

Hepatitis E Vaccine

WHO Position Paper, May 2015

List of References in Position Paper and Grade Tables (with PubMed Abstracts, if available)

- **Aggarwal R. The global prevalence of hepatitis E virus infection and susceptibility: a systematic review. Geneva: World Health Organization; 2010**
(http://whqlibdoc.who.int/hq/2010/WHO_IVB_10.14_eng.pdf).
- **Albinana-Gimenez N, et al. Distribution of human polyomaviruses, adenoviruses, and hepatitis E virus in the environment and in a drinking-water treatment plant. Environ Sci Technol. 2006 Dec 1;40(23):7416-22.**
Large numbers of viruses are excreted in human feces and urine, which even at low concentrations may cause illness when ingested. Some of these viruses have not been traditionally monitored in terms of waterborne diseases and are considered emergent viruses, such as hepatitis E virus (HEV) and JC and BK polyomavirus (JCPyV and BKPyV). The high prevalence of human adenoviruses (HAdV) and polyomaviruses, which both show DNA genomes, in sewage from widely divergent areas has suggested the relevance of evaluating these viruses as possible indicators of viral contamination. The concentration of these viruses was analyzed in sewage and river water and after treatment in a drinking-water treatment plant including chlorination, flocculation, ozonation, and granulate active carbon (GAC) filtration. Samples of GAC-filtered water were collected before a second chlorination treatment. The river used as a source of fresh water presented an average concentration of $2.6 \times 10(1)$ JCPyV and $4 \times 10(2)$ HAdV GC (genome copies)/L. A removal of 2 logarithms (99%) of HAdV and JCPyV was observed in the drinking-water treatment plant. All the GAC-filtered water samples studied contained HAdV, with a mean value of 4.3 HAdV GC/L. HEV strains belonging to genotype 3 were frequently detected in low concentrations in urban sewage and in biosolids or sewage containing swine feces but not in the river water samples studied. The detection of viruses by molecular techniques is useful for genetically describe emergent viruses in community wastewaters and water supplies. Quantification of JCPyV and HAdV using quantitative real-time PCR (QPCR) may be useful for evaluating virus removal efficiency in water treatment plants and as an index of the virological quality of water and of the potential presence of human viruses.
- **Arora NK, et al. Acute viral hepatitis types E, A, and B singly and in combination in acute liver failure in children in northern India. J. Med Virol. 1996; 48(3):215-21.**
The aetiological agents responsible for, and the outcome of, acute liver failure were investigated prospectively in 44 children (29 males, 15 females) attending a tertiary health care facility in India. The children were between the ages of 2 months and 13 years. Studies for viral infections and other etiologies could be carried out in 40 patients. Specific aetiological labels were possible in 35 (87.5%) patients. Thirty (75%) had evidence of acute viral hepatitis. Acute hepatitis E virus (HEV) infection was found in a total of 18 children, with hepatitis A (HAV) in 16, hepatitis B in 5, and C in 1. Seven had isolated infection with hepatitis E, five with A, and four with B. Nine had both E and A infection. Superinfection of HEV was observed in a child with Indian childhood cirrhosis (ICC). Acute HEV infection was confirmed by immunoblot assay in all the patients and in eight of these, HEV-RNA was also detected in the serum. HAV was involved in 37.5% of cases with isolated infection in 10% (4 of 40). The aetiological factors associated with acute liver failure, apart from HAV and HEV, were other hepatotropic viruses

(22.5%), Wilson's disease (5%), ICC (5%), and hepatotoxic drugs (7.5%). In five patients, no serological evidence of acute viral hepatitis could be found, neither did the metabolic screen yield any result. It was observed that enterically transmitted hepatitis viruses (HAV and HEV) were associated with 60% of acute hepatic failure in children. Mixed infection of HAV and HEV formed the single largest aetiological subgroup. In developing countries, where hepatitis A and E infections are endemic, severe complications can arise in the case of mixed infection. This may contribute to most of the mortality from acute liver failure during childhood.

- **Bradley DW. Hepatitis E virus: a brief review of the biology, molecular virology, and immunology of a novel virus. J Hepatol. 1995;22(1 Suppl):140-5.**

Our basic understanding of the biology, molecular virology, and immunology of hepatitis E virus (HEV) is briefly reviewed. HEV is a small, round, nonenveloped virus with morphologic and biophysical properties most similar to viruses found in the family Caliciviridae. The genome of HEV is approximately 7.5 kb in length and consists of a positive-sense, single-stranded RNA molecule that contains three distinct open reading frames (ORF1, ORF2, ORF3) that appear to encode for nonstructural and structural proteins based on the presence of well-defined consensus motifs and genomic organization similar to those of other calici- or calici-like viruses. Limited epitope mapping of the viral genome with synthetic peptides has revealed the presence of highly immunoreactive type-common and type-specific epitopes; these findings are consistent with the results of other studies that used recombinant expressed proteins from both the nonstructural and structural regions of the derived viral proteins encoded by ORFs 1, 2, and 3. Synthetic peptides and recombinant expressed proteins have been used to develop Western blot assays and enzyme immunoassays (EIAs) for the detection of IgA, IgG, and IgM anti-HEV in human and primate sera. Knowledge of the dynamics of HEV antigen and antibody expression in experimentally-infected primates is emerging, and prototype vaccines have been developed with recombinant expressed ORF2 and ORF3 proteins. Limited seroprevalence studies of anti-HEV in endemic and nonendemic regions of the world using one or more of the above assays has revealed a strong correlation between level of sanitation and incidence of disease and prevalence of anti-HEV.

- **Chadha MS, et al. Retrospective serological analysis of hepatitis E patients: a long-term follow-up study. J Viral Hepat. 1999 Nov;6(6):457-61.**

The aim of this study was to evaluate the persistence and protective role of antibodies to hepatitis E virus (anti-HEV) after natural hepatitis E infection. A retrospective analysis of immunoglobulin G (IgG) anti-HEV was performed in 37 patients followed-up for 5 years after epidemics of HEV. Two patients with sporadic hepatitis E (HE) were followed-up for 12 and 8 years. All patients infected during epidemics of HE were positive for IgG anti-HEV at 5 years of follow-up (geometric mean titre: 174.75). The two patients with sporadic HE were positive for IgG anti-HEV at the end of 12 and 8 years of follow-up (the IgG anti-HEV titre was 1: 200 in each patient). This study showed protection against disease by antibodies to HEV. It was therefore concluded that hepatitis E may be preventable by an efficacious vaccine.

