General

The GACVS chairperson presented the major recommendations from the 6-7 June 2006 meeting:* Based on the evidence, GACVS’s previous statement confirming the safety of thiomersal in vaccines remains valid. With respect to the question of potential vaccine-related immune overload in infancy, the committee concluded that the evidence did not support the hypothesis that vaccines as currently used weaken or harm the immune system.

* See No. 28, 2006, pp. 273-278.

Responsible staff must ensure that . . . all adverse events following immunization (AEFI) are monitored by an effective field performance surveillance system.

Currently, GACVS remains of the view that there is no evidence supporting a causal association between neurobehavioural disorders and thiomersal-containing vaccines.

(GACVS considered the) theoretical risk of contamination of vaccines with yeast antigens with resultant mimicry between peptides of yeast and human myelin proteins (and concluded that) humans are universally exposed to yeast in the environment and everyone will have antibodies against yeasts. Without a signal, there is little point at present in pursuing this theoretical concern.
Serious events are defined as:
– those that are life threatening and
– those that result in hospitalization (or prolonged hospitalization)
– those that result in disability (or have the potential to result in disability)
– or death.

In addition to vaccine delivery training, mid-level management courses and in-service refresher training, provision should be made for training on safety and adverse events following immunization (AEFI) monitoring. In order to ensure across-the-board collaboration, relevant partners such as nongovernmental organizations and private practitioners need to be included in these training activities. Moreover, educational establishments should revise their curricula to include injection safety so that the pre-service training of health professionals follows the national standards for safe injection practices.

Whenever a severe vaccine-related adverse event is suspected, it is therefore essential that the UNICEF country office immediately advise the Chief of Immunization, UNICEF Supply Division, and that a copy be sent to the Regional Office.

An adverse event following immunization (AEFI) is any adverse event that follows immunization that is believed to be caused by the immunization.
All immunization programmes should monitor at least the following AEFIs:
(1) All injection site abscesses.
(2) All cases of BCG lymphadenitis
(3) All deaths that are thought by health workers, or the public, to be related to immunization.
(4) All cases requiring hospitalization that are thought by health workers, or the public, to be related to immunization.
(5) Other severe or unusual medical incidents that are thought by health workers, or the public, to be related to immunization.

With respect to the third, fourth, and fifth events, health workers may relate the event to immunization because it occurred within a month of an immunization, as its case definition indicates. However, some medical incidents can be related to immunization even if they have a delayed onset.

For mild problems, health workers should comfort and advise parents and treat the patient. It is not necessary to report these reactions, except for BCG lymphadenitis and injection site abscesses, unless parents’ concerns are significant.

Deaths and hospitalizations should receive immediate attention and should be reported as soon as they are detected. Abscesses, lymphadenitis, and other AEFIs should also be reported immediately if they are causing community concern.

Only the monthly total of (adverse events) and, if there are no cases, zero must be reported. A good system will also describe any trends that the reporter has identified, actions taken in response, and recommendations. Supervisors should monitor the number of cases of each trigger event that have been reported by each health centre each month.
Adverse Events

A case investigation is usually the first major action to be taken when an AEFI is reported and should begin without delay.

On the other hand, in some programmes for certain AEFls no further action is taken after they are reported. Illnesses known to have no causal relation to immunizations such as pneumonia after a DPT injection, are often treated this way. However, even in these cases, if parents or other members of the community are convinced that a medical event was caused by an immunization, they must be given the opportunity to discuss their concerns with health authorities.

Investigation (of an AEFI) should begin as soon as possible, ideally within 24 hours of detection by a health worker.

In most cases, a preliminary investigation can be made by the health worker who detected the case. If no further investigation is made, the health worker will complete a case investigation form and report to a supervisor. Serious AEFls or clusters should be investigated by specially trained health workers from the district or central level.

Following a non-serious AEFI, the health worker should monitor for clustering.
Under no circumstances should vaccine be sent for testing before the case investigation has been carried out. When an investigator does send vaccine, he or she must send a copy of the case investigation report with the sample and give clear instructions on what the vaccine should be tested for.

For example:

- In the case of an injection site abscess, a test must be performed to determine the sterility of the vaccine.
- In the case of a local, long-lasting reaction, a test must be performed to measure the amount of aluminium in the vaccine.
- In the case of a suspected cluster of reactions to a reconstituted vaccine, a test must be performed to identify the diluent.

Treatment must be the first response to an AEFI. Treatment suggestions for such mild symptoms are given in Immunization in Practice, (EPI/WHO), and other publications.

