

Recommendations of HEV Working Group on the use of hepatitis E vaccine

A document prepared for

Strategic Advisory Group of Experts on Immunization (SAGE)

by the

Hepatitis E Vaccine Working Group

Table of contents

1. Executive summary	2
2. Introduction	3
3. Use of hepatitis E vaccine in general population in area with high endemicity	4
4. Use of hepatitis E vaccine in special population groups or situations.....	6
a. Pregnancy / Women of child-bearing age	6
b. Chronic liver disease	7
c. Organ Transplant Recipients and Other Immunosuppressed Persons.....	8
d. Travellers to areas where hepatitis E disease is common	8
e. Prevention and control of outbreaks (including during humanitarian emergencies)	9
5. Final notes.....	11

1. Executive summary

The Hepatitis E Vaccine Working Group recognizes that its recommendations are limited by several information gaps in the available data. These information gaps mainly relate to:

1. Information on safety and efficacy of the vaccine in specific subgroups (pregnant women, persons with chronic liver disease, immunosuppressed persons).
2. Information on safety and efficacy of the vaccine in specific age groups (children <16 years and elderly persons >65 years).
3. Epidemiology of hepatitis E, in particular the incidence and mortality of disease in the general population as well as in special population groups.
4. Efficacy of hepatitis E vaccine against disease caused by HEV belonging to genotypes 1, 2 and 3.
5. Efficacy of schedules of hepatitis E vaccine with fewer than three doses or shorter duration.
6. The duration of protection following hepatitis E vaccine and the possible need for boosters.

Thus, as and when data on some of the current information gaps become available, the recommendations for one or more of the situations discussed above will need reconsideration.

Further, the Working Group's recommendations are meant for general use of vaccine. The Group recognizes that there could be special situations where the risk of disease or that of serious disease or mortality could be particularly high, and that these may override other considerations. The Group's recommendations should not preclude the use of this vaccine in these special situations. However, in all such situations, experience with the use of vaccine, including the occurrence of any adverse events, should be documented.

The Hepatitis E Vaccine Working Group of SAGE makes the following recommendations. Details of the evidence base and justification for the recommendations can be found in the pages to follow.

Recommendations on the use of hepatitis E vaccine:

1. Routine vaccination for populations where epidemic and sporadic hepatitis E disease is common is not recommended at this time.
2. Routine vaccination in pregnant women or in women of child-bearing age living in areas where hepatitis E disease is common is not recommended at this time.
3. Routine vaccination of chronic liver disease patients is not recommended at this time.
4. Routine vaccination of persons on organ transplant wait-list is not recommended at this time.
5. Routine vaccination of travellers from low-endemicity areas to high-endemicity areas is not recommended at this time.
6. Use of the vaccine during outbreaks of hepatitis E could be considered.

2. Introduction

Hepatitis E virus (HEV) infection is associated with an acute hepatitis, which can sometimes be severe leading to acute liver failure. This virus is most often transmitted by the fecal-oral route. The disease manifests as waterborne outbreaks and as frequent sporadic cases in areas where water supplies are prone to contamination with human feces. In these areas, infection is mostly due to genotype 1, and less frequently to genotype 2 virus. Serious illness is particularly common in pregnant women and persons with pre-existing chronic liver disease. Hepatitis E virus (HEV) is the leading cause of acute viral hepatitis in the developing world. Every year an estimated 20 million HEV infections occur globally resulting in more than 3 million cases and 70,000 deaths.

In areas where water supplies are safe, the disease occurs as occasional cases which are believed to be related to zoonotic transmission of genotype 3 or 4 virus, possibly through ingestion of undercooked infected meat (livers from pig, wild boar or deer). In immunosuppressed persons, such infection has the potential to become persistent (lasting longer than 6 months), leading to chronic hepatitis. In these areas, hepatitis E also occurs among travellers to areas where waterborne hepatitis E is common.

A recombinant subunit-protein vaccine has been developed against hepatitis E virus infection, which has been tested in a phase III field trial in China, and was found to be safe and effective against hepatitis E disease. The vaccine has been approved and is currently commercially available (as Hecolin®) in China.

Hepatitis E Vaccine Working Group set up by the WHO's Strategic Advisory Group of Experts (SAGE) on Immunization prepared four background papers and then met to discuss the role of hepatitis E vaccine in various population groups. This current document is a synthesis of the information contained in the four background papers and the discussions during the Working Group meeting. This document should therefore be read in conjunction with the following four background documents:

- (i) Hepatitis E: Epidemiology, surveillance and disease burden,
- (ii) Hepatitis E vaccine pipeline (posted on website only),
- (iii) Hepatitis E vaccine: Composition, safety, immunogenicity and efficacy, and
- (iv) Cost-effectiveness of Hepatitis E vaccine (work still in progress, posted on website only).

