

# **Safety and quality of hepatitis B vaccines: frequently asked questions in the region**

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## **What is new since the St- Petersburg meeting in 2001?**

**Philippe Duclos**

**World Health Organization**

**Meeting on strengthening immunisation systems and  
introduction of hepatitis B vaccine in Central and Eastern  
Europe and the Newly Independent States**

**Kyiv, Ukraine, 25-28 May, 2004**



# Vaccine preparations

- Purified preparations of HBs Ag
- Prepared by harvesting HBs Ag from the plasma of people with chronic infection or by inserting plasmids in yeast or mammalian cells
- Aluminium phosphate or hydroxide
- Sometimes thiomersal as preservative



# Prequalification of vaccines for UN supplies

## ■ WHO advises UNICEF

- Independent opinion/ advice on the vaccine quality

## ■ Goals

- Ensure vaccine safety and efficacy
- Ensure that vaccines meet the needs of the programme (potency, thermostability, presentation, labelling, shipping conditions...)

## ■ Principles and process

- Full assessment of the National Regulatory Authority against established indicators. 6 critical functions.
- Review production process and quality control procedures
- Testing of consistency lots
- Joint NRA/WHO visits to manufacturing plant
- Reassessment every two years
- Random testing of lots
- Continuous monitoring for complaints



# Prequalified Hepatitis B vaccines as of May 2004

- Berna Biotech (Previous Korea Green Cross), Switzerland/South Korea
- Center for Genetic engineering and Biotechnology, Cuba
- GlaxoSmithKline, Belgium, also DTP-HepB and DTP-HepB with Hib
- LG Life Sciences Ltd, South Korea
- Merck and Co. Inc, USA
- Shanta Biotechnics Private Ltd. India

All recombinant products



# Vaccine Safety Issues

## WHO perspective

- **Global issues with some regional differences**
- **Implicate active ingredients or non specific substances and diseases of unknown etiology**
- **“Amalgamation”**
- **Potential of signal generation and systematic search to identify spurious associations and generate false hypothesis**
- **Can generate huge amount of work and undue fear**
- **Need for quick hypothesis testing and international collaboration**
- **Science compounded by legal issues**
- **Misperception that vaccines from developing countries and WHO standards for them are inferior**



# Surveillance, Case report, Case Series: an Incomplete Picture

Example: population 200,000,  
risk of disease 1/10,000  
vaccine coverage 80%

	Disease		Total
	Yes	No	
Vaccinated	16	159,984	160,000
Not vaccinated	4	39,996	40,000

A thick black arrow points from the 'Not vaccinated' row to the 'Disease No' column.



# Abuse of pharmacovigilance data and danger of “fishing expeditions”: example

- Geier et al. *Review of health care and vaccination*  
Expert Opin *Safety*
- Stated concerns about neurological, immunological and dermatological disorders, and
- But
  - Abuse of V
  - Calculated *incidences* as control with *has many medical*, *all bias, age,* *prescription diagnosis*
  - « C *statistics*



# Sources of information for decision making

- Literature review and pharmacovigilance data
- Systematic reviews and meta-analyses (Cochrane)
- Consultations-independent review e.g. for hepatitis B
  - National reviews
    - ANAES and AFSSAPS in France
  - US Institute of Medicine
    - 1994, overall review
    - 2002, demyelinating diseases
  - Viral Hepatitis Prevention Board, 1998
  - European Association for the Study of the Liver, 2002
  - Global Advisory Committee on Vaccine Safety (GACVS), since 1999



# Global Advisory Committee on Vaccine Safety (GACVS)

- Expert scientific and clinical advisory body to WHO
  - To respond promptly, independently to vaccine safety issues of global importance
  - Assessment of relationships between vaccines and events at the local, national, or international level
  - Review of vaccine safety knowledge in collaboration with all parties
  - **Multidisciplinary, global, and under strict conflict of interest and confidentiality rules**
  - Ad hoc task forces and implementation of research
- Deals with issues decided upon by secretariat and committee
  - Referred to by governments and of special complexity
  - Potential to affect national or international programs

Best judgement in front of uncertainty



# Safety Issues Discussed in 2002-2003

- Macrophagic myofasciitis (MMF) and aluminium containing vaccines
- Thiomersal and health effects
- Autoimmune diseases and vaccines
- Potential TSE contamination of vaccines
- Adverse events following mumps vaccination
- Child survival following routine infant immunization
- Safety of yellow fever vaccine
- Risks following immunization in HIV-infected children
- MMR and autism
- Multiple sclerosis and hepatitis B vaccination
- Leukaemia and hepatitis B vaccination
- Oculo-respiratory syndrome following influenza vaccination
- Bell's Palsy following vaccination with intranasal vaccine
- Safety of smallpox vaccines



