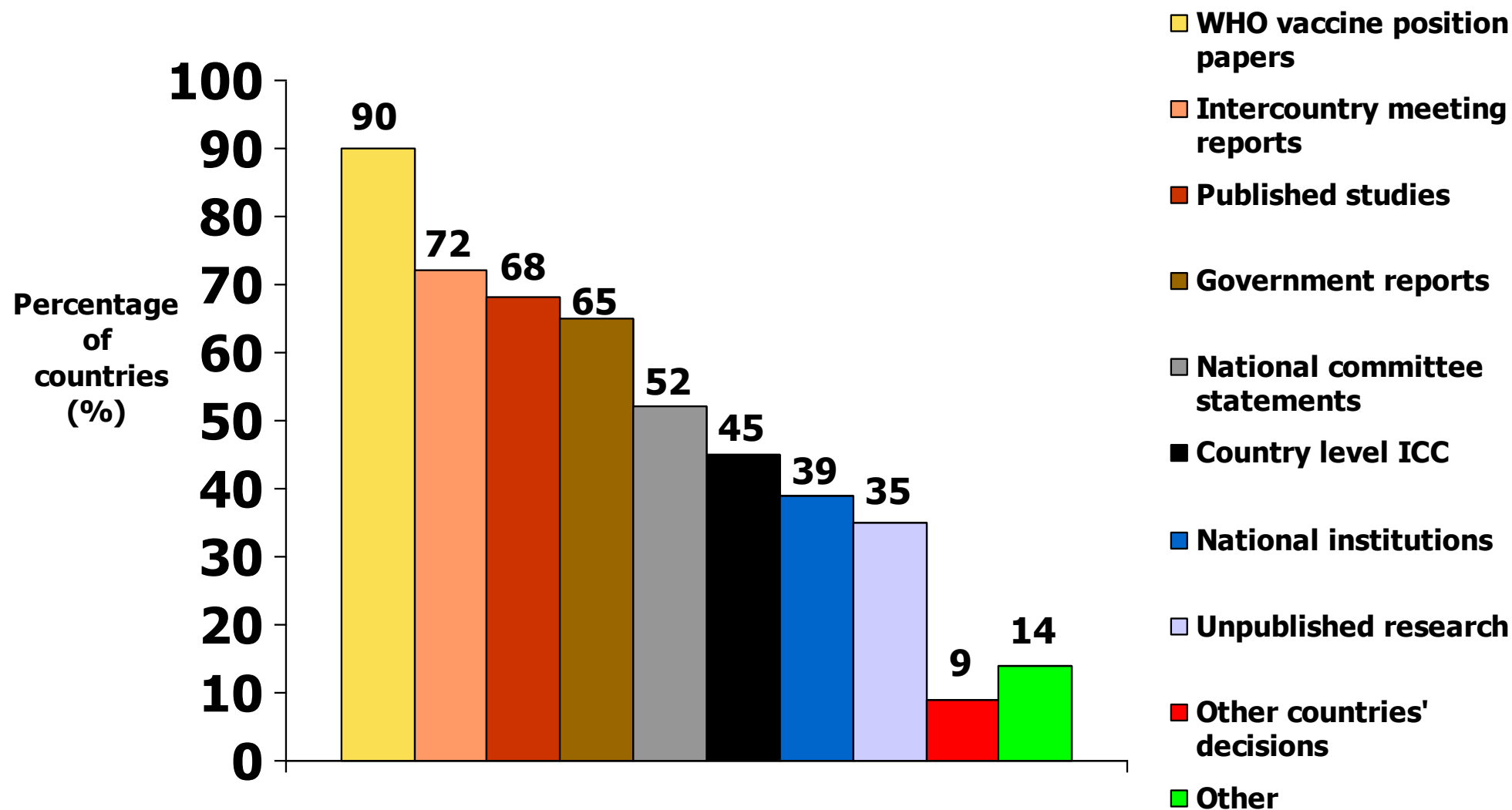
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- [Spanish translation \[pdf 50kb\]](#)
- [References \[pdf 56kb\]](#)

[www.who.int/vaccines/biologics/immunization/vpp/print.html](#)



Sources used to inform policies (N=99)

Global survey of NITAGs



Updating position papers - SAGE working groups

- Establishment and ToRs decided by WHO and SAGE members
- Composition
- In depth review of evidence and related issues in preparation for SAGE discussion/decision
- Not permitted 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 Pfeleiderer, 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.

