
Adverse Event

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 A virosomal intranasal formulation of TIV was withdrawn from the market because of an association with an increased incidence of facial palsy.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.

[WER 2005, vol. 80, 36, pp 279-287](#)
page 284

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.

[WER 2005, vol. 80, 36, pp 279-287](#)
page 285

Contraindications

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Except for anaphylactic allergic reactions to egg or other components of the (trivalent, inactivated influenza) vaccines, there are no contraindications to the use of these vaccines in age groups >6 months.

[WER 2005, vol. 80, 36, pp 279-287](#)
page 284

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Following nasal administration, (t)ransmission of the (influenza) vaccine virus to exposed non-immune people appears to be very rare. However, as a precaution the vaccine should not be given to highly immunosuppressed individuals or their close contacts.

[WER 2005, vol. 80, 36, pp 279-287](#)
page 285

Contraindications for use (of CAIV-T influenza vaccine) include anaphylactic reactions to eggs, a history of Guillain-Barr syndrome, patients aged <18 years on long-term aspirin therapy, pregnancy during the first trimester, and various states of immunosuppression.

Influenza vaccines (WHO position paper)

(Inactivated) influenza vaccination in pregnancy is considered safe and is recommended for all pregnant women during the influenza season. This recommendation is motivated not only by the potential severe course of influenza during pregnancy, but also in order to protect infants against influenza during their vulnerable first months of life.

[WER 2005, vol. 80, 36, pp 279-287](#)
page 286

General

Global Advisory Committee on Vaccine Safety, 12 December 2005

[WER 2006, vol. 81, 2, pp 15-19](#)
page 16

WHO is promoting vaccination strategies that economize on the use of antigens to address the current global shortage of influenza vaccines for epidemics and pandemics. That would entail development and licensing of novel antigen-sparing vaccine formulations.

The GACVS agreed to act as a resource for WHO if such a situation were to arise. The Committee made the following recommendations: develop pharmacovigilance guidelines to enable rapid assessment of pandemic influenza vaccines; promote the extension of such guidelines to evaluate seasonal influenza vaccines; develop an authoritative review of the safety and efficacy of inactivated influenza vaccines with adjuvants. It would be assured that regulators from developing countries are included in WHO meetings to promote regulatory collaboration on pandemic influenza vaccine issues and that lessons from the past, such as those from swine influenza vaccine, are taken into account.

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[WER 2005, vol. 80, 36, pp 279-287](#)
page 286

Based on data from industrialized countries, and listed in order of priority, the following groups of individuals may be targeted for vaccination (against influenza) in order to reduce the incidence of severe illness and premature death.

1. Residents of long-term care facilities for elderly people and the disabled.
2. Elderly non-institutionalized individuals with chronic conditions such as pulmonary and cardiovascular illness, metabolic diseases including diabetes mellitus and renal dysfunction, and various types of immunosuppression, including people with acquired immunodeficiency syndrome (AIDS) and transplant recipients.
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Influenza vaccines (WHO position paper)

[WER 2005, vol. 80, 36, pp 279-287](#)
page 280

WHO encourages initiatives to raise awareness of influenza and influenza vaccination among healthcare workers and the public, including definition of national targets for immunization programmes.

WHO strongly emphasizes the importance of raising the public consciousness of influenza and its complications as well as of the beneficial effects of influenza vaccination. (page 287)

Influenza vaccines (WHO position paper)

[WER 2005, vol. 80, 36, pp 279-287](#)
page 280

Improved coverage of WHO's Global Influenza Surveillance Network should be achieved to obtain better information on the epidemiology of influenza A and B.