The Working Group considered the use of hepatitis E vaccine for the general populations residing in areas with high disease burden and also for some specific population groups which are considered at higher risk of infection (e.g. travellers to disease-endemic areas, persons living in camps for displaced persons with limited access to clean water, or persons at risk for waterborne transmission due to disruption of supplies of clean water e.g. flooding, pregnant women in disease-endemic areas) or more often have serious outcomes of disease (pregnant women, persons with chronic liver disease, and immunosuppressed persons such as solid organ transplant recipients). Evidence and recommendations for each of these groups is discussed below.

3. Use of hepatitis E vaccine in general population in area with high endemicity

Epidemic hepatitis E occurs in geographical areas where water contamination is common; in addition, in these areas, HEV infection is responsible for a proportion of sporadic acute viral hepatitis. In areas where water supplies are safe, hepatitis E does occur; however, the number of cases in these areas is small.

Based on a mathematical modelling study, HEV is estimated to cause nearly 3.4 million clinical cases of acute hepatitis and nearly 70,000 deaths and 3,000 stillbirths annually in Asia and Africa, which are areas with high disease burden. This disease burden may be comparable to that of several other vaccine-preventable-diseases for which universal vaccination is currently recommended.

Table: Global disease burden of various vaccine-preventable diseases in comparison to that of hepatitis E.

<i>Disease</i>	<i>Number of annual deaths worldwide</i>	<i>Estimated global vaccination coverage (2013)³</i>
Hepatitis E (modelling data)	70,000	*
Pertussis (2012) ¹	67,059	84% (3 doses of DTP)
Diphtheria (2012) ¹	2,615	84% (3 doses of DTP)
Tetanus(2012) ¹	66,129	84% (3 doses of DTP)
Measles (2012) ^{1,4}	130,461	84% (at least one dose of measles-containing vaccine)
Rotaviral enteritis (2010) ²	250,900	14% (2 doses of rotavirus vaccine)
Influenza (2010) ²	507,900	No global estimate available
Hepatitis B (2010) ²	786,000	81% (3 doses of Hep B vaccine), 38% (birth dose)

¹WHO Global Health Estimates (GHE) 2014: http://www.who.int/healthinfo/global_burden_disease/estimates/en/index1.html

²Lozano et al. Global and regional mortality from 235 causes of death for 20 age groups in 1990 and 2010: a systematic analysis for the Global Burden of Disease Study 2010: Lancet 2012; 380: 2095–128 (http://ac.els-cdn.com/S0140673612617280/1-s2.0-S0140673612617280-main.pdf?_tid=4e74d82e-1c9d-11e4-a264-00000aab0f01&acdnat=1407242448_c4e9609829c3624b87afa57e8c785e70)

³WHO Global Immunization Data; http://www.who.int/immunization/monitoring_surveillance/data/gloprofile.pdf?ua=1

*HEV vaccine is currently not included in vaccination schedules in any part of the world.

⁴In 2000, measles was estimated to have killed 562,400 children. Between 2000 and 2012, 13.8 million deaths were prevented by the measles vaccine (compared to a scenario of no vaccination).

WHO. Global control and regional elimination of measles, 2000-2012. Weekly Epidemiological Record. 2014;89:45-52.

The available hepatitis E vaccine (Hecolin®) has been studied in a large field trial in China, in which nearly 112,000 healthy adults (16 – 65 years old) of either gender were randomized to receive either Hecolin® or a hepatitis B vaccine in a three dose, 0, 1 and 6 month schedule. Near half the study subjects had pre-existing anti-HEV antibodies. In this phase III trial, the vaccine was shown to be safe and had a protective efficacy of 95.5% [95% confidence interval = 66.3% to 99.4%] in an intention-to-treat analysis and of 100% [95% CI = 72.1% to 100%] in a per-protocol analysis against hepatitis E disease following the completion of immunization. In addition, unpublished follow-up data from this trial indicate an 87% protective efficacy on

intention-to-treat basis, and 93% in those who had completed the full 3-dose schedule, over a period extending up to 4 years after completion of immunization.