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

Challenges of using GRADE

- Since 2008, GRADE tables produced in support of key recommendations in WHO vaccine position papers
- Concern expressed by SAGE working groups
- Limitations for public health interventions, particularly immunisation programmes
- SAGE established a Discussion Group
- Revolution or Constructive Engagement?

For evidence-based policy, is an RCT always best or necessary?

Parachute use to prevent death and major trauma related to gravitational challenge: systematic review of randomised controlled trials

Gordon C S Smith, Jill P Pell

BMJ 2003;327:1459-61



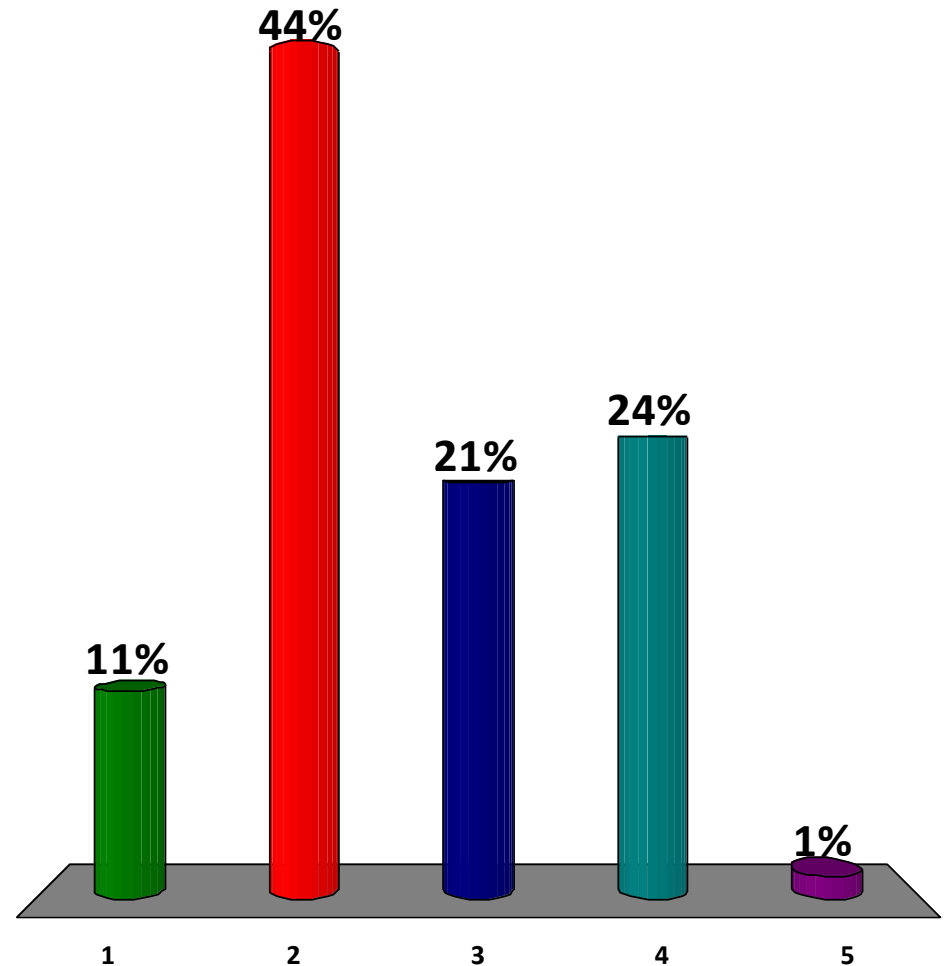
Parachutes reduce the risk of injury after gravitational challenge, but their effectiveness has not been proved with randomised controlled trials

Results We were unable to identify any randomised controlled trials of parachute intervention.

