BCG

Surveillance of Adverse Events Following 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.

Surveillance of Adverse Events Following Immunization

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.

Global Advisory Committee on Vaccine Safety, 910 June 2005

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.

DPT

Surveillance of Adverse Events Following Immunization

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.
Global Advisory Committee on Vaccine Safety, 1011 June 2004

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.

Diphtheria vaccine (WHO position paper)

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.

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Diphtheria vaccine (WHO position paper)

(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.
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.

Although several cases of Guillain-Barr 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.

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.

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, 1011 June 2004

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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.

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The Committee considered the decision taken by the Government of Japan on 30 May 2005 to suspend routine vaccination with the mouse brain-derived Japanese encephalitis (JE) vaccine currently used in Japan (3).

GACVS was advised that there is no definite evidence of an increased risk of acute disseminated encephalomyelitis temporally associated with JE vaccine and a causal link has not been demonstrated.

The national authority recommends vaccination in high-risk areas only and for travel to endemic regions.

GACVS concluded, on the information presently available, that there is no good reason for WHO and national immunization programmes to change the current recommendations for JE vaccination for residents in and travellers to JE-endemic regions.


Global Advisory Committee on Vaccine Safety, 910 June 2005

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, 910 June 2005

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

Global Advisory Committee on Vaccine Safety, 910 June 2005

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.)
Global Advisory Committee on Vaccine Safety, 23 December 2004

(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.

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On the basis of all the available data, GACVS concluded that there is no evidence to support a causal association between the administration of hexavalent (DTaP-Hib-IPV-HepB) vaccines and SUD (sudden unexplained death.) In response to the potential signal observed in the second year of life, the Committee encouraged studies to be conducted that are designed to provide more powerful evidence on the presence or absence of an association.

Global Advisory Committee on Vaccine Safety, 34 December 2003

The attention of the Committee was drawn to the unavailability of a monovalent rubella vaccine in some countries and to the need to provide a rubella-containing combination vaccine to postpartum women seronegative for rubella. GACVS is not aware of any safety issues that would restrict the provision of a rubella-containing combination vaccine in place of single rubella vaccine in those circumstances.

Conclusions and recommendations from the meeting of the immunization Strategic Advisory Group of Experts (SAGE) - November 2006

The GACVS chairperson presented the major recommendations from the 6-7 June 2006 meeting:* Based on the evidence, GACVSs 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.
General

Surveillance of Adverse Events Following Immunization

All immunization programmes should monitor at least the following AEFIs:

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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.

Surveillance of Adverse Events Following Immunization

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.

Surveillance of Adverse Events Following Immunization

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.

Surveillance of Adverse Events Following Immunization

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.

Surveillance of Adverse Events Following Immunization

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

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 AEFIs or clusters should be investigated by specially trained health workers from the district or central level.

(Page 25) A serious AEFI (death or hospitalization) should be reported to the district manager immediately by the quickest means (e.g. telephone, fax). At the same time a case investigation form should be requested, completed and dispatched as soon as possible.

Surveillance of Adverse Events Following Immunization

Following a non-serious AEFI, the health worker should monitor for clustering.

Surveillance of Adverse Events Following Immunization

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.

Surveillance of Adverse Events Following Immunization

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.
Global Advisory Committee on Vaccine Safety, 12 December 2005

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.

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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.

Surveillance of Adverse Events Following Immunization

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.
Global Advisory Committee on Vaccine Safety, 1011 June 2004

(Regarding safety of adjuvants, GACVS) concluded that WHO will have an important role in facilitating dialogue between the scientific community, industry and regulatory agencies, and in establishing standards published in the Technical Report Series, to ensure a consistent regulatory approach in this complex area.

Adverse events attributable to adjuvants need to be documented and reviewed, and the information made available. That is another important role for WHO.

Since many of the new adjuvants are likely to be used in vaccines for conditions endemic in developing countries, scientists from those countries should be involved in these considerations. Systems for safety monitoring and the necessary training will be required.

Global Advisory Committee on Vaccine Safety, 1011 June 2004

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.