The existence of substantial disease burden due to hepatitis E and availability of an efficacious vaccine for its prevention have led to the idea of using the vaccine to interrupt the transmission of this virus, particularly in regions/populations in which outbreaks and sporadic cases of hepatitis E occur frequently.

The Working Group discussed the issue of hepatitis E vaccination for general populations in areas where hepatitis E is highly endemic, in view of the following:

1. The burden of hepatitis E disease is high among populations without consistent access to clean drinking water, sanitation and hygiene. These populations have frequent hepatitis E outbreaks (with genotype 1 and 2 virus), and these outbreaks are associated with significant mortality particularly in vulnerable groups like pregnant women. The disease burden is the highest among young adults.
2. The data on safety and efficacy of this vaccine are strong for healthy adults aged 16-65 years, which overlaps with the age group most affected by the disease.

Recommendation: The Working Group agreed that, based on the available data, routine vaccination for populations where epidemic and sporadic hepatitis E disease is common is not recommended at this time.

The reasons for the above recommendation of the Working Group are as follows:

1. Generalizability of the results of the only one available vaccine trial to other geographic regions and populations may be limited:
 - a. The only available trial was conducted in an area with very low disease incidence. In such situations, the viral inoculum may be low. By contrast, in areas with or during periods of high rate of transmission of HEV infection (e.g. during water-borne outbreaks of hepatitis E), the exposure to HEV may be very high. The efficacy of the vaccine in such situations is not known.
 - b. The phase III trial with the vaccine primarily assessed its efficacy only against genotype 4 (since >90% of infections in the placebo group were caused by genotype 4 virus), and to only a limited extent against genotype 1 disease (occasional cases in the placebo group had infection with genotype 1 HEV). Even though *in vitro* data suggest that the vaccine may be effective against genotype 1, 2 and 3 HEV infection, direct data on this aspect are lacking. By contrast, most of the cases of hepatitis E in areas with high disease endemicity are caused by genotype 1 or 2 viruses.
2. There is lack of data on protection against severe disease and death (such as is seen in pregnant women infected with HEV). The pathogenesis of such disease may be different from the usual hepatitis E.

3. It is unclear whether the use of vaccine would control fecal excretion of the virus or transmission of infection.
4. The anti-HEV antibody titers after vaccination decline with time. Thus far, the protective efficacy of the vaccine is known to last for at least 4 years. Data on long-term protection are not yet available. Lack of information on antibody level threshold for protection against HEV infection or disease means that antibody titer modelling studies cannot be used to predict the likely duration of protection following hepatitis E vaccination. Continuing follow up of participants in the phase III clinical trial should in future provide such data on the duration of protection by the vaccine.
5. Data on efficacy and safety are limited to persons in the age group of 16-65 years, and no data are available in children below 16 years of age and in adults older than 65 years of age. The vaccine is therefore difficult to incorporate into existing immunization schedules which are targeted primarily at children.
6. Data on the incidence of hepatitis E and on the number of deaths due to this disease in the general population, even in areas where hepatitis E disease is common, are quite limited. Moreover, the available data on prevalence of anti-HEV antibodies, a key input into the mathematical modelling for burden of hepatitis E disease, and on incidence and mortality of this disease have limitations related to suboptimal performance characteristics of anti-HEV assays and various types of selection biases in sample studies. These factors imply that there is an inherent uncertainty in the estimates of hepatitis E disease burden.

In addition, the group noted that (i) the existing vaccine production capacity is limited, (ii) the cost of vaccine is high, (iii) there are logistic issues related to large additional cold-chain space requirements with single-dose packaging.

4. Use of hepatitis E vaccine in special population groups or situations

a. Pregnancy / Women of child-bearing age

In areas of the world where water-borne hepatitis E is frequent, pregnant women are at a higher risk of developing clinical disease than men and non-pregnant women. This subgroup is also at a higher risk of developing severe disease, i.e. fulminant hepatic failure and death. In an outbreak in Kashmir valley in India, of the 208 pregnant women, 36 (17.3%) developed acute hepatitis and 8 (4% of all pregnant women) developed fulminant liver failure. By contrast, of the 7172 non-pregnant women and men, 178 (2.5%) developed acute hepatitis and 3 developed fulminant hepatic failure. These data translate to risk ratios of 7.0 (95% confidence intervals = 5.0 to 9.7) and 92.0 (95% confidence intervals = 24.6 to 344.1), for acute viral hepatitis and fulminant hepatic failure, respectively, among pregnant women as compared to men and non-pregnant women. In addition, hepatitis E in pregnancy is also associated with adverse fetal outcomes such as stillbirth, premature delivery, increased risk of neonatal complications such as hypoglycemia, and mother-to-infant transmission of HEV infection. However, to-date there are no population-based data on the incidence of or mortality related to hepatitis E among pregnant women or neonates in any region of the world.