- **Clemente-Casares P, et al. Hepatitis E virus epidemiology in industrialized countries. Emerg Infect Dis. 2003 Apr;9(4):448-54.**

To determine the prevalence of Hepatitis E virus (HEV) in industrialized nations, we analyzed the excretion of HEV strains by the populations of Spain, France, Greece, Sweden, and the United States. Twenty of 46 (43.5%) urban sewage samples collected in Barcelona from 1994 to 2002 tested positive for HEV. We identified 15 HEV strains, which were similar to two HEV isolates previously described in Barcelona in clinical samples and to strains from diverse geographic HEV-nonendemic areas. We also identified two HEV strains in sewage samples from Washington, D.C., and Nancy, France; these samples were also positive for Hepatitis A

virus. In addition, we studied the role of pigs as a reservoir for HEV and identified one new swine HEV strain. Our results suggest that HEV may be more prevalent than previously considered in industrialized countries and that variants of the virus circulate simultaneously in one region.

- **Cost-effectiveness background on Hepatitis E. Geneva, World Health Organization, 2014** (http://www.who.int/immunization/sage/meetings/2014/october/5_HEV_Cost-effectiveness_section_V3.pdf?ua=1, accessed December 2014).
- **Crum-Cianflone NF, et al. Hepatitis E virus infection in HIV-infected persons. *Emerg Infect Dis* 2012; 18:502-6.**
To determine whether hepatitis E virus (HEV) is a cause of hepatitis among HIV-infected persons, we evaluated 1985-2009 data for US military beneficiaries. Evidence of acute or prior HEV infection was detected for 7 (4%) and 5 (3%) of 194 HIV-infected persons, respectively. HEV might be a cause of acute hepatitis among HIV-infected persons.
- **Drobeniuc J, et al. Serologic assays specific to immunoglobulin M antibodies against hepatitis E virus: pangenotypic evaluation of performances. *Clin. Infect. Dis.* 51, e24–e27 (2010).**
Six immunoassays for detecting immunoglobulin M antibodies to hepatitis E virus were evaluated. Serum samples representing acute infection by each of the 4 viral genotypes as well as nonacute hepatitis E virus infection constituted the test panels. Diagnostic sensitivities and specificities as well as interassay agreement varied widely. Analytical sensitivity limits also were determined and were found to be particularly disparate.
- **Fujiwara S, et al. Chronic hepatitis E: a review of the literature. *J Viral Hepat.* 2014 Feb;21(2):78-89.**
In 1978, the first case of hepatitis E was identified as non-A, non-B hepatitis. Hepatitis E virus (HEV) infection is believed to be one of the common causes of enterically transmitted acute hepatitis in developing countries and is rare in developed countries, except in patients with a history of travel. However, an increasing number of chronic HEV infection cases have recently been reported in developed countries. In these countries, immunosuppressed patients with HEV infection, such as organ transplant recipients, human immunodeficiency virus (HIV)-infected patients or patients with haematological malignancies, could develop chronic hepatitis E (CHE) infection. Approximately 60% of HEV infections in immunocompromised patients after solid organ transplantation evolve to CHE without antiviral treatment. Clinical manifestations of CHE are often nonspecific symptoms. Many patients with CHE infection are asymptomatic, but some have jaundice, fatigue, abdominal pain, fever and asthenia. Several extrahepatic manifestations have also been reported. Although chronic HEV infection can result in progressive severe liver failure and cirrhosis, diagnosis is often controversial because of the lack of specific diagnostic criteria. Many CHE cases are diagnosed by HEV RNA-positive serum or stool for >6 months. Immunosuppressive drugs, interferon-alpha and ribavirin have been used for treatment. Diagnostic reverse-transcription polymerase chain reaction is useful for estimating treatment efficacy. Preventive measures for HEV infection have been discussed, while systematic guidelines have not yet been reported.
- **Girones R, et al. Chlorine inactivation of hepatitis E virus and human adenovirus 2 in water. *J Water Health.* 2014; 12(3): 436-442.**
Hepatitis E virus (HEV) is transmitted via the fecal-oral route and has been recognized as a common source of large waterborne outbreaks involving contaminated water in developing

countries. Thus, there is the need to produce experimental data on the disinfection kinetics of HEV by chlorine in water samples with diverse levels of fecal contamination. Here, the inactivation of HEV and human adenovirus C serotype 2 (HAdV2), used as a reference virus, was monitored using immunofluorescence and quantitative reverse transcription polymerase chain reaction (RT-qPCR) assays. HEV has been shown to be susceptible to chlorine disinfection and presented equivalent kinetics to human adenoviruses. The C(t) values observed for a 2-log reduction of HEV were 0.41 in buffered demand-free water and 11.21 mg/L × min in the presence of 1% sewage. The results indicate that the inactivation kinetics of HEV and HAdV2 are equivalent and support the use of chlorine disinfection as an effective strategy to control HEV waterborne transmission.