Communication with parents, health workers not involved in the investigation and other people in the community must take place no matter what the circumstances of the event. Rumours or public inquiries must be responded to. This is particularly important when public anxiety is high.

If the investigator tracks an error to one health worker, that health worker's immunization activities should be terminated immediately, at least until he or she masters the missing skill.
BCG

The (GACVS) concluded that the isolation and identification of a low level of isoniazid resistance of BCG strains from 5 patients presenting with lymphadenitis do not justify a change in standard policy.

Global Advisory Committee on Vaccine Safety, 9–10 June 2005

All immunization programmes should monitor at least the following AEFIs:

1. All injection site abscesses.
2. All cases of BCG lymphadenitis
3. All deaths that are thought by health workers, or the public, to be related to immunization.
4. All cases requiring hospitalization that are thought by health workers, or the public, to be related to immunization.
5. Other severe or unusual medical incidents that are thought by health workers, or the public, to be related to immunization.

With respect to the third, fourth, and fifth events, health workers may relate the event to immunization because it occurred within a month of an immunization, as its case definition indicates. However, some medical incidents can be related to immunization even if they have a delayed onset.

For mild problems, health workers should comfort and advise parents and treat the patient. It is not necessary to report these reactions, except for BCG lymphadenitis and injection site abscesses, unless parents’ concerns are significant.
In most cases, diphtheria toxoid is administered in fixed combination with other vaccines. For childhood vaccination, DTwP or DTaP is generally used, often in combination with other antigens administered at the same time, such as Haemophilus influenzae type b, poliomyelitis, and hepatitis B vaccines, in order to reduce the number of injections. This is a positive development as long as adverse events remain infrequent and the immunogenicity of the individual components is ensured.


(W)ith the increasing number of doses (of diphtheria toxoid) that are now recommended, reactogenicity is likely to increase. Although further purification of extraneous proteins residing in the toxoid may help to ameliorate this problem, optimal future diphtheria vaccines should provide protection of longer duration, with fewer injections.


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Adverse Events

At its December 2003 meeting, GACVS commissioned a special task force, independent of the Committee, to review the evidence for a deleterious effect (if any) of DTP vaccination on child survival.

Advised by the report of the task force, GACVS decided to regard the issue of a deleterious effect on childhood survival of DTP vaccination as not supported by the evidence and to set the matter aside unless new and persuasive evidence were to emerge in the future.

Global Advisory Committee on Vaccine Safety, 10–11 June 2004

SAGE commends the work of GACVS in carefully examining the evidence on the nonspecific effects of vaccines on mortality, and endorses the conclusion reached by GACVS that on the evidence currently available an association between DTP and increased mortality has not been demonstrated.


A case investigation is usually the first major action to be taken when an AEFI is reported and should begin without delay.

On the other hand, in some programmes for certain AEFIs no further action is taken after they are reported. Illnesses known to have no causal relation to immunizations such as pneumonia after a DPT injection, are often treated this way. However, even in these cases, if parents or other members of the community are convinced that a medical event was caused by an immunization, they must be given the opportunity to discuss their concerns with health authorities.

Surveillance of Adverse Events Following Immunization

Hepatitis B

GACVS considered the possible association between hepatitis B vaccination and chronic fatigue syndrome and concluded that, based on the evidence available, there are no grounds to support the association.

Global Advisory Committee on Vaccine Safety, 1–2 December 2005

14 February 2008
**Adverse Events**

(Following hepatitis B vaccination,) reports of severe anaphylactic reactions are very rare. Available data do not indicate a causal association between hepatitis B vaccine and Guillain-Barré syndrome, or demyelinating disorders including multiple sclerosis, nor is there any epidemiological data to support a causal association between hepatitis B vaccination and chronic fatigue syndrome, arthritis, autoimmune disorders, asthma, sudden infant death syndrome, or diabetes.

*Hepatitis B vaccines (WHO position paper)*

All serious adverse events (suspected by health workers or the public to be associated with hepatitis B immunization) should be reported to the district health authorities and then to national immunization staff in the health ministry of the country in question.

*Introduction of hepatitis B vaccine into childhood immunization services. Management guidelines, including information for health workers and parents* WHO/V&B/01.31

**Influenza**

During some influenza seasons, TIVs (trivalent, inactivated influenza vaccines) have been associated with a slight increase in the risk of Guillain-Barré syndrome in older adults (about 1 case added to the background incidence of about 20 cases per million vaccine recipients). A virosomal intranasal formulation of TIV was withdrawn from the market because of an association with an increased incidence of facial palsy. A sporadic, self-limiting oculorespiratory syndrome has been reported following TIV immunization, especially in relation with the use of a particular vaccine product in Canada. This excess risk was corrected through a modification of the manufacturing process. Except for anaphylactic allergic reactions to egg or other components of the vaccines, there are no contraindications to the use of these vaccines in age groups >6 months.