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[WER 2005, vol. 80, 36, pp 279-287](#)
page 284

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[WER 2005, vol. 80, 36, pp 279-287](#)
page 284

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[WER 2005, vol. 80, 36, pp 279-287](#)
page 285

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[WER 2005, vol. 80, 36, pp 279-287](#)
page 285

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[WER 2005, vol. 80, 36, pp 279-287](#)
page 286

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Further exploration of the safety and cost-effectiveness of introducing influenza vaccination into national immunization programmes is clearly warranted

[WER 2005, vol. 80, 36, pp 279-287](#)
page 287

Conclusions and recommendations from the Strategic Advisory Group of Experts (SAGE) - 9-11 November 2005

SAGE recommended that . . . (a)ll countries should develop pandemic preparedness plans that include strategies for the deployment of vaccines when these become available. SAGE stressed that countries must not depend solely on vaccines for pandemic control because lack of vaccine or at best shortage will be a reality in most countries.

[WER 2006, vol. 81, 1, pp 2-11](#)
page 6

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[WER 2006, vol. 81, 1, pp 2-11](#)
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SAGE recommended that WHO should provide support to developing countries for the development of national, seasonal and pandemic influenza vaccination policies. All countries should develop pandemic preparedness plans that include strategies for the deployment of vaccines when these become available. SAGE stressed that countries must not depend solely on vaccines for pandemic control because lack of vaccine or at best shortage will be a reality in most countries. With the goal of facilitating equitable and timely access, WHO should continue to play a role in advising on priority groups for immunization with pandemic vaccine (http://www.who.int/csr/resources/publications/influenza/WHO_CDS_CSR_RMD_2004_8/en/index.html).

WHO should provide advice for enhanced surveillance for early detection of new influenza strains and of the onset of a pandemic, if it occurs. WHO should pursue its efforts in strengthening the capability in developing countries of health ministries and national regulatory authorities to facilitate the movement of samples and to ensure prompt registration of pandemic vaccines. Global regulatory convergence should be considered, and WHO should facilitate progress in this direction.

WHO should support research and development for pandemic and seasonal vaccines, including alternative and more effective methods of vaccine delivery such as intradermal and intranasal vaccination, improved vaccines and novel production technologies. SAGE noted that there is currently no influenza vaccine production capacity in the African region. Where appropriate, WHO should facilitate developing countries in establishing local capacity for production of influenza vaccine (including pandemic vaccine) based on manufacturers of vaccines of assured quality and should provide support for relevant technology transfer.

WHO should collaborate with expert groups to model the impact of different vaccination strategies in pandemic control, including the possibility of strategic deployment of vaccines, under various epidemiological settings. The risks and benefits of diverting some current vaccine production facilities to the production of influenza vaccines should be investigated. This should be taken forward urgently by WHO as it may provide a means of expanding vaccine production capacity more effectively than reliance on increasing use of seasonal influenza vaccination. The possible negative impacts on supplies of other vaccines should be considered.

WHO should ensure that the expertise in rapid mobilization for mass immunization is included in influenza preparedness planning. In addition, similar considerations should be given to access and distribution of antiviral medication.

Temperature sensitivity of vaccines

[WHO/IVB/06.10](#)
page 36

Live attenuated influenza vaccines have been used for several decades in Russia and have recently been developed in the USA, for intranasal application.

It must be stored frozen (-15oC to -25oC), and thawed for up to 60 hours at +2oC to +8oC before use, but it should not be refrozen. Because temperature cycling could affect product stability, it should be stored in a frost-free freezer. A refrigerator stable formulation (to be kept at +2oC to +8oC) is in development.

Influenza vaccines (WHO position paper)

In 2003, the World Health Assembly urged Member States with influenza vaccination policies to increase vaccination coverage of all people at high risk and to aim at vaccination coverage of elderly people of at least 50% by 2006 and 75% by 2010.

[WER 2005, vol. 80, 36, pp 279-287](#)
page 280

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Furthermore, studies are strongly encouraged to characterize risk factors and the impact of influenza in resource-limited countries. Studies to evaluate the effectiveness of vaccines in such populations are recommended.

[WER 2005, vol. 80, 36, pp 279-287](#)
page 280

Conclusions and recommendations from the Strategic Advisory Group of Experts (SAGE) - 10-11 April 2006

(Regarding pandemic influenza vaccine, more) research is therefore needed in 4 major areas: correlates for protection, novel adjuvants, whole virion vaccines, and immunogenicity and growth of vaccine strains.