Hepatitis B vaccines (WHO position paper)

(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-Barr 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.

Influenza vaccines (WHO position paper)

During some influenza seasons, TIVs (trivalent, inactivated influenza vaccines) have been associated with a slight increase in the risk of Guillain-Barr 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.
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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.

Measles vaccines (WHO position paper)

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.

Yellow fever vaccine (WHO position paper)

Adverse events following YF (yellow fever) vaccination are usually minor, although hypersensitivity to vaccine components may occasionally occur, and very rare cases 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.

Yellow fever vaccine (WHO position paper)

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.
Diphtheria vaccine (WHO position paper)

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.

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The national authority recommends vaccination in high-risk areas only and for travel to endemic regions.

GACVS concluded, on the information presently available, that there is no good reason for WHO and national immunization programmes to change the current recommendations for JE vaccination for residents in and travellers to JE-endemic regions.


Global Advisory Committee on Vaccine Safety, 910 June 2005

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, 910 June 2005

GACVS proposed that WHO consider the need for improved monitoring and analysis of vaccine-related adverse events globally. The Committee suggested that WHO convene an in-depth consultation with a view to developing the current system further for detecting, reporting, analysing and communicating vaccine-related adverse events. The consultation would include international experts in drug safety, drug regulation and vaccine safety, including scientists from industry.
Global Advisory Committee on Vaccine Safety, 910 June 2005

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

Global Advisory Committee on Vaccine Safety, 910 June 2005

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.)

Global Advisory Committee on Vaccine Safety, 23 December 2004

Increasingly in the future there will be a need in developing countries for surveillance of vaccine adjuvant safety following vaccine registration. This applies not only to new vaccines but also to vaccines already available and used for new indications. GACVS will participate in developing such safety surveillance.

Global Advisory Committee on Vaccine Safety, 23 December 2004

(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.

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On the basis of all the available data, GACVS concluded that there is no evidence to support a causal association between the administration of hexavalent (DTaP-Hib-IPV-HepB) vaccines and SUD (sudden unexplained death.) In response to the potential signal observed in the second year of life, the Committee encouraged studies to be conducted that are designed to provide more powerful evidence on the presence or absence of an association.

Global Advisory Committee on Vaccine Safety, 34 December 2003

The attention of the Committee was drawn to the unavailability of a monovalent rubella vaccine in some countries and to the need to provide a rubella-containing combination vaccine to postpartum women seronegative for rubella. GACVS is not aware of any safety issues that would restrict the provision of a rubella-containing combination vaccine in place of single rubella vaccine in those circumstances.
Mass measles immunization campaigns: Reporting and investigating adverse events following immunization

An adverse event following immunization (AEFI) is any adverse event that follows immunization that is believed to be caused by the immunization.

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

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

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.

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

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

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.

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.

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.

Ensuring the quality of vaccines at country level: Guidelines for health staff

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.
Introduction of hepatitis B vaccine into childhood immunization services. Management guidelines, including information for health workers and parents

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.

'First, do no harm' Introducing auto-disable syringes and ensuring injection safety in immunization systems of developing countries

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.

Mumps virus vaccines (WHO position paper)

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.

(2) Global meeting on mumps vaccine and immunization policy, Geneva, 24-25 May 2001.

Mumps virus vaccines (WHO position paper)

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.

WHO-UNICEF effective vaccine store management initiative: Modules 1 - 4

Responsible staff must ensure that . . . all adverse events following immunization (AEFI) are monitored by an effective field performance surveillance system.
Conclusions and recommendations from the meeting of the immunization Strategic Advisory Group of Experts (SAGE) - November 2006

The GACVS chairperson presented the major recommendations from the 6-7 June 2006 meeting:

Based on the evidence, GACVSs 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.

Pneumococcal conjugate vaccine for childhood immunization (WHO position paper)

PCV-7 has been tested in trials in different parts of the world and has been proven to be safe and well tolerated even among children infected with HIV.

However, slight swelling and tenderness at the injection site may occur and transient fever of =39°C has been reported in up to 4.7%. The incidence and severity of adverse reactions have not been reported to increase with subsequent doses.

