Why review the evidence on non-specific effects of vaccines on mortality in children under 5 years of age?

What are the questions for SAGE today?

Terry Nolan
Chair, SAGE Working Group on non-specific effects of vaccines

non-specific effects of vaccines

Some studies have suggested that vaccines may reduce, or increase, **all-cause mortality** beyond what is expected simply from protection against the disease for which they are intended.

Hypotheses: non-specific effects of vaccines

Specific hypotheses have been proposed:

- BCG and measles vaccines reduce and DT_wP vaccines increase all-cause mortality in some populations and,
- that these effects may be modified by the order in which those vaccines are given, the age of the child and co-administration with Vitamin A.

OVERVIEW OF SELECTED WHO ACTIONS (1)

Date	Action	Conclusions
2000	WHO consultants conducted field visit to research sites	Not possible to make definitive conclusions additional data needed
2001	SAGE commends the work of GACVS in examining the evidence relating to the non-specific effects of vaccines on mortality.	SAGE endorses GACVS's conclusion that, on the basis of the evidence currently available, no association between diphtheria–tetanus–pertussis (DTP) vaccine and increased mortality has been demonstrated. SAGE supports GACVS steps to commission additional studies aimed at determining whether the findings reported from Guinea-Bissau (BMJ 9 Dec 2000) are reproducible in Guinea-Bissau and elsewhere in developing countries, and awaits the outcome of these studies.

OVERVIEW OF SELECTED WHO ACTIONS (2)

Date	Action	Conclusions
2003	Review a series of published and unpublished epidemiology papers suggesting a non-specific and potentially adverse effect of DTP, measles and BCG vaccines on morbidity and mortality in children in the developing world	Two task forces should be established: 1. **Epidemiology** (experts in epidemiology, statistics, immunology and clinical study design) to critically review the science, biological plausibility, epidemiology and conclusions of the studies and advise GACVS if it should reconsider its position (report in June 2004) 2. **Broader issues** - such as whether vaccines affects the immune system to determine whether perturbation of the immune system by infant immunisation might occur, and whether this could be deleterious under certain conditions
2004	GACVS subgroup reviewed evidence to ascertain whether perturbations to the immune system may occur and this may be deleterious Observational studies in Philippines and Papua New G	Critical issue but need further evidence Evidence available is not without bias (WER Jan 2004 & Folb P et al AJPH Nov 2004)

OVERVIEW OF SELECTED WHO ACTIONS (3)

Date	Action	Conclusions
2006	Acknowledgement of workshop to be organized in late 2007, partially sponsored by the Danish National Research Foundation, to consider the methodological issues arising in these kinds of study	No need to revise previous statements at this point in time
2008-2010	GACVS reviewed outcomes of independent workshop on epidemiological studies methods and issues Review of evidence regarding measles vaccination and NSE on child mortality as part of the measles research agenda	Conclusive evidence unlikely to be obtained from observational studies Methods are critical for finding interpretation (observational studies – bias, confounding; RCTs in different settings; ethical considerations) (WER 2008, Farrington et al TMIH 2009 & Fine P et al TMIH 2009)

SAGE Meeting, Nov 2011

- **Director IVB**
  - described previous WHO actions regarding NSE and
  - acknowledged recent publications on the topic

- **SAGE**
  - recommended that the non-specific effects of vaccines be reviewed

SAGE Working Group on non-specific effects of vaccines

The Working Group was established in early 2013 to determine:

- if the current evidence on non-specific effects of BCG, DTP and measles containing vaccines on all-cause mortality in children under 5 years of age **is sufficient to lead to adjustments in policy recommendations or to warrant further scientific investigation**, and

- if so, to **define the path towards obtaining unequivocal evidence** on these issues that would support future robust, evidence-based adjustments in immunization policies, if warranted.

Working Group Membership

- Terry Nolan (Australia, SAGE, Chair)
- Christine Stabell Benn (Denmark)
- Zulfiqar Bhutta (Pakistan/Canada, SAGE)
- Mike Brennan (USA)
- Stephen Evans (UK)
- Paul Fine (UK)
- Brad Gessner (France)
- Dianne Griffin (USA)
- Martin Mermikwu (Nigeria)
- Kate O'Brien (USA, SAGE)
- Walt Orenstein (USA)
- Jaleela Sayed (Bahrain)
- Dipika Sur (India)

Outline of key steps

WORKING GROUP

2013

Review of two protocols and extraction forms for reviews

2014

Review of DRAFT outcomes of systematic reviews
Review of DRAFT assessment of risk of bias
Review of final reports of the two systematic reviews
Face to face meeting of the Working Group
Discussion and deliberation leading to the development of **proposed** conclusions and recommendations

SAGE

SAGE discussion, deliberation, and
SAGE recommendation regarding the proposed recommendations to WHO

POLICY QUESTION

P children **less than 5 years of age**

I vaccination with **BCG, DTP or measles** containing vaccines

C **no vaccination** (BCG, DTP or measles), or simultaneous administration of other vaccine, or order of vaccine administration

O deaths from causes other than those conditions that the vaccine is designed to prevent, i.e. death from all causes (e.g. all-cause mortality, child survival)

Today's questions

- Is the current evidence on non-specific effects of vaccines sufficient to lead to **adjustments in policy recommendations**?
- Is the current evidence on non-specific effects of vaccines sufficient to **warrant further scientific investigation**?

Presentations

1. Introduction and scope
2. Immunology systematic review
3. International survey of order of vaccination
4. Epidemiologic systematic review
5. Conclusions and Recommendations for SAGE consideration
6. SAGE Discussion