- **Hepatitis E Vaccine Working Group. Hepatitis E: epidemiology and disease burden.** Geneva, World Health Organization, 2014
(http://www.who.int/immunization/sage/meetings/2014/october/1_HEV_burden_paper_final_03_Oct_14_yellow_book.pdf?ua=1, accessed December 2014).
- **Hepatitis E Vaccine Working Group. Hepatitis E vaccine pipeline.** Geneva, World Health Organization, 2014
(http://www.who.int/immunization/sage/meetings/2014/october/4_Hepatitis_E_vaccine_pipeline_final_29_Sept_14.pdf?ua=1, accessed December 2014).
- **Hepatitis E Vaccine Working Group. Hepatitis E vaccine: Composition, safety, immunogenicity and efficacy.** Geneva, World Health Organization, 2014
(http://www.who.int/immunization/sage/meetings/2014/october/2_HepEvaccsafety_immunogenicity_efficacy_final_1Oct2014.pdf?ua=1, accessed December 2014).
- **Hewitt PE, et al. 2. Hepatitis E virus in blood components: a prevalence and transmission study in southeast England. Lancet 2014; 384:1766-73.**
BACKGROUND: The prevalence of hepatitis E virus (HEV) genotype 3 infections in the English population (including blood donors) is unknown, but is probably widespread, and the virus has been detected in pooled plasma products. HEV-infected donors have been retrospectively identified through investigation of reported cases of possible transfusion-transmitted hepatitis E. The frequency of HEV transmission by transfusion and its outcome remains unknown. We report the prevalence of HEV RNA in blood donations, the transmission of the virus through a range of blood components, and describe the resulting morbidity in the recipients. **METHODS:** From Oct 8, 2012, to Sept 30, 2013, 225,000 blood donations that were collected in southeast England were screened retrospectively for HEV RNA. Donations containing HEV were characterised by use of serology and genomic phylogeny. Recipients, who received any blood components from these donations, were identified and the outcome of exposure was ascertained. **FINDINGS:** 79 donors were viraemic with genotype 3 HEV, giving an RNA prevalence of one in 2848. Most viraemic donors were seronegative at the time of donation. The 79 donations had been used to prepare 129 blood components, 62 of which had been transfused before identification of the infected donation. Follow-up of 43 recipients showed 18 (42%) had evidence of infection. Absence of detectable antibody and high viral load in the donation rendered infection more likely. Recipient immunosuppression delayed or prevented seroconversion and extended the duration of viraemia. Three recipients cleared longstanding infection after intervention with ribavirin or alteration in immunosuppressive therapy. Ten recipients developed prolonged or persistent infection. Transaminitis was common, but short-term morbidity was rare; only one recipient developed apparent but clinically mild post-transfusion hepatitis. **INTERPRETATION:** Our findings suggest that HEV genotype 3 infections are widespread in the English population

and in blood donors. Transfusion-transmitted infections rarely caused acute morbidity, but in some immunosuppressed patients became persistent. Although at present blood donations are not screened, an agreed policy is needed for the identification of patients with persistent HEV infection, irrespective of origin, so that they can be offered antiviral therapy.

- **Huzly D, et al. Transfusion-transmitted hepatitis E in Germany, 2013. Euro Surveill 2014; 19:20812.**

The reported IgG seroprevalence against hepatitis E virus (HEV) in German blood donations is 6.8%, and HEV RNA detected in 0.08%, but documented evidence for HEV transmission is lacking. We identified two donations from a single donor containing 120 IU HEV RNA/mL plasma and 490 IU/mL. An infectious dose of 7,056 IU HEV RNA was transmitted via apheresis platelets to an immunosuppressed patient who developed chronic HEV. Further, transmission was probable in an immunocompetent child.

- **Kamar N, et al. Hepatitis E virus: what transplant physicians should know. Am J Transplant. 2012 Sep;12(9):2281-7**

Hepatitis E virus (HEV) infection is an underdiagnosed disease in the developed world. In pediatric and adult organ transplant patients HEV infection can cause chronic hepatitis, which can lead to cirrhosis. Extra-hepatic manifestations, such as neurological symptoms and kidney injury, have been also reported in transplant patients. In this comprehensive mini review, we summarize the current knowledge on HEV infection in transplant patients, that is, its prevalence, incidence, natural history and therapy.

- **Kamar N, et al. Hepatitis E. Lancet. 2012 Jun 30;379(9835):2477-88.**

Hepatitis E virus (HEV) was discovered during the Soviet occupation of Afghanistan in the 1980s, after an outbreak of unexplained hepatitis at a military camp. A pooled faecal extract from affected soldiers was ingested by a member of the research team. He became sick, and the new virus (named HEV), was detected in his stool by electron microscopy. Subsequently, endemic HEV has been identified in many resource-poor countries. Globally, HEV is the most common cause of acute viral hepatitis. The virus was not initially thought to occur in developed countries, but recent reports have shown this notion to be mistaken. The aim of this Seminar is to describe recent discoveries regarding HEV, and how they have changed our understanding of its effect on human health worldwide.

- **Khudyakov Y, et al. Serological diagnostics of hepatitis E virus infection. Virus Res. 2011 Oct;161(1):84-92.**

Development of accurate diagnostic assays for the detection of serological markers of hepatitis E virus (HEV) infection remains challenging. In the course of nearly 20 years after the discovery of HEV, significant progress has been made in characterizing the antigenic structure of HEV proteins, engineering highly immunoreactive diagnostic antigens, and devising efficient serological assays. However, many outstanding issues related to sensitivity and specificity of these assays in clinical and epidemiological settings remain to be resolved. Complexity of antigenic composition, viral genetic heterogeneity and varying epidemiological patterns of hepatitis E in different parts of the world present challenges to the refinement of HEV serological diagnostic assays. Development of antigens specially designed for the identification of serological markers specific to acute infection and of IgG anti-HEV specific to the convalescent phase of infection would greatly facilitate accurate identification of active, recent and past HEV infections.

- **Khuroo MS, et al. Aetiology and prognostic factors in acute liver failure in India. J Viral Hepat. 2003 May;10(3):224-31.**

The early prognostic indicators for acute liver failure in endemic zones for hepatitis E virus have not been determined. All consecutive patients with acute liver failure from a geographically defined region endemic for hepatitis E virus were studied over the period April 1989-April 1996. Demographic, clinical and biochemical parameters were recorded at presentation and serum samples were analysed for known viral hepatitis (A-E) markers. Multiple parameters were compared in survivors and non-survivors in a univariate analysis. All significant factors on univariate analysis were entered into a stepwise logistic regression analysis to identify independent variables of prognosis. The sensitivity and specificity of significant prognostic factors was then assessed. A total of 180 [69 males and 111 females: age (mean +/- SD) 31.1 +/- 14.7 years] with acute liver failure were studied. Of these, 131 (72.8%) patients died. Hepatitis E virus was the aetiological cause in 79 (43.9%) patients, while hepatitis A virus, hepatitis B virus, hepatitis C virus and non-A, non-E agent/s could be incriminated in four (2.1%), 25 (13.9%), 13 (7.2%) and 56 (31.1%) patients respectively. Of 83 women in childbearing age, 49 (59.0%) were pregnant, 33 (67.3%) of these were in the third trimester. Forty-seven (95.8%) pregnant women had HEV infection. Nine variables differed significantly between survivors and non-survivors on univariate analysis. Of these, four variables which predicted the adverse outcome on multivariate analysis were non-hepatitis-E aetiology, prothrombin time >30 s, grade of coma >2 and age >40 years in that order of significance. Pregnancy per se or duration of gestation did not adversely affect the prognosis. In endemic areas, hepatitis E virus is the commonest cause of acute liver failure. Acute liver failure occurs in a high proportion of pregnant women, mostly in third trimester. Early predictors of a poor outcome are non-E aetiology, prothrombin time >30 s, grade of coma >2 and age >40 years.