As with the introduction of any new vaccine, however, continued surveillance for possible unexpected effects is important.

(Page 103) The safety and efficacy of PCV-7, as well as of other formulations of pneumococcal conjugate vaccines, have been well established in numerous settings both in industrialized and developing countries, and among infants with HIV infection

Surveillance of Adverse Events Following Immunization

WHO encourages a mutually trusting relationship where peripheral health workers feel confident they can report such incidents (adverse events) to their supervisors, and the supervisors will support them in correcting any programme error which might be contributing to the incidents.
HIV/AIDS and immunosuppression

**Pneumococcal conjugate vaccine for childhood immunization (WHO position paper)**

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**Hepatitis B**

**Global Advisory Committee on Vaccine Safety, 12 December 2005**

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.

**Hepatitis B vaccines (WHO position paper)**

(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-Barr 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.

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

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Influenza

Influenza vaccines (WHO position paper)

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JE

Global Advisory Committee on Vaccine Safety, 910 June 2005

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GACVS was advised that there is no definite evidence of an increased risk of acute disseminated encephalomyelitis temporally associated with JE vaccine and a causal link has not been demonstrated.

The national authority recommends vaccination in high-risk areas only and for travel to endemic regions.

GACVS concluded, on the information presently available, that there is no good reason for WHO and national immunization programmes to change the current recommendations for JE vaccination for residents in and travellers to JE-endemic regions.

### MMR

#### Measles vaccines (WHO position paper)

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#### Global Advisory Committee on Vaccine Safety, 34 December 2003

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### Measles

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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.

#### Measles vaccines (WHO position paper)

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.

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

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

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

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.

Meningococcal

Global Advisory Committee on Vaccine Safety, 12 December 2005

Although several cases of GuillainBarr 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.
Mumps

Mumps virus vaccines (WHO position paper)

(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.

(2) Global meeting on mumps vaccine and immunization policy, Geneva, 24-25 May 2001.

Mumps virus vaccines (WHO position paper)

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

Global Advisory Committee on Vaccine Safety, 910 June 2005

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).

Global Advisory Committee on Vaccine Safety, 23 December 2004

On the basis of all the available data, GACVS concluded that there is no evidence to support a causal association between the administration of hexavalent (DTaP-Hib-IPV-HepB) vaccines and SUD (sudden unexplained death.) In response to the potential signal observed in the second year of life, the Committee encouraged studies to be conducted that are designed to provide more powerful evidence on the presence or absence of an association.
Policy

Surveillance of Adverse Events Following 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.

Surveillance of Adverse Events Following Immunization

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.

Surveillance of Adverse Events Following Immunization

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.

Surveillance of Adverse Events Following Immunization

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.

Surveillance of Adverse Events Following Immunization

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

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 AEFIs or clusters should be investigated by specially trained health workers from the district or central level.

(Page 25) A serious AEFI (death or hospitalization) should be reported to the district manager immediately by the quickest means (e.g. telephone, fax). At the same time a case investigation form should be requested, completed and dispatched as soon as possible.

Surveillance of Adverse Events Following Immunization

Following a non-serious AEFI, the health worker should monitor for clustering.

Surveillance of Adverse Events Following Immunization

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.

Surveillance of Adverse Events Following Immunization

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.

Surveillance of Adverse Events Following Immunization

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.
Hepatitis B vaccines (WHO position paper)

(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-Barr 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.

Influenza vaccines (WHO position paper)

During some influenza seasons, TIVs (trivalent, inactivated influenza vaccines) have been associated with a slight increase in the risk of Guillain-Barr 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 oculo-respiratory 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)

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.

Measles vaccines (WHO position paper)

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.

Yellow fever vaccine (WHO position paper)

Adverse events following YF (yellow fever) vaccination are usually minor, although hypersensitivity to vaccine components may occasionally occur, and very rare cases 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.
**Yellow fever vaccine (WHO position paper)**

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.

**Diphtheria vaccine (WHO position paper)**

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.