[WER 2006, vol. 81, 21, pp 210-220](#)
page 218

Conclusions and recommendations from the Strategic Advisory Group of Experts (SAGE) - 10-11 April 2006

SAGE supported the efforts of WHO to scale up activities relating to influenza pandemic vaccine development, evaluation and capacity building, and the monitoring of seasonal influenza vaccine supply and uptake.

[WER 2006, vol. 81, 21, pp 210-220](#)
page 218

Conclusions and recommendations from the Strategic Advisory Group of Experts (SAGE) - 10-11 April 2006

SAGE recognized the critical role that WHO should play in the international coordination of research and evaluation of influenza pandemic vaccines.

[WER 2006, vol. 81, 21, pp 210-220](#)
page 218

Conclusions and recommendations from the Strategic Advisory Group of Experts (SAGE) - 10-11 April 2006

(Regarding influenza vaccine development,) SAGE encouraged manufacturers and national regulatory authorities to strengthen mechanisms to rapidly share the results of clinical trials with the global community.

SAGE stressed the importance of investigating the use of pandemic vaccines to prime populations against H5N1 viruses and to anticipate the regulatory and other criteria relevant to their use;

[WER 2006, vol. 81, 21, pp 210-220](#)
page 218

Conclusions and recommendations from the Strategic Advisory Group of Experts (SAGE) - 10-11 April 2006

SAGE encouraged all countries to consider their preparedness for a potential influenza pandemic, recognizing that it would occur before strain-specific vaccine can be made in significant quantities.

[WER 2006, vol. 81, 21, pp 210-220](#)
page 218

State of the art of new vaccines: research and development

[WHO/IVB/06.01](#)

page 18

A trivalent live cold-adapted vaccine (Flumist) has been developed for intranasal spray delivery . . .

The vaccine has been licensed in the USA for vaccination of persons from 5-49 years of age, in view of side effects in younger children (wheezing, nasal congestion) and absence of data in the elderly. The vaccine is safe, effective, and shows remarkable genetic stability, but it has to be kept at -18C.

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

[WER 2006, vol. 82, 1, pp 1-16](#)

page 6

WHO's global action plan identifies 3 main approaches that may be used to increase the capacity for producing pandemic influenza vaccines. These are: increase seasonal vaccine uptake to stimulate market forces and increase production capacity, increase or establish production capacity for pandemic vaccines in industrialized and developing countries independent of the demand for seasonal influenza vaccine, and implement research and development of vaccines based on new technologies.

WHO has developed procedures to facilitate the rapid transfer of strains and the release of sequence information and details of the procedures could be found on WHO's web site (http://www.who.int/csr/disease/avian_influenza/guidelines/h5n1sequences2006_08_23/en/index.html).

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[WER 2006, vol. 82, 1, pp 1-16](#)

page 6

SAGE recommends that while influenza vaccine research has considerable momentum, investigation into the development of vaccines against subtypes with pandemic potential other than H5N1 should continue (for example, H7).

So far, mainly healthy adults have been enrolled in clinical trials with H5N1 candidate vaccines. SAGE stresses the importance of evaluating their safety and immunogenicity in children and immunosuppressed individuals.

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[WER 2006, vol. 82, 1, pp 1-16](#)

page 6

WHO should ensure that there is unrestricted sharing of samples and vaccine strains internationally.

HIV/AIDS and immunosuppression

Influenza vaccines (WHO position paper)

[WER 2005, vol. 80, 36, pp 279-287](#)
page 286

Based on data from industrialized countries, and listed in order of priority, the following groups of individuals may be targeted for vaccination (against influenza) in order to reduce the incidence of severe illness and premature death.