# GACVS Communications

2002, 77, 330-404

No. 47

## Weekly epidemiological record Relevé épidémiologique hebdomadaire

22 NOVEMBER 2002, 77th YEAR / 22 NOVEMBRE 2002, 77<sup>e</sup> ANNÉE  
No. 47, 2002, 77, 330-404  
<http://www.who.int/wer>



### Contents

- 380 Global Advisory Committee on Vaccine Safety 20-21 June 2002
- 394 Draft WHO Guidelines on the Use of Vaccines and Antisera during Influenza Pandemics

### Sommaire

- 380 Comité consultatif mondial sur la Sécurité des Vaccins, 20-21 juin 2002
- 394 Projet de recommandations de l'OMS sur l'utilisation de vaccins et d'antisérum lors des pandémies de grippe

### Global Advisory Committee on Vaccine Safety, 20-21 June 2002

The Global Advisory Committee on Vaccine Safety (GACVS) was established in 1999 by WHO to respond promptly, efficiently, independently (of WHO), and with scientific rigour to vaccine safety issues of potential global importance. The Committee meets twice a year on a regular basis.

GACVS is a scientific and clinical advisory body that aims to provide a reliable and independent assessment of vaccine safety issues through:

### Comité consultatif mondial sur la Sécurité des Vaccins, 20-21 juin 2002

L'OMS a créé le Comité consultatif mondial sur la Sécurité des Vaccins (GACVS) pour répondre rapidement, efficacement et indépendamment (vis-à-vis de l'OMS) à des questions de sécurité vaccinale pouvant concerner le monde. Le Comité se réunit deux fois par an.

Compétent dans les domaines scientifique et clinique, le GACVS est un organe indépendant chargé de procéder de manière indépendante à l'étude des problèmes de sécurité des vaccins par:

Health topics

Publications

Research tools

WHO sites

GACVS home

About us

Topics

Committee reports

Causality assessment process

## Global Advisory Committee on Vaccine Safety (GACVS)

The Global Advisory Committee on Vaccine Safety was established in 1999 to respond promptly, efficiently, and with scientific rigour to vaccine safety issues of potential global importance.

### Safety of smallpox vaccines

At its 8th meeting held on 11-12 June 2003, the Committee concluded that there is a real risk of serious adverse events following immunization with smallpox vaccine, including safety issues that have not previously been recognized, that there may be significant potential risks to contacts of vaccinees, and that implementation of immunization would require significant capacity and resources.

[More information](#)



Source : CDC

### Adverse events following mumps vaccination

At its 8th meeting held on 11-12 June 2003, the Committee concluded that risk estimates of vaccine-derived mumps meningitis vary between studies, reflecting differences in study settings and circumstances, and degrees of surveillance. [More information](#)

Hepatitis B	Thiomersal	BCG
<a href="#">Latest reports on hepatitis B and leukaemia</a>	<a href="#">August 2003 report on thiomersal and vaccines</a>	<a href="#">BCG in immunocompromised individuals</a>

## Глобальный консультативный комитет по безопасности вакцин, 3-4 декабря 2003 г.

Глобальный консультативный комитет по безопасности вакцин (ГККБВ), или Global Advisory Committee on Vaccine Safety (GACVS), был создан Всемирной организацией здравоохранения (ВОЗ) в 1999 году с целью осуществлять оперативные, эффективные и независимые (от ВОЗ) научно обоснованные действия по проблемам безопасности вакцин, имеющим глобальное значение [см. «Weekly Epidemiological Record», 1999, №41, с.337-340]. Комитет функционирует как консультативный орган ВОЗ по научным и клиническим вопросам.

[Smallpox](#)  
[Thiomersal](#)  
[Hepatitis b and leukaemia](#)

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[www.who.int/vaccine\\_safety/en/](http://www.who.int/vaccine_safety/en/)



# Networking

- **Links between GACVS/WHO & qualified sites (Good Information Practices)**
- **Advance release of information on emerging issues to key partners**
- **Advantages**
  - **Identify emerging concerns**
  - **Increase ability to answer legitimate questions**
  - **Improve likelihood of site identification in searches**
  - **Added credibility of sites through GIPs qualification**
- **Criteria for reliable websites**



# **Suggested criteria for GACVS to use when evaluating websites**

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- ◆ **Credibility (essential criteria)**
- ◆ **Content (important criteria)**
- ◆ **Accessibility (practical criteria)**
- ◆ **Design (desired criteria)**



# Safety Profile

- Pain and tenderness in 15% (3%-29%) of vaccinations and fever  $> 37.7^{\circ}\text{C}$  in 1%-6%
- Fever, headache, muscle aches and pain, nausea, vomiting, loss of appetite, and fatigue occur at same rate as in placebo
- Anaphylactic reaction 1 per 600,000 doses
- Cases of rheumatoid arthritis, thyroiditis, lupus, hematological disorders and demyelinating diseases (multiple sclerosis) reported but no causal link demonstrated
- No association with GBS
- No association with diabetes
- No association with hair loss