- **Khuroo MS, et al. Aetiology, clinical course and outcome of sporadic acute viral hepatitis in pregnancy. J Viral Hepat. 2003 Jan;10(1):61-9**

Hepatitis E causes large-scale epidemics in endemic areas. The disease, during epidemics, has increased incidence and severity in pregnant women. Sporadic acute viral hepatitis (AVH) is common in endemic areas. The relationship of sporadic AVH and pregnancy has not been well studied. Over a 3-year period we prospectively studied 76 pregnant women and 337 non-pregnant women of childbearing age with sporadic acute viral hepatitis for aetiology, clinical course and outcome of disease. The aetiology in sporadic AVH was hepatitis A virus (HAV) in six (1.5%), hepatitis B virus (HBV) in 62 (15%), hepatitis C virus (HCV) in seven (1.7%), hepatitis D virus (HDV) co-infection in six (1.5%), hepatitis E virus (HEV) in 205 (49.6%), and hepatitis non-A-to-E (HNAE) in 127 (30.7%). Sixty-five (85.5%) pregnant women and 140 (41.5%) nonpregnant women had hepatitis E. The proportion of pregnant women was 31.7% in HEV group and 5.3% in non-HEV group [$P < 0.001$; OR=8.3 (95%CI 4.2-16.3)]. The prevalence of HEV in pregnant women in first trimester (76.9%), second trimester (88.9%), third trimester (83.8%) and puerperium (100%) did not differ significantly ($P=0.09$). Forty-seven (61.8%) of the 76 pregnant women developed fulminant hepatic failure (FHF), 69.2% in HEV group and 10% in non-HEV group ($P < 0.001$). Thirty-four (10.1%) nonpregnant women developed fulminant hepatic failure, 10% in HEV group and 9.7% in non-HEV group ($P=0.86$). FHF had occurred in four (40%) of 10 patients with HE in first trimester as against 41 (74.5%) of 55 patients in second trimester and beyond ($P=0.015$). Amongst the major complications of fulminant hepatic failure, cerebral oedema (53.2%) and disseminated intravascular coagulation (21.3%) occurred more often in pregnant women than in nonpregnant women (29.4% and 2.8%; $P=0.03$ and 0.016 , respectively) while infections occurred more often in nonpregnant women (36.1%) than in pregnant women (10.6%; $P=0.003$). Fifty (61.7%) patients with FHF died [25 (53.2%) pregnant women and 25 (69.5%) nonpregnant women ($P=0.06$)]. Cerebral oedema

and HEV aetiology were independent variables of survival in patients with FHF. Patients with cerebral oedema had worse prognosis and patients with HEV aetiology had best chances of survival. Hence HEV was the most common cause of sporadic AVH in this endemic area. High proportion of pregnant women and increased severity of disease in pregnancy were limited to patients with hepatitis E. Sporadic AVH caused by agents other than HEV did not show any special predilection to or increased severity in pregnancy. FHF in pregnant women caused by HEV was an explosive disease with short pre-encephalopathy period, rapid development of cerebral oedema and high occurrence of disseminated intravascular coagulation and may represent a severe manifestation of a Schwartzmann-like phenomenon.

- **Khuroo MS. Seroepidemiology of a second epidemic of hepatitis E in a population that had recorded first epidemic 30 years before and has been under surveillance since then. *Hepatol Int.* 2010 Feb 3;4(2):494-9.**

PURPOSE: Large-scale waterborne epidemics of hepatitis E occur in developing countries. It is not known why these epidemics occur repeatedly and selectively in adult population?

METHODS: We studied seroepidemiology of an outbreak of hepatitis E in one of 15 villages that had recorded first epidemic of hepatitis E 30 years back. Another village not affected by the second epidemic was taken as a control. Overall, 1,216 sera were collected (638 from the epidemic village and 578 from the control village) for serological markers of both hepatitis A virus (HAV) and hepatitis E virus (HEV). **RESULTS:** The seroprevalence of anti-HEV in this population following the first epidemic in 1978 was 29.4%. Antibodies were detected in only 47% of the 45 patients affected by icteric HEV infection 14 years after the first epidemic. At 30-year follow-up, the seroprevalence of anti-HEV was only 4.5% (26/578). In the village affected by second epidemic, 138 (21.6%) subjects had serological evidence of recent HEV infection. The attack rate was 23.6% (78/330) in children (≤ 14 years) and 19.4% (60/308) in adults ($P = 0.21$). The attack rate of anicteric HEV infection was 21.8% (72/330) in children and 14.6% (45/308) in adults ($P = 0.02$). **CONCLUSIONS:** Following hepatitis E epidemics, there is a gradual loss of antibodies in the community over the decades and poor exposure to HEV infection in the cohort of population born during the interepidemic period. The next epidemic occurs when antibody levels fall to critically low levels and there is associated gross fecal contamination of water resources. During epidemic, persons of all age groups are exposed to infection, with predominant anicteric disease in children.

- **Kim JH, et al. A systematic review of the epidemiology of hepatitis E virus in Africa. *BMC Infect Dis.* 2014 Jun 5;14:308.**

BACKGROUND: Hepatitis E Virus (HEV) infection is a newly recognized serious threat to global public health and Africa is suspected to be among the most severely affected regions in the world. Understanding HEV epidemiology in Africa will expedite the implementation of evidence-based control policies aimed at preventing the spread of HEV including policies for the use of available resources such as HEV vaccines. **METHODS:** Here we present a comprehensive review of HEV epidemiology in Africa based on published data. We searched for articles on HEV epidemiology in Africa from online databases such as PubMed, Scopus, and ISI Web of Science and critically reviewed appropriate publications to extract consistent findings, identify knowledge gaps, and suggest future studies. **RESULTS:** Taking a particularly high toll in pregnant women and their fetuses, HEV has infected human populations in 28 of 56 African countries. Since 1979, 17 HEV outbreaks have been reported about once every other year from Africa causing a reported 35,300 cases with 650 deaths. **CONCLUSIONS:** In Africa, HEV infection is not new, is widespread, and the number of reported outbreaks are likely a significant underestimate. The authors suggest that this is a continent-wide public health problem that deserves the attention of local, regional and international agencies to

implement control policies that can save numerous lives, especially those of pregnant women and their fetuses.