The only currently licensed hepatitis E vaccine is not approved for use during pregnancy. There are no data on vaccine immunogenicity specifically in pregnant women. Though the phase III trial of this vaccine had pregnancy as an exclusion criterion, 37 pregnant women inadvertently received the vaccine, and 18 of them opted to continue the pregnancy to term (the other 19 underwent elective termination of pregnancy). None of these 18 women had a serious adverse event or poor fetal outcome. These data are too limited to infer vaccine safety during pregnancy and further data on vaccine safety during pregnancy are needed. However, since the vaccine is a recombinant subunit vaccine, its safety profile can be reasonably expected to be similar to other recombinant vaccines which have been quite safe. There are no data yet on whether hepatitis E vaccine prevents the particularly severe hepatitis E seen during pregnancy.

Use of vaccine to prevent hepatitis E in pregnancy also poses some logistic issues pertinent to vaccine schedule and when to vaccinate. There are two possible approaches to reach this group, i.e. immunizing (i) women in child-bearing age group before they become pregnant, and/or (ii) women in early pregnancy or those in mid-pregnancy with the use of an accelerated schedule. Large variations in age of child-bearing between populations and within each population make it difficult to target the hepatitis E vaccine, whose long-term efficacy is uncertain, to a particular age group. The approach of immunization in early pregnancy poses difficulties of identifying and reaching women in early phase of pregnancy, the time taken to achieve protective efficacy, and safety of vaccine when administered during pregnancy. There are no data yet on the use of accelerated schedules for hepatitis E vaccine.

Recommendation: In view of limited data on safety and efficacy during pregnancy, the Working Group does not currently recommend at this time the routine use of vaccine in pregnant women or in women of child-bearing age living in areas where hepatitis E disease is common.

The Working Group felt that the above recommendation should be reconsidered as soon as further data on safety and immunogenicity of the vaccine in pregnant women, or better data on population incidence of hepatitis E and mortality due to this disease become available.

b. Chronic liver disease

In several clinical case series, patients with pre-existing chronic liver disease have been shown to have an increased risk of severe disease when they develop hepatitis E virus infection.

However, exact frequency of HEV infection and disease in this subgroup of patients is not known. Thus, there are no data on the absolute or relative risk of disease or death due to HEV infection among patients with chronic liver disease.

Immunogenicity and efficacy of hepatitis E vaccine have not been studied in persons with chronic liver disease. The phase III trial of this vaccine specifically excluded patients with chronic liver disease. It did include people with chronic hepatitis B virus infection (healthy carriers), in whom the vaccine was found to be as safe and immunogenic as those without such infection; however, this group cannot be considered as having chronic liver disease. Thus, currently, no data are available on safety, immunogenicity or efficacy of this vaccine in this special group.

Recommendation: In view of the increased risk of severe disease associated with HEV infection in this special population group, it would be useful to take steps to prevent HEV infection in

them. However, in view of the lack of safety and immunogenicity data in this group of patients, the Working Group does not currently recommend the routine use of this vaccine in this group of patients.

The Working Group felt that the above recommendation should be reconsidered as soon as data on safety and immunogenicity of the vaccine in patients with chronic liver disease become available.

c. Organ Transplant Recipients and Other Immunosuppressed Persons

Chronic HEV infections have been recently recognized in the immunosuppressed population, particularly in recipients of solid organ transplants, in European countries and North America. In France, chronic HEV infection was identified in ~3% of solid-organ transplant recipients. These cases have been linked to infection with genotype 3 HEV, except for one recent pediatric case with genotype 4 HEV infection. It remains unclear whether HEV genotypes 1 and 2 are associated with chronicity. Chronic HEV infection may rapidly progress to hepatic fibrosis and cirrhosis. A reduction of immunosuppressive therapy leads to viral clearance in around 30% of cases. Treatment with ribavirin for 3 months is effective in most of the cases, but is contraindicated in some patient groups e.g. kidney transplant recipients.

Safety, immunogenicity and protective efficacy of the available hepatitis E vaccine in immunosuppressed people, including those who are waiting for or have received a solid-organ transplant, have not been studied. This is important since these groups may be less likely to develop specific antibodies because of the underlying disease or because they are receiving immunosuppressive drugs. In any case, if the vaccine is used for transplant recipients, the best time for its administration may be in the pre-transplant phase, before the institution of immunosuppressive drugs.

