# A Global Perspective on Vaccine Safety and Public Health: The Global Advisory Committee on Vaccine Safety

Established in 1999, the Global Advisory Committee on Vaccine Safety advises the World Health Organization (WHO) on vaccine-related safety issues and enables WHO to respond promptly, efficiently, and with scientific rigor to issues of vaccine safety with potential global importance. The committee also assesses the implications of vaccine safety for practice worldwide and for WHO policies. We describe the principles on which the committee was established, its modus operandi, and the scope of the work undertaken, both present and future. We highlight its recent recommendations on major issues, including the purported link between the measles–mumps–rubella vaccine and autism and the safety of the mumps, influenza, yellow fever, BCG, and smallpox vaccines as well as that of thiomersal-containing vaccines. (*Am J Public Health.* 2004;94:1926–1931)

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**THE SUCCESSFUL IMPLEMENTATION** of large-scale comprehensive national immunization programs and the consequent eradication or reduction of smallpox, polio, measles, pertussis, meningococcal meningitis, diphtheria, hepatitis B, congenital rubella syndrome, and tetanus were among the most notable public health achievements of the 20th century. Even in countries where resources for national health programs are severely limited, it has been possible to achieve significant progress.[1] There is good reason to expect that these advances will be sustained in the 21st century. It has been suggested that there are 4 elements of successful public health efforts: highly credible scientific evidence, passionate advocates, media campaigns, and law and regulation, usually at the national level[2] (to which might be added adequate resources and political will).

It is thus paradoxical that, as vaccines have become increasingly more effective, safe, and of good quality, public concerns about their safety have increased, especially in the developed world.[3] In recent years, the World Health Organization (WHO) has taken steps to meet these modern challenges to vaccination, including the establishment, in 1999, of the Global Advisory Committee on Vaccine Safety (GACVS). The GACVS provides advice to the WHO on all vaccine-related safety issues, enabling the organization to respond promptly, efficiently, and with scientific rigor to safety issues of potential global importance.[4] The committee also assesses the implications of vaccine safety issues for practice worldwide and for WHO policies. In doing so, the GACVS often draws on the advice, experience, and analysis of outside experts.

We report on the principles upon which the GACVS was established, the modus operandi of the committee, and the scope, rather than the details, of the work undertaken by the committee over the past 4 years. We also consider future challenges facing the committee.

## THE GACVS: TERMS OF REFERENCE

Several specifications and guidelines led the establishment of the GACVS. First, the committee should be able to consider and make recommendations regarding all aspects of vaccine safety that might be of interest and importance to member states and to the WHO and that are of sufficient importance to affect WHO or national policies. The decisions of the committee should be free of vested interests, including the interests of the WHO itself or of other organizations involved in achieving the goals of universal immunization coverage and national programs for immunization.

Second, committee members should collectively bring the expertise necessary for evaluation and decisionmaking in the field of vaccine safety, including familiarity with the drug regulatory process, with special reference to the needs of the developing world. The committee should be free to make decisions and recommendations not necessarily in line with the special interests of the institutions at which the committee members work, in accordance with the high standards set by the WHO in terms of absence of conflicts of interest among members of the organization's various committees. Third, all decisions and recommendations of the committee should be based on the best available scientific evidence and expertise and should be authoritative, defensible, and explicable in terms of fact, scientific evidence, and process.

## CAUSALITY ASSESSMENT OF ADVERSE POSTIMMUNIZATION EVENTS

One of the first responsibilities of GACVS was to determine a set of criteria according to which the causes of adverse postimmunization events could be judged.