Conclusions As with many interventions intended to prevent ill health, the effectiveness of parachutes has not been subjected to rigorous evaluation by using randomised controlled trials. Advocates of evidence based medicine have criticised the adoption of interventions evaluated by using only observational data. We think that everyone might benefit if the most radical protagonists of evidence based medicine organised and participated in a double blind, randomised, placebo controlled, crossover trial of the parachute.

How is Grading of Recommendations Assessment, Development and Evaluation (GRADE) rating of quality of evidence scheme suited to public health interventions? Score from 1 (very problematic) to 5 (ideally suited)

1. Very problematic
2. Quite problematic
3. Neither problematic nor well suited
4. Quite well suited
5. Ideally suited



SAGE decision 2011

- Extensive productive interactions with members of ACIP, ECDC, STIKO, GACVS, GRADE working group
- **GRADE adjusted** to accommodate vaccine-relevant evidence, particularly **vaccine population effects and surveillance data.**

G Model

JVAC-12934; No. of Pages 8

ARTICLE IN PRESS

Vaccine xxx (2012) xxx–xxx



ELSEVIER

Contents lists available at SciVerse ScienceDirect

Vaccine

journal homepage: www.elsevier.com/locate/vaccine



Developing evidence-based immunization recommendations and GRADE[☆]

P. Duclos^{a,*}, D.N. Durrheim^{b,1}, A.L. Reingold^{c,2}, Z.A. Bhutta^{d,3}, K. Vannice^{e,4}, H. Rees^{f,5}

Quality of evidence	Quality starting factor is first assigned base on Study Design	Quality score is lowered¹ if	Quality score is raised¹ 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	1)Strength of association: +1 RR or OR>2 (or <0.5) in 2+ studies +2 RR or OR >5 (or <0.2) in 2+ studies
We are moderately confident in the estimate of effect on health outcome. The true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different (3)		2)Inconsistency: -1 Serious -2 Very serious 3)Indirectness: ² -1 Serious -2 Very serious	2)Dose response (population based): +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
Our confidence in the estimate of the effect on the health outcome is limited . The true effect may be substantially different from the estimate of the effect (2)	Observational studies, disease surveillance and post marketing safety surveillance data	4)Imprecision: -1 Serious -2 Very serious	3) Antagonistic bias and confounding: +1 All major confounders would have reduced the effect 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 have very little confidence in the estimate of the effect on the health outcome. The true effect is likely to be substantially different from the estimate of effect (1)		5)Publication Bias: -1 Likely -2 Very likely	

¹ 1= move up or down one grade (for example from high to intermediate), 2= move up or down two grades (for example from low to high)

² Should be commensurate with study design

GRADE and Q.I.

“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.” Austin Bradford Hill, 1965

Extra slides



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

1. Introduction

- 1.1 Background
- 1.2 Past use of GRADE in WHO vaccine position papers

2. SAGE process for reviewing the evidence

- 2.1 Definition of questions to inform recommendations
- 2.2 Identification of critical questions to which the GRADE approach should be applied
- 2.3 Systematic review of the literature and of unpublished data
- 2.4 Identifying study limitations through risk of bias
- 2.5 Scoring of the quality of evidence
- 2.6 Discussion and deliberation leading to the development of proposed recommendations
- 2.7 Presentation of proposed recommendations to SAGE along with the supporting evidence
- 2.8 SAGE discussion, deliberation and ultimate decision regarding the proposed recommendations to WHO

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

3. Scoring of the quality of evidence

- 3.1 Categorization of studies
- 3.2 GRADE quality assessment criteria
- 3.3 Quality of evidence rating
- 3.4 Application of GRADE to recommendations
- 3.5 Presentation of GRADE tables

4. Vaccine recommendation development — beyond scoring the evidence

- 4.1 Other considerations when making recommendations
- 4.2 Updating recommendations
- 4.3 Emergency situations

5. Conclusions

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

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