Also, in the phase III clinical trial of the hepatitis E vaccine, protective efficacy was primarily against disease related to genotype 4 (and to some extent, genotype 1) HEV infection. However, in *in vitro* experiments, the vaccine induced antibodies appeared to bind to and neutralize genotype 3 HEV.

Recommendation: In view of lack of data on immunogenicity and safety in this group of patients, and on protective efficacy of the vaccine against genotype 3 HEV infection, the Working Group does not currently recommend the routine use of this vaccine in persons on organ transplant waiting lists at this time.

The Working Group felt that the above recommendation should be reconsidered as soon as data on immunogenicity of the vaccine in this special group become available.

d. Travellers to areas where hepatitis E disease is common

In developed countries where water supplies are clean, hepatitis E disease is less common. In the 1990s and early 2000s, hepatitis E in these areas mainly occurred among returning travellers after visiting countries with high endemicity. The number of such travel-related cases has gradually decreased over time, even though international travel has increased. Most of these travel-associated cases have occurred among travellers to the Indian subcontinent. The clinical manifestation of disease is usually mild self-limited illness with jaundice. Most cases

were due to infection by HEV genotype 1 but recently travellers to South East Asia have returned with genotype 4 infection.

Whilst many countries do not systematically collect data on travel-related hepatitis E, enhanced surveillance data from England and Wales showed that 28% of cases with hepatitis E confirmed in 2012 were related to travel; the remaining cases were believed to be indigenous. There are no studies of seroprevalence of anti-HEV antibodies among returning travellers to the US or other countries. A study based on the NHANES survey in the US showed a slight elevation of anti-HEV seroprevalence among persons with history of travel abroad than those without such history; however, no further epidemiological information on history of travel-associated illnesses was available for the persons with history of prior travel.

The burden of hepatitis E from international travel is not substantial. Hepatitis E transmission from persons who acquire infection during international travel to family contacts has not been reported. With a recent increase in autochthonous cases with relatively different clinical presentation and severity mainly due to disease occurrence in persons with immune incompetence, travel-related hepatitis E may not be a significant enough problem to warrant targeting for vaccination. Furthermore, risk of hepatitis E infection could be reduced by educating travellers on how to prevent waterborne and foodborne infections.

Hecolin[®] is efficacious when provided at 0, 1, and 6 months, which is a difficult regimen for travellers who usually do not plan for travel more than 6 months in advance. Immunogenicity and protective efficacy of a shorter-duration (accelerated) schedule, or fewer doses, particularly among previously unexposed persons has not been formally studied. In the phase II and phase III trials, partial protection was observed among those persons who received two doses of the vaccine; however, the data on this aspect are not sufficiently robust.

Recommendation: Based on the currently-available limited epidemiologic data that show a low disease burden among travellers, the ability to prevent such infections by standard precautions, and lack of data on protection afforded by short-duration schedules of hepatitis E vaccine, the Working Group does not currently recommend the use of Hecolin[®] among travellers from low-endemicity areas to high-endemicity areas.

The Working Group recognizes that there may be some special situations where travellers may be (i) at a higher risk of hepatitis E virus infection, such as humanitarian relief workers travelling to areas where an outbreak of hepatitis E is on, or (ii) at a higher risk of serious disease, such as pregnancy. Under such circumstances, each person should be evaluated individually for risks and benefits.

The Working Group felt that the above recommendation should be reconsidered if and when data on immunogenicity and efficacy of shorter vaccine schedules become available.

e. Prevention and control of outbreaks (including during humanitarian emergencies)

Many large outbreaks have occurred in developing countries across the Indian Subcontinent, and other parts of Asia and Africa. These outbreaks are waterborne and may be associated with high attack rates. Case-fatality rate is the highest for pregnant women, but a substantial

number of deaths also occur among other persons. Water, sanitation and hygiene (WASH) interventions are the mainstay for prevention and control of hepatitis E outbreaks.

In recent years, some large outbreaks of hepatitis E have occurred in the setting of humanitarian emergencies. In outbreaks among displaced persons/refugees transmission tends to run over a long period with some outbreaks lasting longer than a year (multiple incubation periods). Most outbreaks are caused by genotype 1 HEV and some by genotype 2 HEV. Implementing outbreak control measures, including WASH interventions, in such settings is challenging. Thus, it is pertinent to consider the use of hepatitis E vaccine as a complement to the WASH activities for control of hepatitis E outbreaks, particularly in humanitarian emergencies.