*Influenza vaccines (WHO position paper)*

**14 February 2008**
Adverse Events

In terms of protective efficacy, the live influenza vaccines appear to be comparable with the TIVs (trivalent, inactivated influenza vaccines.) However, CAIV-T (cold-adapted influenza vaccine) is licensed only for healthy people aged 5-49 years, given reports of an increase in reactive airway disease in vaccinees <5 years of age and insufficiently documented protective efficacy in older people.

*Influenza vaccines (WHO position paper)*

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JE

Both the mouse-brain derived and the cell culture-based vaccines are considered efficacious and to have an acceptable safety profile for use in children. However, with the mouse-brain derived vaccine, rare cases of potentially fatal acute disseminated encephalomyelitis (ADEM) and hypersensitivity reactions have been reported among vaccinated children in endemic regions and in travellers from non-endemic locations. Because of the rarity of these adverse events, and the high benefit-to-risk ratio of routine vaccination, the introduction of immunization against JE in public health programmes should not be deferred (page 332.)

The three types of JE vaccines that are currently in large-scale use are considered efficacious and acceptably safe for use in children. However, following immunization with the mouse brain-derived vaccine, rare cases of potentially fatal ADEM and hypersensitivity reactions have been reported among children in endemic regions and in travellers from non-endemic locations. An increased awareness of these specific adverse events is recommended, for example when assessing the actual risk of JE for the individual traveller. However, because of the rarity of these adverse events, and the greater benefit to risk ratio of routine vaccination, the introduction of immunization against JE in public health programmes should not be deferred (page 339.)

*Japanese encephalitis vaccines (WHO position paper)*

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The cell culture-based, live attenuated (JE) vaccine appears to require fewer doses for longterm protection, is in most cases less expensive, and seems to represent an attractive alternative to the mouse brain-derived vaccine. However, more needs to be known on its safety and efficacy when used in immunodeficient people, as well as on the impact of co-administrating this vaccine with other vaccines (page 332.)

The live attenuated vaccine induces protection for several years after 1 or 2 doses, whereas durable protection by the mouse brain-derived vaccine may require 2-3 initial doses followed by boosters at intervals of approximately 3 years. As the price per dose of the mouse brain-derived vaccine in most countries is higher than that of the live attenuated vaccine, the need for repeated doses renders the former vaccine unaffordable in many JE-endemic countries (page 339)
Adverse Events

All manufacturers of JE vaccines should comply with the international standards for Good Manufacturing Practices and meet the WHO requirements for production and quality control.

Whether locally produced or purchased from outside the country, the safety and immunogenicity of the vaccine must be assessed by independent national control authorities before it may be approved for use (page 332.)

The rare, but potentially dangerous, adverse events associated with this (mouse brain-derived JE) vaccine make strict attention to current international quality requirements crucial for its continued production. Whether locally produced or purchased from outside the country, the safety and immunogenicity of the vaccine must be assessed by independent national control authorities before it may be approved for use (page 340.)

In general, the mouse brain-derived JE vaccine has been considered safe, although local reactions such as tenderness, redness and swelling occur in about 20% of vaccinated subjects. A similar percentage of vaccines may experience mild systemic symptoms, including headache, myalgia, gastrointestinal symptoms and fever. Acute disseminated encephalomyelitis (ADEM) temporally coinciding with JE immunization using the mouse brain-derived vaccine has been reported at frequencies corresponding to 1 case per 50 000-1 000 000 doses administered, but no definitive studies are available. Based on observations of a case of ADEM temporarily associated with JE vaccination, the recommendation for routine childhood JE vaccination has been withdrawn in Japan. However, the Global Advisory Committee on Vaccine Safety* concluded recently that there was no definite evidence of an increased risk of ADEM temporally associated with JE vaccination and that there was no good reason to change current recommendations for immunization with JE vaccines.

* See No. 28, 2005, pp. 242-247.
Adverse Events

Occasionally (with mouse brain-derived JE vaccine,) hypersensitivity reactions, in some cases serious generalized urticaria, facial angio-oedema or respiratory distress, have been reported, principally in vaccine recipients from non-endemic areas. The reported rates of such reactions in prospective and retrospective studies are usually in the range of 18-64 per 10 000 vaccinated subjects. A complicating factor is that such reactions may occur as late as 12-72 hours following immunization. Sensitization to gelatine, a vaccine stabilizer, has been suspected in some cases in Japan, but the underlying cause remains uncertain.