Building on the work of the United States surgeon general and his team from 1964, the committee decided that the following generally established criteria are most relevant in determining causality in assessments of vaccine-related events.[5,6]

• *Consistency*: The association of a purported adverse event with the administration of a vaccine should be consistent; that is, the findings should be replicable in different localities, by different investigators not unduly influencing one another, and by different methods of investigation, all leading to the same conclusion(s).
• *Strength of the association*: The association should be strong in terms of magnitude (in an epidemiological sense) and the dose–response relationship of the vaccine with the adverse effect.
• *Specificity*: The association should be distinctive; that is, the adverse event should be linked uniquely or specifically with the vaccine concerned rather than occurring frequently, spontaneously, or commonly in association with other external stimuli or conditions.
• *Temporal relation*: There should be a temporal relationship between the vaccine and the adverse event, in that receipt of the vaccine should precede the earliest manifestation of the event.
• *Biological plausibility*: The association should be coherent, that is, plausible and explicable according to known facts in the natural history and biology of the disease.

Not all of these criteria need be present for a causal relationship to be determined, and neither does each carry equal weight. In addition to these principles, there are a number of conditions and provisos that should be applied in evaluating causality in the field of vaccine safety. First, the requirement for biological plausibility should not unduly influence consideration of causality. Biological plausibility is a less robust criterion than the others. If an adverse event does not fit with known facts and the previous understanding of the adverse event or the vaccine under consideration, it does not necessarily follow that new or hitherto unexpected events are improbable.

Second, there must be consideration of whether the vaccine is serving as a trigger. A *trigger* in this context is an agent that causes an event to occur earlier that would have occurred some time later anyway. When acting as a trigger, the vaccine could hypothetically expose an underlying or preexisting condition or illness. Finally, with live attenuated vaccines, the adverse event may be attributable to the pathogenicity of the attenuated vaccine–related microorganism and not distinguishable (except in severity) from the disease for which the vaccine is administered. Identification of the vaccine strain of the microorganism or its genetic material in diseased tissue or the patient's body fluids in such a situation would add weight to causality.

An association between vaccine administration and an adverse event is most likely to be considered *strong and consistent* when the evidence is based on the following:

• Well-conducted human studies that demonstrate a clear association with a design testing a priori the hypothesis of such an association. Such studies will normally be randomized controlled clinical trials, case–control investigations, or cohort studies. Case reports, however numerous and complete, do not fulfill the requirements for testing hypotheses.
• Associations demonstrated in more than one human study and showing consistency between studies conducted by different investigators in different settings, with results that are consistent despite different research designs. An association between dose and adverse effect strengthens the causal association between the vaccine and the effect. This is not necessarily the case if there is a hypersensitivity effect.
• Similarity of the adverse event to the disease the live vaccine is intended to prevent, with a nonrandom temporal relationship between administration and the adverse incident.

There should ideally be a strict definition of the adverse event in clinical, pathological, and biochemical terms. The frequency of the adverse event should be substantially lower in the nonimmunized population than in the immunized population in which the event is described, and there should not be obvious alternative reasons for its occurrence that are unrelated to immunization.

## SCOPE OF THE WORK CONSIDERED BY THE GACVS

The committee has reviewed the following safety issues: macrophagic myofasciitis and aluminum-containing vaccines, the health effects of thiomersal-containing vaccines, autoimmune diseases and vaccines, potential contamination of vaccines with transmissible spongiform encephalopathy, adverse events following mumps vaccination, mortality following routine infant immunizations, the safety of yellow fever vaccine, risks following immunization in HIV-infected children, the safety of BCG vaccine in immunocompromised individuals, the measles–mumps–rubella (MMR) vaccine and autism, the safety of MMR versus rubella vaccine in the postpartum period, multiple sclerosis and hepatitis B vaccination, acute lymphatic leukemia and hepatitis B vaccination, oculorespiratory syndrome following influenza vaccination, Bell's palsy following vaccination with an inactivated intranasal flu vaccine licensed in Switzerland, influenza vaccination of women during pregnancy, the safety of smallpox vaccines, the safety of polio vaccination in the context of eradication, and enhancement of electronic communications of vaccine safety issues and establishment of a Web site reference.