There are no data on the use of hepatitis E vaccine to control hepatitis E outbreaks. The hepatitis E vaccine has, up until the review by the Working Group, only been studied in a 3-dose schedule administered over a 6-month period (0-1-6 month schedule). The implementation logistics and effectiveness of a 3-dose vaccine in an outbreak, particularly in a challenging humanitarian crisis setting, such as in camps for displaced persons, needs further investigation. However, limited data from a phase II and the phase III vaccine trial suggest that two doses of hepatitis E vaccine may provide at least partial protection against hepatitis E disease. There is no information on whether the vaccine can reduce fecal excretion of HEV by persons with clinical disease or subclinical infection, and hence reduce the transmission of HEV infection during outbreaks. Effectiveness of hepatitis E vaccine when administered after a person has been exposed to HEV remains unknown. However, during an outbreak, the vaccine could be expected to work by increasing the proportion of population that is immune to the disease (herd immunity), and thereby reducing both clinical cases as well as disease transmission.

The use of vaccine to control outbreaks of hepatitis E faces certain challenges. These include: (i) the outbreaks are often identified late; (ii) the incubation period of the disease is 2-10 weeks, hence many persons may already be infected and in the incubation period when the outbreak is identified; (iii) immunity induced by the vaccine depends on the number of doses and may take time to develop; (iv) during outbreaks, a proportion of cases occur among children (<16 years) of age who are currently not eligible to receive the available vaccine; and (v) the inoculum of HEV to which people are exposed during outbreaks may be much higher than that encountered during the usual clinical trial situations.

Some outbreaks of hepatitis E (particularly those in humanitarian emergencies and where water quality and quantity cannot be improved rapidly) have been prolonged and have lasted for several months. In such outbreaks, the continued high risk of symptomatic disease within a geographically-limited population outweighs many uncertainties associated with the decision to use hepatitis E vaccine in the general population.

The available data for protection following hepatitis E vaccine are primarily against genotype 4 virus, whereas water-borne outbreaks are caused by genotype 1 or 2 HEV.

Recommendation: The Working Group recommends that the use of hepatitis E vaccine during outbreaks of hepatitis E could be considered. If the vaccine is used in this situation, it would be reasonable to vaccinate a large proportion of the affected population as quickly as possible.

Though the vaccine is currently approved only for ages 16 to 65 years, the health authority in charge may consider the use of vaccine in the other age groups. When the vaccine is used in such a setting, every effort must be made to record data and to collect information on vaccine efficacy, adverse events and the possible effect of such vaccine use on the outbreak dynamics.

When use of a vaccine during an outbreak is contemplated, it must be kept in mind that the vaccine is packaged in single dose vials. In view of need for keeping the vaccine within the cold chain, careful calculation and planning are necessary for appropriate transport and storage facilities.

The Working Group felt that the above recommendation should be reconsidered as and when further data on immunogenicity and efficacy of shorter vaccine schedules, on efficacy of the vaccine against genotype 1 or 2 hepatitis E, or on safety and efficacy in children, pregnant women and elderly persons become available.

5. Final notes

The Working Group recognizes that its recommendations are limited by several information gaps in the available data. These information gaps mainly relate to:

1. Information on safety and efficacy of the vaccine in specific subgroups (pregnant women, persons with chronic liver disease, immunosuppressed persons).
2. Information on safety and efficacy of the vaccine in specific age groups (children <16 years and elderly persons >65 years).
3. Epidemiology of hepatitis E, in particular the incidence and mortality of disease in the general population as well as in special population groups.
4. Efficacy of hepatitis E vaccine against disease caused by HEV belonging to genotypes 1, 2 and 3.
5. Efficacy of schedules of hepatitis E vaccine with fewer than three doses or shorter duration.
6. The duration of protection following hepatitis E vaccine and the possible need for boosters.

Thus, as and when data on some of the current information gaps become available, the recommendations for one or more of the situations discussed above will need reconsideration.

Further, the Working Group's recommendations are meant for general use of vaccine. The Group recognizes that there could be special situations where the risk of disease or that of serious disease or mortality could be particularly high, and that these may override other considerations. The Group's recommendations should not preclude the use of this vaccine in these special situations. However, in all such situations, experience with the use of vaccine, including the occurrence of any adverse events, should be documented.