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Influenza vaccines (WHO position paper)

[WER 2005, vol. 80, 36, pp 279-287](#)
page 285

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Immunization Coverage

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[WER 2005, vol. 80, 36, pp 279-287](#)
page 280

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Outbreak Control

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WER 2006, vol. 81, 1, pp 2-11
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Policy

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[WER 2005, vol. 80, 36, pp 279-287](#)
page 286

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[WER 2005, vol. 80, 36, pp 279-287](#)
page 280

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page 284

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[WER 2005, vol. 80, 36, pp 279-287](#)
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[WER 2005, vol. 80, 36, pp 279-287](#)
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[WER 2005, vol. 80, 36, pp 279-287](#)
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[WHO/IVB/06.10](#)
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State of the art of new vaccines: research and development

[WHO/IVB/06.01](#)
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Conclusions and recommendations from the meeting of the immunization Strategic Advisory Group of Experts (SAGE) - November 2006

[WER 2006, vol. 82, 1, pp 1-16](#)
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Pregnant Women

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[WER 2005, vol. 80, 36, pp 279-287](#)

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[WER 2005, vol. 80, 36, pp 279-287](#)

page 286

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Procurement

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[WER 2006, vol. 81, 21, pp 210-220](#)
page 218

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[WER 2006, vol. 82, 1, pp 1-16](#)
page 6

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Program Management

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[WER 2006, vol. 81, 21, pp 210-220](#)
page 218

SAGE encouraged all countries to consider their preparedness for a potential influenza pandemic, recognizing that it would occur before strain-specific vaccine can be made in significant quantities.

Research

Influenza vaccines (WHO position paper)

WHO strongly encourages the implementation of epidemiological surveillance, disease burden assessments and, where appropriate infrastructure is available, demonstration projects to estimate the impact of vaccination on disease in poor countries.

Further exploration of the safety and cost-effectiveness of introducing influenza vaccination into national immunization programmes is clearly warranted

[WER 2005, vol. 80, 36, pp 279-287](#)
page 287

Influenza vaccines (WHO position paper)

Furthermore, studies are strongly encouraged to characterize risk factors and the impact of influenza in resource-limited countries. Studies to evaluate the effectiveness of vaccines in such populations are recommended.

[WER 2005, vol. 80, 36, pp 279-287](#)
page 280

Conclusions and recommendations from the Strategic Advisory Group of Experts (SAGE) - 10-11 April 2006

(Regarding pandemic influenza vaccine, more) research is therefore needed in 4 major areas: correlates for protection, novel adjuvants, whole virion vaccines, and immunogenicity and growth of vaccine strains.

[WER 2006, vol. 81, 21, pp 210-220](#)
page 218

Conclusions and recommendations from the Strategic Advisory Group of Experts (SAGE) - 10-11 April 2006

SAGE recognized the critical role that WHO should play in the international coordination of research and evaluation of influenza pandemic vaccines.

[WER 2006, vol. 81, 21, pp 210-220](#)
page 218

Conclusions and recommendations from the Strategic Advisory Group of Experts (SAGE) - 10-11 April 2006

(Regarding influenza vaccine development,) SAGE encouraged manufacturers and national regulatory authorities to strengthen mechanisms to rapidly share the results of clinical trials with the global community.

SAGE stressed the importance of investigating the use of pandemic vaccines to prime populations against H5N1 viruses and to anticipate the regulatory and other criteria relevant to their use;

[WER 2006, vol. 81, 21, pp 210-220](#)
page 218

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

[WER 2006, vol. 82, 1, pp 1-16](#)
page 6

WHO's global action plan identifies 3 main approaches that may be used to increase the capacity for producing pandemic influenza vaccines. These are: increase seasonal vaccine uptake to stimulate market forces and increase production capacity, increase or establish production capacity for pandemic vaccines in industrialized and developing countries independent of the demand for seasonal influenza vaccine, and implement research and development of vaccines based on new technologies.

WHO has developed procedures to facilitate the rapid transfer of strains and the release of sequence information and details of the procedures could be found on WHO's web site (http://www.who.int/csr/disease/avian_influenza/guidelines/h5n1sequences2006_08_23/en/index.html).