Outcomes of the deliberations of the committee on these and other issues are reported routinely in the *Weekly Epidemiological Record*, and relevant information can be found at http://www.who.int/vaccine_safety/en. What follows has been selected as illustrative of the work of the committee, in terms of both its proactive approach and its reactive response to reports and concerns brought to it.

## NONSPECIFIC EFFECTS OF VACCINES

The GACVS has given considerable attention to the purported nonspecific adverse effects of the diphtheria–tetanus–pertussis (DTP) vaccine on infants aged 18 months or younger in low-

income countries.[7–9] It has also been suggested by Kristensen et al. that BCG has an overall nonspecific beneficial effect and that measles vaccine is associated with reduced mortality and morbidity that cannot be explained by prevention of measles alone.[7] The GACVS believes that this set of theories raises critical issues pertaining to the safety of vaccines and immunization practices and that there is a need for further systematic research in the area of vaccine safety. For the time being, the GACVS has found that the reported results and conclusions are not without potential bias and that the results have not been confirmed by others in different settings.

## MMR AND AUTISM

There is ongoing debate as to whether autism has a genetic or environmental cause (including the possibility of a prenatal insult), or both. Autistic spectrum disorders represent a continuum of cognitive and neurobehavioral disorders, including autistic disorder or autism. Prevalence rates of autism vary considerably according to intensity of case ascertainment, ranging from 0.7 to 21.1 per 10 000 children (median: 5.2 per 10 000).

Concerns about a possible link between vaccination with MMR and autism were raised in the late 1990s, after the publication of a series of studies claiming an association between both natural and vaccine strains of the measles virus and inflammatory bowel diseases and autism. The authors of more recent studies have also claimed findings supporting such an association. Since public concerns have remained high, in 2002 WHO, on the recommendation of the GACVS, commissioned a review of the risk of autism associated with MMR vaccination. The findings of the review, conducted by an independent researcher, were presented to the GACVS for its consideration. Eleven epidemiological studies were reviewed in detail, taking into consideration study design and limitations.[10-20] Three laboratory studies were also reviewed.[21–23] The conclusion of the review was that existing studies do not show evidence of an association between the risk of autism or autistic spectrum disorders and the MMR vaccine.

On the basis of the results of this review, the GACVS agreed and concluded that there is no evidence for a causal association between MMR vaccine and autism or autistic spectrum disorders. It is the opinion of the committee that additional epidemiological studies are unlikely to add to the existing data but that there is a need for a better understanding of the causes of autism. The committee also concluded that there is no evidence to support the preferred use of monovalent MMR vaccines over the combined vaccine. On the grounds that administration of the single vaccines at intervals carries a higher risk of incomplete immunization and longer periods during which children are unprotected from these diseases, the GACVS did not recommend a change in current MMR vaccination practices.

## SAFETY OF MUMPS VACCINES

In 2003, the committee commissioned a comprehensive review of the literature on the safety of mumps vaccination, with special attention to vaccine-derived mumps meningitis. High rates of aseptic meningitis have been described for the Urabe, Leningrad–Zagreb, and Leningrad-3 vaccines relative to the Jeryl–Lynn vaccine. There is no known viral explanation for this difference based on virus genotype or phenotypic properties. Intensive surveillance of the safety of mumps vaccines during and after mass vaccination campaigns[24–28] may have contributed to distorted assessments of risk. Risk estimates have varied between studies, reflecting differences in study settings and circumstances and in degrees of surveillance. The available data are insufficient to distinguish between the safety profiles of the Urabe, Leningrad–Zagreb, and Leningrad-3 strains with respect to risk for aseptic meningitis. All reported cases of vaccine-derived mumps meningitis have been associated with recovery, without neurological sequelae.