The only contraindication to the use of this vaccine is a history of hypersensitivity reactions to a previous dose. However, pregnant women should be vaccinated only when at high risk of exposure to the infection. Mouse brain-derived vaccine has been given safely in various states of immunodeficiency, including HIV infection.

Neither hypersensitivity reactions nor acute encephalitis have been associated with this (cell culture-derived, live attenuated JE) vaccine. However, for immunization of pregnant women or immunodeficient individuals, the live attenuated vaccine should be replaced by one of the inactivated JE vaccines until further evidence has been generated.

The JE vaccine may cause severe delayed allergic reactions. Because of this, use of the vaccine requires careful evaluation of risks and benefits. Patients must be advised to be near a health facility for ten days after receiving the vaccine.
**Adverse Events**

### Measles

The (GACVS) Committee reviewed the purported relationship between measles immunization and the occurrence of SSPE.

Available epidemiological data are consistent with a directly protective effect of vaccine against SSPE mediated by preventing measles.

Available epidemiological data, in line with virus genotyping data, do not suggest that measles vaccine virus can cause SSPE. Furthermore, epidemiological data do not suggest that the administration of measles vaccine can accelerate the course of SSPE or trigger SSPE in an individual who would have developed the disease at a later time without immunization. Neither can the vaccine lead to the development of SSPE where it would not otherwise have occurred in a person who has already a benign persistent wild measles infection at the time of vaccination.

*Global Advisory Committee on Vaccine Safety, 1–2 December 2005*

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**Database ID** 75_5  
**Year** 2006

Several carefully conducted studies have been unable to confirm preliminary reports alleging an association between receipt of live attenuated measles vaccine or MMR and the occurrence of autism or chronic bowel inflammation.

*Measles vaccines (WHO position paper)*

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**Database ID** 58_3  
**Year** 2004

Parents should be given advance notice of the chance of ‘mild measles’ 6-12 days after immunization.

*Mass measles immunization campaigns: Reporting and investigating adverse events following immunization*
Adverse Events

To avoid programme errors (involving measles vaccine):
• careful epidemiological investigation of an AEFI is needed to pinpoint the cause and to correct immunization practices.

Even if a national programme has not yet developed a functioning adverse events surveillance system, some form of adverse event monitoring is essential in mass (measles) campaigns. The surveillance should be simple, flexible and rapid.
A list of reportable events is suggested in Appendix 42_5; countries with limited reporting capacity should decide which of these events should be reported during a campaign.

The reported AEFI (following mass measles immunization campaign) must be investigated if it:
• may have been caused by programme error
• is a serious event requiring hospitalization or resulting in death
• is a serious event of unexplained cause
• is causing significant parental or community concern
Certain events (toxic shock syndrome, sepsis, and abscess) are likely to arise from programme errors (and may result in clusters) and must always be investigated so the appropriate corrective action can be taken.

When an (AEFI) investigation is deemed necessary, it is important to initiate it urgently so that the cause may be determined (where possible) and additional cases prevented, in order to avoid compromising the rest of the (measles immunization) campaign as a result of ongoing community concern.
A working hypothesis should be established as soon as there is sufficient information. The working hypothesis may change during the course of the investigation. The focus of the investigation should then be to seek to confirm the working hypothesis. No action should be taken based on the hypothesis, until it is confirmed with reasonable certainty. Laboratory testing may sometimes confirm or rule out the suspected cause: the vaccine and diluent may be tested for sterility and chemical composition; and the needles and syringe for sterility. Testing should be requested on a clear suspicion and not as routine, and never before the working hypothesis has been formulated.
Adverse Events

Appropriate actions to protect the community should be taken throughout the (AEFI) investigation. Upon completion of the investigation, the cause of the event(s) needs to be communicated to the community. This must include information about the steps being taken to remedy the situation and to prevent a recurrence, if such steps are needed. If the cause is identified as a programme error, it is vital not to lay personal blame on anyone, but to focus on system-related problems which resulted in the programme error(s) and steps being taken to correct the problem. It is never appropriate to discontinue the immunization programme while awaiting the completion of the investigation.

Mass measles immunization campaigns: Reporting and investigating adverse events following immunization

The AEFI surveillance system should be evaluated at the end of the campaign to determine its effectiveness. The criteria for this evaluation should include:
• timeliness, completeness and accuracy of AEFI reporting;
• timeliness and completeness of investigation;
• audit of corrective action.
In a newly introduced surveillance system, if no AEFI cases are reported (e.g., in a particular district), efforts should be made through interviews with supervisory staff to identify possible obstacles to reporting.
The AEFI data should be analysed and included in the campaign report.