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

[WER 2006, vol. 82, 1, pp 1-16](#)
page 6

SAGE recommends that while influenza vaccine research has considerable momentum, investigation into the development of vaccines against subtypes with pandemic potential other than H5N1 should continue (for example, H7).

So far, mainly healthy adults have been enrolled in clinical trials with H5N1 candidate vaccines. SAGE stresses the importance of evaluating their safety and immunogenicity in children and immunosuppressed individuals.

SAGE

Global Advisory Committee on Vaccine Safety, 12 December 2005

[WER 2006, vol. 81, 2, pp 15-19](#)
page 16

WHO is promoting vaccination strategies that economize on the use of antigens to address the current global shortage of influenza vaccines for epidemics and pandemics. That would entail development and licensing of novel antigen-sparing vaccine formulations.

The GACVS agreed to act as a resource for WHO if such a situation were to arise. The Committee made the following recommendations: develop pharmacovigilance guidelines to enable rapid assessment of pandemic influenza vaccines; promote the extension of such guidelines to evaluate seasonal influenza vaccines; develop an authoritative review of the safety and efficacy of inactivated influenza vaccines with adjuvants. It would be assured that regulators from developing countries are included in WHO meetings to promote regulatory collaboration on pandemic influenza vaccine issues and that lessons from the past, such as those from swine influenza vaccine, are taken into account.

SAGE - recommend to WHO

Conclusions and recommendations from the Strategic Advisory Group of Experts (SAGE) - 9-11 November 2005

[WER 2006, vol. 81, 1, pp 2-11](#)
page 6

SAGE recommended that WHO should provide support to developing countries for the development of national, seasonal and pandemic influenza vaccination policies. All countries should develop pandemic preparedness plans that include strategies for the deployment of vaccines when these become available. SAGE stressed that countries must not depend solely on vaccines for pandemic control because lack of vaccine or at best shortage will be a reality in most countries. With the goal of facilitating equitable and timely access, WHO should continue to play a role in advising on priority groups for immunization with pandemic vaccine

(http://www.who.int/csr/resources/publications/influenza/WHO_CDS_CSR_RMD_2004_8/en/index.html).

WHO should provide advice for enhanced surveillance for early detection of new influenza strains and of the onset of a pandemic, if it occurs. WHO should pursue its efforts in strengthening the capability in developing countries of health ministries and national regulatory authorities to facilitate the movement of samples and to ensure prompt registration of pandemic vaccines. Global regulatory convergence should be considered, and WHO should facilitate progress in this direction.

WHO should support research and development for pandemic and seasonal vaccines, including alternative and more effective methods of vaccine delivery such as intradermal and intranasal vaccination, improved vaccines and novel production technologies. SAGE noted that there is currently no influenza vaccine production capacity in the African region. Where appropriate, WHO should facilitate developing countries in establishing local capacity for production of influenza vaccine (including pandemic vaccine) based on manufacturers of vaccines of assured quality and should provide support for relevant technology transfer.

WHO should collaborate with expert groups to model the impact of different vaccination strategies in pandemic control, including the possibility of strategic deployment of vaccines, under various epidemiological settings. The risks and benefits of diverting some current vaccine production facilities to the production of influenza vaccines should be investigated. This should be taken forward urgently by WHO as it may provide a means of expanding vaccine production capacity more effectively than reliance on increasing use of seasonal influenza vaccination. The possible negative impacts on supplies of other vaccines should be considered.

WHO should ensure that the expertise in rapid mobilization for mass immunization is included in influenza preparedness planning. In addition, similar considerations should be given to access and distribution of antiviral medication.

Conclusions and recommendations from the Strategic Advisory Group of Experts (SAGE) - 10-11 April 2006

[WER 2006, vol. 81, 21, pp 210-220](#)
page 218

SAGE supported the efforts of WHO to scale up activities relating to influenza pandemic vaccine development, evaluation and capacity building, and the monitoring of seasonal influenza vaccine supply and uptake.