Now that all mumps virus strains can be characterized by nucleotide sequencing and polymerase chain reaction, it should be possible to address scientifically a number of unresolved questions regarding mumps vaccine safety. These issues include defining the molecular determinants of virus attenuation; characterizing the genetic determinants of virulence; determining the safety of the vaccines in relation to either pure or mixed virus populations, along with their antigenicity; and determining at what stage mutations occur in the virus. The presence of subvariant viruses in different vaccines could be studied. Such knowledge would support the development of more scientifically based mumps vaccines and contribute to a better understanding of the pathogenesis of adverse effects. Molecular assays would distinguish wild-type from vaccine strains of the mumps virus and thus assist quality control assessments of both existing and future vaccines. The committee has recommended establishment of an international reference laboratory for mumps vaccine virus isolates from vaccinated subjects.

## SAFETY OF YELLOW FEVER VACCINE

The GACVS considered the cases of fatal viscerotropic disease following yellow fever vaccination reported in the United States, Brazil, and Australia.[29–31] The cases were attributable to a vaccine-type virus and not to a reversion of the vaccine strain to wild type. In contrast to the viscerotropic complications of yellow fever vaccination, recent neurotropic cases have not been fatal. The latter have been presumed to fall into one of 3 different clinical forms: Guillain–Barré syndrome (immune mediated), encephalopathy (owing to virus invasion), and acute demyelinating encephalomyelitis (caused either by direct virus invasion or by an immune-mediated response). Neurotropic complications of yellow fever vaccine are age related; individuals aged 65 years or older who are first-time vaccine recipients are at higher risk than younger individuals, but the young are not excluded from risk.

The GACVS noted the need for improved ability to predict who is at risk of the serious complications of yellow fever vaccine and what are the predisposing factors. An important and unresolved issue is the safety and efficacy of yellow fever vaccine among HIV-positive individuals. It remains to be determined whether HIV-positive status and the resultant immune deficiency

affect seroconversion, risk of invasion of the nervous system, and risk of encephalopathy and at what stage of HIV disease yellow fever immunization should be regarded as contraindicated. Clarification is needed to determine whether there are differences in the incidence rates of minor and major adverse reactions to the vaccine among HIV-positive individuals.

## INFLUENZA VACCINATION OF WOMEN DURING PREGNANCY

The committee has considered the safety of influenza vaccination of women during pregnancy. Manufacturers and national drug regulatory authorities tend to caution against routine use of influenza vaccine in pregnancy because there is a dearth of information regarding the vaccine's safety during the first trimester. The concern is that influenza during pregnancy carries a risk of morbidity significantly higher than usual, along with a greater prospect of hospitalization and of a fatal outcome. The committee has concluded that the risks and benefits of influenza virus vaccination during all stages of pregnancy should be reconsidered, taking into account the high risk to the mother—and to the fetus—of the disease itself. Such advice would not apply to situations in which risk of influenza is low or to live attenuated influenza vaccines, which are not indicated in pregnancy.

## BCG IMMUNIZATION IN HIV-POSITIVE INFANTS

The committee recently reviewed the available data on the benefits and risks of BCG immunization in the case of infants living in areas with high prevalence rates of tuberculosis, with and without concurrent high rates of HIV infection. Only limited population-based data are available on the effectiveness of BCG vaccine in preventing severe tuberculosis in HIV-positive infants, as well as on its safety. On the basis of the evidence available, the committee has advised that (1) no changes be made in the current recommendations for BCG immunization of infants in countries with high prevalence rates of tuberculosis; (2) that population-based studies be undertaken to determine the efficacy and safety of BCG and related vaccines in HIV-negative and HIV-positive children, respectively, in instances in which there are high endemic rates of tuberculosis; and (3) an international reference laboratory be established to systematically differentiate BCG strains and relate data to the antigenicity, efficacy, and safety of different strains.