Mass measles immunization campaigns: Reporting and investigating adverse events following immunization

Meningococcal

Although several cases of Guillain–Barré Syndrome (GBS) were recently reported in the United States following the introduction of a tetravalent conjugated meningococcal vaccine, the number of cases reported was similar to what would normally have been expected in this population. The GACVS recommended no change in vaccination policies based on these reports.

Global Advisory Committee on Vaccine Safety, 1–2 December 2005

Adverse Events

MMR

Several carefully conducted studies have been unable to confirm preliminary reports alleging an association between receipt of live attenuated measles vaccine or MMR and the occurrence of autism or chronic bowel inflammation.

Measles vaccines (WHO position paper)

Global Advisory Committee on Vaccine Safety, 3–4 December 2003

Mumps

The available data suggest that vaccines using certain strains may have higher rates of aseptic meningitis, which should be considered when deciding on the introduction of mumps vaccine and selecting specific vaccines. A recent meeting on mumps vaccines (2) recommended that WHO should continue to compile and analyse available data on adverse events related to the use of mumps vaccines. Nevertheless, the meeting concluded that in terms of safety, all available mumps vaccine preparations are acceptable for use in immunization programmes.

Mumps virus vaccines (WHO position paper)

Adverse Events

Countries planning to use mumps vaccine during mass campaigns should give special attention to planning, including critical review of the mumps vaccine strain selected, provision of guidelines for monitoring, investigation and management of AEFIs (which tend to be more noticeable in a campaign setting), and training of health workers on expected rates of AEFIs, as well as community advocacy and health education.


Pentavalent and Hexavalent

GACVS concluded that (available) data are inconsistent with any association between hexavalent (diphtheria, tetanus, acellular pertussis, Haemophilus influenzae type b, poliovirus and hepatitis B (DTaP-Hib-IPV-HepB combination)) vaccines and SID (sudden infant death) or SUD (sudden unexplained death.)


Pertussis

While in terms of severe adverse events, aP (acellular pertussis) and wP (whole cell pertussis) vaccines appear to have the same high level of safety, mild to moderate adverse reactions are more commonly associated with wP vaccine; wP vaccines are not recommended for use in adolescents and adults.


14 February 2008
Adverse Events

Rotavirus

GACVS was asked to consider whether the use of tetravalent rhesus reassortant rotavirus vaccine (commercially known as RotaShield®) might be associated with a significantly lower risk of vaccine-induced intussusception if immunization is completed before 2 months of age.

The Committee concluded as follows:
1. The studies provide clarification and confirmation of a high risk of RotaShield®-associated intussusception in infants immunized after day 60.
2. The available evidence is not sufficient to conclude that the use of RotaShield® at an age less than 60 days is associated with a lower relative risk of intussusception.
3. Even strict recommendations for adherence to an early immunization schedule would be extremely difficult to implement in the field in many countries.

Yellow Fever

(With yellow fever vaccine,) if a serious reaction does occur, health workers should report the problem to supervisors immediately.

Adverse events following YF (yellow fever) vaccination are usually minor, although hypersensitivity to vaccine components may occasionally occur, and very rare case of viral encephalitis or multiple organ failures have been reported. The rare adverse events should not deter the appropriate use of this highly valuable vaccine.
**Adverse Events**

Improved surveillance and reporting of any potential adverse event following (yellow fever) vaccination is recommended in order to correct any programmatic errors that may be involved and to facilitate improved understanding of the pathogenic mechanisms causing the recently described serious adverse events.

**Yellow fever vaccine (WHO position paper)**

When promoting increased use of YF (yellow fever) vaccine in at risk areas, the outstanding safety and effectiveness profile, the long duration of protection and the cost effectiveness of the 17D vaccine should continue to be emphasized. However, recent reports of severe, but very rare, vaccine-associated adverse events highlight the importance of careful post-licensure surveillance, even for well established vaccines. Enhanced surveillance of such events and careful molecular analyses of the 17D strains isolated from potential new cases as well as from the actual vaccine batches should contribute to the understanding of the pathogenetic mechanisms involved.

**Yellow fever vaccine (WHO position paper)**

The issue of deaths following YF (yellow fever) vaccination was highly sensitive where few YF cases exist, and vaccination should be postponed in such countries. WHO believed the vaccine to be safe but more data were necessary.