# Hepatitis B Vaccination and Acute Lymphoblastic Leukaemia (ALL)

- **Berkeley study reported an association between hep B vaccine and risk of ALL**
- **Investigators suggested that thiomersal may play a role**
- **Review by the GACVS, since June 2002**
  - **Association suggested from one source with no strong supportive evidence**
  - **Statistical error and epidemiological bias were not excluded**
  - **Four additional studies did not support association**
  - **CDC review nullified initial findings**
- **No association, no modification of recommendations**



# Thiomersal in Vaccines

- 1999, concerns in the US as cumulative amount of mercury exceeded threshold set by one agency for methyl mercury
- GACVS review since June 2002
  - Pharmacokinetic profiles of ethyl mercury (thiomersal) and methyl mercury different
  - Two large epidemiological studies support the safety of thiomersal-containing vaccines
  - **GACVS conclusion:**
    - no evidence of toxicity of thiomersal in vaccines
    - no reason to change current immunization practices
    - little evidence to extrapolate data from well nourished term babies to preterm or malnourished infants
    - WHO should commission further research



# Hepatitis B Vaccination in France

- **1982** Recommendation for health care workers and high risk groups
- **1991** **Compulsory for health care workers**
- **1994-95** **Universal vaccination**
  - **Infants**
  - **Adolescents: school-based**
- **1998** **Over 25 million vaccinated**
- **1999** **34 to 45% of population vaccinated**
  - **18 million of adults**
  - **9 million of children  $\leq$  15 year**
  - **1.8 million of children  $\leq$  2 year**
- **Overall, 60% of doses given to adults 20-44 years**



# France: suggestion of a link between hep B vaccine and MS

- 1991 Case reports of MS in Lancet
- 1994 Official pharmacovigilance survey
- 1995 Dear Doctor Letter
- 1995-98 Growing pressure
- Oct 98 Temporarily suspension of school-based adolescent vaccination program

## ■ But

- Universal infant immunization programs continued
- Vaccine still recommended for adults at increased risk
- Continued support for adolescent vaccination through primary care physician



# French Post-Market Surveillance Data as of December 31, 2000

- 771 nervous central demyelinating diseases (569 MS) and 91 cases of peripheral demyelinating disease
- 1 day to 5 years after vaccination - median 60 days
- 20 MS in children  $\leq 15$  years including 19 first episodes;  
0 case in  $< 24$  months
- Age and sex distribution similar to age and sex distribution of MS in general population
- Increased reporting between 1998 and 1999 due to visibility
- *Observed versus expected cases unremarkable*
- France accounts for the vast majority of MS reports globally



# Hepatitis B Vaccination and Multiple Sclerosis (MS)

## ■ June 2002 :

- “The analysis of data from spontaneous reports and results of 9 epidemiological studies do not support a causal relationship between MS and hep B vaccination. The most likely explanation is a coincidence” There is no reason to suggest that the recommendations for universal infant and adolescent immunization coverage with hepatitis B vaccine should change. “

## ■ December 2003

- Review of an unpublished presentation of a study proposing a possible association (Hernan et al.)
- Apparent increased risk of onset of MS within 3 years of vaccination
- Possibility of bias and chance finding (small numbers)
- No change in previous GACVS conclusions and recommendations



# Macrophagic Myofasciitis (MMF)

- **Localized histopathological lesion with focus of macrophages and containing aluminium**
  
- **Hypothesis**
  - **Link with general syndrome or not?**
  - **Result or cause?**
  
- **Since 1999, broad consultation on this issue with GACVS**
  - **Microscopic lesions related to immunization**
  - **Preliminary results of animal studies and study of macrophagic function further support a vaccine "tattoo"**
  - **Need for epidemiological study to establish whether or not there is an association between local MMF lesions and a generalized condition**
  - **French exploratory epidemiologic study: more fatigue when lesion but absence of specific pathology**
  - **No evidence for a health risk from aluminium containing vaccines**



# Frequently asked questions!

- Is it acceptable to have thiomersal containing vaccines offered through vaccine fund and UNICEF whereas other countries use thiomersal free vaccine?
  - Absolutely
- Are thiomersal containing hepatitis B vaccines safe enough to be offered at birth?
  - Yes
- Can a birth dose of hepatitis B vaccine be given simultaneously with BCG?
  - Yes
  - Actually a study by Ota et al.
    - demonstrates that co administration increases response (particularly Ab response) to hep B vaccination
    - no difference in reactogenicity (yet low numbers)
- Other questions?