## SAFETY OF SMALLPOX VACCINATION

The committee has considered the safety of smallpox vaccination, including an updated account of the safety of vaccination practices in the United States since January 2003. Interim reports of the US experience have been published in *Morbidity and Mortality Weekly Report*.[32,33] Adverse effects consistently reported have included myopericarditis at frequencies that exceeded what might occur by coincidence. The committee has noted the importance for smallpox immunization programs to be supported by adverse event monitoring and recognizes that data are insufficient to define the incidence of adverse events among primary vaccinees as opposed to individuals revaccinated after a long interval.[34,35]

## THIOMERSAL IN CHILDREN'S VACCINES

In the late 1990s, concerns were raised in the United States about the safety of thiomersal, a preservative used in some vaccines that has the ability to prevent bacterial contamination of multidose vials and contains ethyl mercury. These concerns were based on the realization that as the number of immunizations increased, the cumulative amount of mercury in the US infant immunization schedule could potentially exceed the most conservative recommended threshold for exposure to methyl mercury set by US government agencies. Methyl mercury has been reported to cause neurological abnormalities in newborns after fetal exposure resulting from mothers ingesting large doses over a long period of time.

In 1999, as a result of concern regarding this theoretical risk, 2 US immunization advisory bodies and the European Commission on Proprietary Medicinal Products recommended the expedited removal of thiomersal from vaccines. The change in the United States has placed pressure on other countries to follow this country's lead. However, removal of thiomersal may lead to changes in vaccine potency, stability, and reactogenicity, and this process must proceed with great caution. Furthermore, since thiomersal is an important component in terms of maintenance of sterility in certain multidose vaccine vial preparations, its removal might have serious repercussions for safe vaccine delivery.

Subsequent to the decision having been made in the United States, reassuring additional information about the safety of thiomersal-containing vaccines has become available. In particular, it has been shown that the pharmacokinetic profile of ethyl mercury is substantially different from that of methyl mercury, the former being rapidly excreted through the gut. In addition, several recently completed epidemiological studies have provided reassuring evidence with respect to the safety of thiomersal in the amounts contained in vaccines. The GACVS has reviewed the issue and found no scientific evidence of toxicity from thiomersal-containing vaccines. As a result, the WHO Strategic Advisory Group of Experts,[36] at its June 2002 meeting, strongly affirmed that vaccines containing thiomersal should continue to be available so that safe immunization practices can be maintained.

Thiomersal has been used for more than 60 years as an antimicrobial agent in vaccines and other pharmaceutical products to prevent unwanted growth of microorganisms. There is a specific need for preservatives in multidose presentations of inactivated vaccines such as DTP and hepatitis B. Repeated puncture of the rubber stopper to withdraw additional amounts of vaccine at different intervals poses risks of contamination and consequent transmission to children. Removal of thiomersal could potentially compromise the quality of childhood vaccines used in global programs. Live bacterial or viral vaccines (e.g., measles vaccines) do not contain preservatives because they would interfere with the active ingredients. In the case of certain vaccines, thiomersal is also used during the manufacturing process.

## THE WAY FORWARD

Since there will probably continue to be challenges raised by allegations of adverse events linked to immunization, it is expected that the role of the GACVS will continue to expand, with special attention to the following:

• Standards involving consultations with the pharmaceutical industry, national governments, and drug regulatory authorities need to be improved. Decisions will increasingly be made on the basis of the comprehensive vaccine safety database being developed by the committee, which will contain all of the relevant materials, published as well as unpublished, that the committee takes into account. The critiques of data made by the committee will be openly available for consideration and review by others. Decisions of the committee may be appealed or challenged. The committee aims at generating a growing sense of confidence that its decisions and recommendations are open-minded, thoroughly sound scientifically and medically, and in the interests of public health.
• The committee has a desire to work more with, and give support to, national drug regulatory authorities in promoting sound and informed regulatory practices, including ongoing review of vaccine safety issues after registration.
• In the future, the committee can be expected to provide more support for the initiatives of the WHO Department of Immunization, Vaccines, and Biologicals to facilitate the department's work with countries (especially developing countries) with vaccine manufacturing capabilities and high numbers of vaccine exports to other countries. ■


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All of the authors substantially contributed to the review of the issues presented in their capacity as members of the Global Advisory Committee on Vaccine Safety, and all actively participated in the drafting and editing of the article.


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