Conclusions and recommendations from the Strategic Advisory Group of Experts (SAGE) - 10-11 April 2006

[WER 2006, vol. 81, 21, pp 210-220](#)
page 218

SAGE recognized the critical role that WHO should play in the international coordination of research and evaluation of influenza pandemic vaccines.

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

[WER 2006, vol. 82, 1, pp 1-16](#)
page 6

WHO should ensure that there is unrestricted sharing of samples and vaccine strains internationally.

Schedule

Influenza vaccines (WHO position paper)

[WER 2005, vol. 80, 36, pp 279-287](#)
page 286

Based on data from industrialized countries, and listed in order of priority, the following groups of individuals may be targeted for vaccination (against influenza) in order to reduce the incidence of severe illness and premature death.

1. Residents of long-term care facilities for elderly people and the disabled.
2. Elderly non-institutionalized individuals with chronic conditions such as pulmonary and cardiovascular illness, metabolic diseases including diabetes mellitus and renal dysfunction, and various types of immunosuppression, including people with acquired immunodeficiency syndrome (AIDS) and transplant recipients.
3. All adults and children aged >6 months with any of the conditions mentioned above.
4. Elderly individuals who are above a nationally defined age limit, irrespective of other risk factors. Although the appropriate age for general vaccination may be considerably lower in countries with poor living conditions, most countries define the age limit to be >65 years.
5. Other groups defined on the basis of national data and capacities, such as contacts of high-risk people, pregnant women, health-care workers and others with key functions in society, as well as children 6-23 months of age.

Influenza vaccines (WHO position paper)

[WER 2005, vol. 80, 36, pp 279-287](#)
page 285

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.

State of the art of new vaccines: research and development

[WHO/IVB/06.01](#)

page 18

A trivalent live cold-adapted vaccine (Flumist) has been developed for intranasal spray delivery . . .

The vaccine has been licensed in the USA for vaccination of persons from 5-49 years of age, in view of side effects in younger children (wheezing, nasal congestion) and absence of data in the elderly. The vaccine is safe, effective, and shows remarkable genetic stability, but it has to be kept at -18C.

VPD Surveillance

Influenza vaccines (WHO position paper)

[WER 2005, vol. 80, 36, pp 279-287](#)

page 280

Improved coverage of WHO's Global Influenza Surveillance Network should be achieved to obtain better information on the epidemiology of influenza A and B.

Surveillance (of influenza) is of particular importance in rural areas where potential animal hosts and humans live in close proximity, since it is in such areas that new viral recombinants are likely to originate.

Influenza vaccines (WHO position paper)

[WER 2005, vol. 80, 36, pp 279-287](#)

page 287

WHO strongly encourages the implementation of epidemiological surveillance, disease burden assessments and, where appropriate infrastructure is available, demonstration projects to estimate the impact of vaccination on disease in poor countries.

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Vaccine Administration

Influenza vaccines (WHO position paper)

[WER 2005, vol. 80, 36, pp 279-287](#)

page 284

TIVs (trivalent, inactivated influenza vaccines) are injected into the deltoid muscle (vaccinees aged >1 year) or the antero-lateral aspect of the thigh (vaccinees aged between 6 and 12 months). Inactivated influenza vaccines will not interfere with concomitantly administered diphtheria/tetanus/pertussis (DTP) or other childhood vaccines.

Vaccine Handling

Temperature sensitivity of vaccines

[WHO/IVB/06.10](#)
page 36

Live attenuated influenza vaccines have been used for several decades in Russia and have recently been developed in the USA, for intranasal application.

It must be stored frozen (-15oC to -25oC), and thawed for up to 60 hours at +2oC to +8oC before use, but it should not be refrozen. Because temperature cycling could affect product stability, it should be stored in a frost-free freezer. A refrigerator stable formulation (to be kept at +2oC to +8oC) is in development.

State of the art of new vaccines: research and development

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Vaccine Quality

Global Advisory Committee on Vaccine Safety, 12 December 2005

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