- **Kumar A, et al. Hepatitis E in pregnancy. Int J Gynaecol Obstet. 2004;85(3): 240-244.**
OBJECTIVES: To study the spectrum and the clinical and biochemical course of viral hepatitis E during pregnancy. **METHODS:** In this prospective study, sera of 62 pregnant women having jaundice in the third trimester of pregnancy were analyzed for markers of hepatitis A, B, C and E viruses. The cord blood samples of hepatitis E virus (HEV)-positive pregnant women at the time of delivery were tested for IgM anti-HEV antibodies by enzyme-linked immunosorbent assay and HEV-RNA by reverse transcriptase polymerase chain reaction.
RESULTS: Of the 62 patients, 45.2% had HEV infection and nine developed fulminant hepatic failure (FHF). Eighty-one percent of FHF cases and 37.25% of acute viral hepatitis cases were caused by HEV. Approximately two-thirds of the pregnant women with HEV infection had preterm deliveries. The mortality rate among the HEV-positive pregnant women was 26.9%. Vertical transmission was observed in 33.3% of cases. **CONCLUSIONS:** One-third of the pregnant women with HEV infection had a severe form of hepatitis in the third trimester of pregnancy, i.e. FHF. Hepatitis E in pregnancy is associated with high rates of preterm labor and mortality.
- **Li SW, et al. A bacterially expressed particulate hepatitis E vaccine: antigenicity, immunogenicity and protectivity in primates. Vaccine. 2005; 23: 2893-901.**
It was evaluated its antigenicity, immunogenicity and efficacy of a candidate recombinant hepatitis E virus (HEV) vaccine, referred hitherto as HEV 239 vaccine. The vaccine peptide has a 26 amino acids extension from the N terminal of another peptide, E2, of the HEV capsid protein, which has been shown to protect monkeys against HEV infection previously. The vaccine peptide is similar as E2 in that: first, the vaccine peptide migrates predominantly as dimer in SDS-PAGE and it is dissociated into monomers by heating; second, its dimeric form of which predominantly recognized by HEV reactive human serum; and third, it shows the same pattern of reaction as E2 with a panel of eight monoclonal antibodies that had been raised against E2. In contrast to E2, the vaccine peptide aggregates to form particles of 13 nm mean radius, and consequently, it is more than 240 times more immunogenic than E2. Using alum as adjuvant, immunizing dose determined in mice was 80-250 ng for the vaccine and >60 microg for E2. Rhesus monkeys twice vaccinated with a 10 microg or a 20 microg formulation of this vaccine showed essentially the same antibody response, whereas the response to a 5 microg formulation was delayed but reached similar antibody levels. All the three vaccine formulations afford complete protection against infection with 10(4) genome equivalent dose of the homologous genotype 1 virus. At higher virus dose of 10(7), the same vaccine formulation partially protected against the infection and completely protected against hepatitis. The efficacy of the vaccine was essentially the same for the homologous genotype 1 virus and heterologous genotype 4 virus.
- **Li SW, et al. Mutational analysis of essential interactions involved in the assembly of hepatitis E virus capsid. J Biol Chem. 2005; 280: 3400-6.**
The hepatitis E virus (HEV) capsid consists of a single structural protein, a portion of which is engaged in isosahedral contact to form a basal shell, and another portion in dimeric contact to form the homodimers protruding from the shell. Previous studies revealed that homodimers of the truncated HEV capsid proteins, E2 (amino acids 394-606) and p239 (amino acids 368-606), model dominant antigenic determinants of HEV. Immunization with these proteins protected rhesus monkeys against the virus, and three monoclonal antibodies against the homodimers could neutralize HEV infectivity and/or immune-capture of the virus. Furthermore, homodimers of p239 further interact to form particles of 23 nm diameter,

rendering it an efficacious candidate vaccine. In light of this we postulate that the interactions involved in the formation of the homodimers and particles might be similar to those involved in assembly of the virus capsid. Presently, mutational analysis was carried out to identify these sites of interactions. The site of dimeric interactions was located to a cluster of six hydrophobic amino acids residues, Ala597, Val598, Ala599, Leu601, and Ala602; furthermore, the site involved in particle formation was located at amino acids 368-394. The possibility that these sites are also involved in assembly of the virus capsid is supported by the fact that they are located at two major and highly conserved hydrophobic regions of the HEV structural protein.

- **Matsuda H, et al. Severe hepatitis E virus infection after ingestion of uncooked liver from a wild boar. *J Infect Dis.* 2003 Sep 15;188(6):944. Available at:**

<http://jid.oxfordjournals.org/content/188/6/944.long>

To the Editor —As was reported in the *Journal* by Takahashi et al. [1] as well as by the authors of a letter to the editor about Takahashi et al.'s article [2], hepatitis E virus (HEV) infection caused by genotypes III and IV seems to be cryptically endemic in Japan, with the transmission mode yet to be resolved. Zoonotic risks have been suggested for sporadic HEV infections, particularly in industrialized countries [3]. We hereby report our recent experience in Japan, which may support the zoonosis hypothesis. A 53-year-old man (patient A) was admitted to one of our hospitals for acute hepatitis on 12 March 2003. His hepatitis was a severe type, as indicated by the levels of total bilirubin (10.2 mg/dL) and prothrombin (only 17%). Despite the initial severity of the disease, he showed a rapid recovery, without developing fulminant hepatic failure. Convalescence serum obtained on 15 April was positive for both IgM and IgG classes of anti-HEV but was negative for HEV RNA. Acute-phase serum from this patient was not available. Later, to our surprise, it was revealed that, on the same day that patient A had been admitted, one of his friends (a 70-year-old man; patient B) had been admitted to another hospital, for similarly severe hepatitis (total bilirubin, 17.1 mg/dL; prothrombin, 40%). Patient B developed hepatic coma and died of fulminant hepatic failure on 13 April. Acute-phase serum obtained on 13 March was found, retrospectively, to be positive for HEV RNA. Determination of a 326-nt partial open-reading frame-1 sequence of his HEV RNA (accession no. AB114178) indicated that this isolate segregates to genotype IV. During the 3 months preceding the onset of disease, neither patient A nor patient B had traveled to areas where HEV is endemic, but patient A mentioned that he and patient B had enjoyed eating uncooked boar liver together a total of 5 times from late January to early February. Among the patients' family members and friends, no one had eaten the boar liver and no one had contracted hepatitis. Chandler et al. [4] reported serological evidence suggesting boars and pigs as candidate animal reservoirs for HEV. Although we could not prove that the uncooked boar liver was the source of the HEV infection (since it all had been eaten), it appears likely that this was the case. We Japanese are notorious for the peculiarity of our eating habits: we like to eat uncooked fish (sashimi or sushi) and, less frequently, raw meat (including liver from mammals). These eating habits may, at least partially, explain the cryptic endemicity of HEV infection in Japan.