**Diphtheria vaccine (WHO position paper)**

(With 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.

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

An adverse event following immunization (AEFI) is any adverse event that follows immunization that is believed to be caused by the immunization.

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

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

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.

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The reported AEFI (following mass measles immunization campaign) must be investigated if it:
- may have been caused by programme error
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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.

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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.
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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.

Ensuring the quality of vaccines at country level: Guidelines for health staff

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.

Introduction of hepatitis B vaccine into childhood immunization services. Management guidelines, including information for health workers and parents

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.
'First, do no harm’ Introducing auto-disable syringes and ensuring injection safety in immunization systems of developing countries

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.

Mumps virus vaccines (WHO position paper)

(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.

(2) Global meeting on mumps vaccine and immunization policy, Geneva, 24-25 May 2001.

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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.

WHO-UNICEF effective vaccine store management initiative: Modules 1 - 4

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

Surveillance of Adverse Events Following Immunization

WHO encourages a mutually trusting relationship where peripheral health workers feel confident they can report such incidents (adverse events) to their supervisors, and the supervisors will support them in correcting any programme error which might be contributing to the incidents.
Program Management

Mumps virus vaccines (WHO position paper)

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.

Research

Diphtheria vaccine (WHO position paper)

With 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.

Global Advisory Committee on Vaccine Safety, 23 December 2004

On the basis of all the available data, GACVS concluded that there is no evidence to support a causal association between the administration of hexavalent (DTaP-Hib-IPV-HepB) vaccines and SUD (sudden unexplained death.) In response to the potential signal observed in the second year of life, the Committee encouraged studies to be conducted that are designed to provide more powerful evidence on the presence or absence of an association.

Global Advisory Committee on Vaccine Safety, 12 December 2005

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.
Global Advisory Committee on Vaccine Safety, 1011 June 2004

(Regarding safety of adjuvants, GACVS) concluded that WHO will have an important role in facilitating dialogue between the scientific community, industry and regulatory agencies, and in establishing standards published in the Technical Report Series, to ensure a consistent regulatory approach in this complex area.

Adverse events attributable to adjuvants need to be documented and reviewed, and the information made available. That is another important role for WHO.

Since many of the new adjuvants are likely to be used in vaccines for conditions endemic in developing countries, scientists from those countries should be involved in these considerations. Systems for safety monitoring and the necessary training will be required.

Global Advisory Committee on Vaccine Safety, 910 June 2005

GACVS proposed that WHO consider the need for improved monitoring and analysis of vaccine-related adverse events globally. The Committee suggested that WHO convene an in-depth consultation with a view to developing the current system further for detecting, reporting, analysing and communicating vaccine-related adverse events. The consultation would include international experts in drug safety, drug regulation and vaccine safety, including scientists from industry.

Global Advisory Committee on Vaccine Safety, 23 December 2004

Increasingly in the future there will be a need in developing countries for surveillance of vaccine adjuvant safety following vaccine registration. This applies not only to new vaccines but also to vaccines already available and used for new indications. GACVS will participate in developing such safety surveillance.

Schedule

Influenza vaccines (WHO position paper)

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.
Travellers

Global Advisory Committee on Vaccine Safety, 910 June 2005

The Committee considered the decision taken by the Government of Japan on 30 May 2005 to suspend routine vaccination with the mouse brain-derived Japanese encephalitis (JE) vaccine currently used in Japan (3).

GACVS was advised that there is no definite evidence of an increased risk of acute disseminated encephalomyelitis temporally associated with JE vaccine and a causal link has not been demonstrated.

The national authority recommends vaccination in high-risk areas only and for travel to endemic regions.

GACVS concluded, on the information presently available, that there is no good reason for WHO and national immunization programmes to change the current recommendations for JE vaccination for residents in and travellers to JE-endemic regions.


VPD Surveillance

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.

Vaccine Administration

Diphtheria vaccine (WHO position paper)

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Yellow Fever

Yellow fever vaccine (WHO position paper)

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Yellow fever vaccine (WHO position paper)

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