- **Navaneethan U, et al. Hepatitis E and pregnancy: understanding the pathogenesis. *Liver Int.* 2008 Nov;28(9):1190-9.**

Hepatitis E virus (HEV) is a single-stranded RNA virus that causes large-scale epidemics of acute viral hepatitis, particularly in developing countries. In men and non-pregnant women, the disease is usually self-limited and has a case-fatality rate of less than <0.1%. However, in pregnant women, particularly from certain geographical areas in India, HEV infection is more severe, often leading to fulminant hepatic failure and death in a significant proportion of patients. In contrast, reports from Egypt, Europe and the USA have shown that the course and severity of viral hepatitis during pregnancy is not different from that in non-pregnant women.

The reasons for this geographical difference are not clear. The high mortality rate in pregnancy has been thought to be secondary to the associated hormonal (oestrogen and progesterone) changes during pregnancy and consequent immunological changes. These immunological changes include down regulation of the p65 component of nuclear factor (NF-kappaB) with a predominant T-helper type 2 (Th2) bias in the T-cell response along with host susceptibility factors, mediated by human leucocyte antigen expression. Thus far, researchers were unable to explain the high HEV morbidity in pregnancy, why it is different from other hepatitis viruses such as hepatitis A with similar epidemiological features and the reason behind the difference in HEV morbidity in pregnant women in different geographical regions. The recent developments in understanding the immune response to HEV have encouraged us to review the possible mechanisms for these differences. Further research in the immunology of HEV and pregnancy is required to conquer this disease in the near future.

- Nelson KE, et al. The epidemiology of hepatitis E virus infections in developed countries and among immunocompromised patients. Expert Rev Anti Infect Ther. 2011 Dec;9(12):1133-48.** Hepatitis E virus (HEV) is an important cause of acute hepatitis in humans worldwide, both as epidemic and sporadic disease. Since the virus was identified in 1983, epidemics have occurred regularly in many countries across South and Southeast Asia when seasonal floods have contaminated drinking water supplies and in Africa during humanitarian crises among refugee populations without access to clean water. In addition, sporadic cases and small clusters of HEV infections have been recognized throughout the world in developed countries over the past couple of decades. This review will focus on emerging evidence of HEV infection as an under-recognized pathogen in Europe, the USA and other industrialized countries. We will discuss some of the issues associated with the recognition, diagnosis and treatment of these sporadic cases. We will also summarize the recent literature on autochthonous HEV infection among populations in developed countries in industrialized Europe, the USA, Japan and other industrialized Asian countries. We will review recent reports of acute and chronic HEV infections among transplant recipients and other immuno-compromised individuals including HIV/AIDS patients.
- Pischke S, et al. Ribavirin treatment of acute and chronic hepatitis E: a single-centre experience. Liver Int. 2013 May;33(5):722-6.**
BACKGROUND: The role of ribavirin for treatment of severe acute or chronic hepatitis E virus (HEV) infection is not well defined. **AIMS:** To investigate the applicability and efficacy of ribavirin therapy in acute and chronic HEV infections within a large single-centre cohort. **MATERIALS & METHODS:** Clinical courses of forty-four German HEV-infected individuals were analysed. **RESULTS:** In a prospective case series, we observed spontaneous recovery from acute symptomatic HEV-infection in 10/11 immunocompetent individuals. Ribavirin therapy was initiated in one patient with severe acute HEV-genotype-1e infection who rapidly improved liver function and cleared HEV. Of 15 organ transplant recipients with prolonged HEV viraemia, reduction in immunosuppression led to HEV-clearance in three patients, while ribavirin therapy was initiated in 11 subjects. A rapid response with undetectable HEV-RNA occurred in nine subjects. One patient died after experiencing a virological breakthrough associated with ribavirin dose reduction because of severe anaemia. **DISCUSSION:** Ribavirin is a safe treatment option for HEV infections. However, the optimal dose of ribavirin for the treatment of chronic hepatitis E remains to be determined as treatment failure may occur.
- Ramalingaswami V, et al. Waterborne non-A, non-B hepatitis. Lancet. 1988;1(8585): 571-573.** Waterborne non-A, non-B hepatitis (NANB) is responsible for outbreaks of hepatitis with a predilection for young adults. The disease is usually mild, except in pregnant women, who

have a high case-fatality rate from fulminant hepatic failure. Diagnosis is largely based on the epidemiological findings of faecal contamination of drinking water and serological exclusion of hepatitis A and B virus infection. Histological features of liver biopsy specimens are characteristic and virus-like particles in the stool are aggregated by antibody present in acute and convalescent phase sera of the test subject. NANB is widespread in India and several countries of South-East Asia; it is increasingly recognised in Africa and may occur in Latin America. Control measures include provision of clean water supplies, safe disposal of human excreta, and sound personal and food hygiene practices. Passive immunisation with immunoglobulin derived from healthy donors resident in the countries affected by the disease may protect vulnerable groups.

- **Recombinant Hepatitis E Vaccine. Xiamen innovax Biotech. 2012. Available at <http://www.innovax.cn/en/pro1.aspx?CatelD=52#103>, accessed 17.12.2014**
- **Rein DB, et al. The global burden of hepatitis E genotypes 1 and 2 in 2005. *Hepatology*. 2012; 55(4):988-97.**
We estimated the global burden of hepatitis E virus (HEV) genotypes 1 and 2 in 2005. HEV is an emergent waterborne infection that causes source-originated epidemics of acute disease with a case fatality rate thought to vary by age and pregnancy status. To create our estimates, we modeled the annual disease burden of HEV genotypes 1 and 2 for 9 of 21 regions defined for the Global Burden of Diseases, Injuries, and Risk Factors Study (the GBD 2010 Study), which represent 71% of the world's population. We estimated the seroprevalence of anti-HEV antibody and annual incidence of infection for each region using data from 37 published national studies and the DISMOD 3, a generic disease model designed for the GBD Study. We converted incident infections into three mutually exclusive results of infection: (1) asymptomatic episodes, (2) symptomatic disease, and (3) death from HEV. We also estimated incremental cases of stillbirths among infected pregnant women. For 2005, we estimated 20.1 (95% credible interval [Cr.I.]: 2.8-37.0) million incident HEV infections across the nine GBD Regions, resulting in 3.4 (95% Cr.I.: 0.5-6.5) million symptomatic cases, 70,000 (95% Cr.I.: 12,400-132,732) deaths, and 3,000 (95% Cr.I.: 1,892-4,424) stillbirths. We estimated a probability of symptomatic illness given infection of 0.198 (95% Cr.I.: 0.167-0.229) and a probability of death given symptomatic illness of 0.019 (95% Cr.I.: 0.017-0.021) for nonpregnant cases and 0.198 (95% Cr.I.: 0.169-0.227) for pregnant cases. **CONCLUSION:** The model was most sensitive to estimates of age-specific incidence of HEV disease.
- **Robbins A, et al. Severe acute hepatitis E in an HIV infected patient: Successful treatment with ribavirin. *J Clin Virol*. 2014;60(4): 422-423.**
In industrialized countries, most cases of hepatitis E virus (HEV) infection in humans are autochthonous, mainly through foodborne and zoonotic transmission routes. In Europe, genotype 3 is a cause of acute self-limiting viral hepatitis, but can also be responsible for chronic hepatitis in immunocompromised patients. Ribavirin has been successfully used in the treatment of chronic hepatitis E and in a few cases of severe acute hepatitis E in immunocompetent patients. We report here the case of a 39 year-old man infected with HIV presenting with acute hepatitis E (genotype 3c). Unlike most cases, evolution was severe with a fall of prothrombin time down to 45%. Treatment with ribavirin allowed rapid viral clearance and a gradual normalization of liver function tests.
- **Shao W. Li et al. A bacterially expressed particulate hepatitis E vaccine: antigenicity, immunogenicity and protectivity in primates. *Vaccine* 23 (2005) 2893–2901**
It was evaluated its antigenicity, immunogenicity and efficacy of a candidate recombinant hepatitis E virus (HEV) vaccine, referred hitherto as HEV 239 vaccine. The vaccine peptide has a 26 amino acids extension from the N terminal of another peptide,

E2, of the HEV capsid protein, which has been shown to protect monkeys against HEV infection previously. The vaccine peptide is similar as E2 in that: first, the vaccine peptide migrates predominantly as dimer in SDS-PAGE and it is dissociated into monomers by heating; second, its dimeric form of which predominantly recognized by HEV reactive human serum; and third, it shows the same pattern of reaction as E2 with a panel of eight monoclonal antibodies that had been raised against E2. In contrast to E2, the vaccine peptide aggregates to form particles of 13 nm mean radius, and consequently, it is more than 240 times more immunogenic than E2. Using alum as adjuvant, immunizing dose determined in mice was 80-250 ng for the vaccine and >60 microg for E2. Rhesus monkeys twice vaccinated with a 10 microg or a 20 microg formulation of this vaccine showed essentially the same antibody response, whereas the response to a 5 microg formulation was delayed but reached similar antibody levels. All the three vaccine formulations afford complete protection against infection with 10(4) genome equivalent dose of the homologous genotype 1 virus. At higher virus dose of 10(7), the same vaccine formulation partially protected against the infection and completely protected against hepatitis. The efficacy of the vaccine was essentially the same for the homologous genotype 1 virus and heterologous genotype 4 virus.

- **Teshale EH, et al. Hepatitis E: Epidemiology and Prevention. World J. Hepatol. 2011; 3(12):285-91.**

Hepatitis E is caused by the hepatitis E virus (HEV), the major etiologic agent of enterically transmitted non-A hepatitis worldwide. HEV is responsible for major outbreaks of acute hepatitis in developing countries, especially in many parts of Africa and Asia. The HEV is a spherical, non-enveloped, single-stranded, positive sense RNA virus that is approximately 32 nm to 34 nm in diameter and is the only member in the family Hepeviridae and genus Hepevirus. There are four distinct genotypes of HEV (genotypes 1-4). While genotype 1 is predominantly associated with large epidemics in developing countries, genotype 3 has recently emerged as a significant pathogen in developed countries. The clinical manifestations and the laboratory abnormalities of hepatitis E are not distinguishable from that caused by other hepatitis viruses. However, high mortality among pregnant women particularly during the third trimester distinguishes HEV from other causes of acute viral hepatitis. Specific etiologic diagnosis among infected cases can be made by serological testing or detection of viral nucleic acid by reverse transcription polymerase chain reaction. Although there are vaccine candidates that had been shown to be safe and efficacious in clinical trials, none are approved currently for use. There is no specific therapy for acute hepatitis E as treatment remains supportive.

- **Teshale EH, et al. Evidence of person-to-person transmission of hepatitis E virus during a large outbreak in Northern Uganda. Clin Infect Dis. 2010 Apr 1;50(7):1006-10.**

BACKGROUND: Outbreaks of infection with hepatitis E virus (HEV) are frequently attributed to contaminated drinking water, even if direct evidence for this is lacking. **METHODS:** We conducted several epidemiologic investigations during a large HEV infection outbreak in Uganda. **RESULTS:** Of 10,535 residents, 3218 had HEV infection; of these, 2531 lived in households with >1 case. HEV was not detected in drinking water or zoonotic sources. Twenty-five percent of cases occurred > or = 8 weeks after onset of hepatitis in an index case in the household. Households with > or = 2 cases were more likely to have a member(s) who attended a funeral, had close contact with a jaundiced person, or washed hands in a common basin with others (P < .05 for all). **CONCLUSIONS:** A high attack rate in households, lack of a common source of infection, and poor hygienic practices in households with > or = 2 cases suggest person-to-person transmission of HEV during this outbreak.

- **Teshale EH, et al. Hepatitis E epidemic, Uganda. Emerg Infect Dis. 2010 Jan;16(1):126-9.**
In October 2007, an epidemic of hepatitis E was suspected in Kitgum District of northern Uganda where no previous epidemics had been documented. This outbreak has progressed to become one of the largest hepatitis E outbreaks in the world. By June 2009, the epidemic had caused illness in >10,196 persons and 160 deaths.
- **Thomson K, et al. Investigation of Hepatitis E outbreak among refugees – Upper Nile, South Sudan, 2012-2013. MMWR. 2013; 62(29); 581-586.**
During the week of July 2, 2012, the deaths of two pregnant women and one child were reported by household mortality surveillance in Jamam refugee camp, Maban County, Upper Nile State, South Sudan. All were reported to have yellow eyes before death. During July 27-August 3, 2012, three adult males with acute onset jaundice were admitted to the Médecins Sans Frontières (MSF) hospital in Jamam camp; two died within 4 days of admission. The Republic of South Sudan Ministry of Health, United Nations High Commissioner for Refugees (UNHCR), CDC, and humanitarian organizations responded through enhanced case surveillance, a serosurvey investigation, and targeted prevention efforts. As of January 27, 2013, a total of 5,080 acute jaundice syndrome (AJS) cases had been reported from all four Maban County refugee camps (Doro, Gendrassa, Jamam, and Yusuf Batil). Hepatitis E virus (HEV) infection was confirmed in a convenience sample of cases in each camp. A cross-sectional serosurvey conducted in Jamam camp in November 2012 indicated that 54.3% of the population was susceptible to HEV infection. Across all camps, an AJS case-fatality rate (CFR) of 10.4% was observed among pregnant women. The outbreak response has focused on improving safe drinking water availability, improving sanitation and hygiene, conducting active case finding, and optimizing clinical care, especially among pregnant women. Sustaining these improvements, along with strengthening community outreach, is needed to improve outbreak control. Further investigation of the potential role for the newly developed HEV vaccine in outbreak control also is needed.
- **Tsarev SA, et al. Infectivity titration of a prototype strain of hepatitis E virus in cynomolgus monkeys. J Med Virol. 1994 Jun;43(2):135-42.**
The infectivity titer of a standard stock of the SAR-55 strain of hepatitis E virus (HEV) was determined in cynomolgus macaques (*Macaca fascicularis*) and the effect of dose on the course of the infection was examined by weekly monitoring of alanine aminotransferase (ALT) and anti-HEV levels. Antibody to HEV (anti-HEV) was measured with ELISAs based on ORF-2 recombinant antigens consisting of either a 55 kDa region expressed in insect cells or shorter regions expressed as fusion proteins in bacteria. The ELISA based on the 55 kDa antigen was generally more sensitive. The infectivity titer of SAR-55 was 10⁶ cynomolgus 50% infectious doses per gram of feces. The infectivity titer corresponded to the HEV genome titer of the inoculum as determined by reverse transcriptase-polymerase chain reaction (RT-PCR). Anti-HEV IgM was detected in only a portion of the animals that had an anti-HEV IgG response. Biochemical evidence of hepatitis was most prominent in animals that were inoculated with the higher concentrations of virus and the incubation period to seroconversion was prolonged in animals that received the lower doses.
- **Tsega E, et al. Hepatitis E virus infection in pregnancy in Ethiopia. Ethiop Med J. 1993 Jul;31(3):173-81.**
Thirty-two pregnant and 34 nonpregnant Ethiopian women between 15 and 45 years of age with sporadic acute viral hepatitis were studied consecutively. Demographic data including family size, monthly income and nutritional status as well as hepatitis virus markers were compared in the pregnant and nonpregnant groups. Only 3 nonpregnant women had hepatitis

A infection. Hepatitis B infection was diagnosed in 4 pregnant and 9 nonpregnant women. Nineteen (59%) pregnant women had hepatitis E virus (HEV) infection as compared to 7 (22%) in the nonpregnant group (Relative risk = 2.88; 95% Confidence interval = 1.4-5.9). The remaining 9 pregnant and 15 nonpregnant women had non-A, non-B, non-E (NANBNE) hepatitis. Of a total of 10 maternal deaths, 9 occurred (7 during the third trimester) in the pregnant group, 8 in association with HEV infection. Two deaths, one from each group, were due to NANBNE hepatitis. In addition to 6 foetal losses as a result of maternal death, there were 2 foetal deaths and 7 premature deliveries as a direct result of acute viral hepatitis, all but 2 associated with HEV infection. Comparison of socioeconomic and nutritional status, clinical features, mean aminotransferase and bilirubin levels did not show differences in the two groups. Thus, pregnant women are more at risk to acquire HEV infection than nonpregnant women and HEV infection in this group of Ethiopian pregnant women is associated with high maternal mortality and neonatal complications

- **Verghese VP, et al. A systematic review of hepatitis E virus infection in children. Clin Infect Dis. 2014 Sep 1;59(5):689-97**

A systematic review was conducted, seeking all literature relevant to the epidemiology, clinical and laboratory features, and outcome of hepatitis E virus (HEV) infection in children. Transmission is thought to be primarily from fecal-oral transmission, with the role of transmission from animal reservoirs not being clear in children. Worldwide, seroprevalence is <10% up to 10 years of age, with the exception of 1 of 5 studies from India and the sole study from Egypt. Seroprevalence increases with age, but it is not clear if it is increasing over time. The clinical presentation of HEV infection has broad similarities to hepatitis A virus (HAV) infection, with most cases being subclinical. However, HEV differs from HAV in that infectivity is lower, perinatal transmission can result in neonatal morbidity and even mortality, and a chronic carrier state exists, accounting for chronic hepatitis in some pediatric solid organ transplant recipients.

- **Viswanthan R. Infectious hepatitis in Delhi 1955-56 .Epidemiology. Indian J Med Res 1957,x1v, Suppl.1-29.**

- **Wu T, et al. Safety of the hepatitis E vaccine for pregnant women: a preliminary analysis. Hepatology. 2012; 55: 2038. Available at:**

<http://onlinelibrary.wiley.com/doi/10.1002/hep.25522/full>

To the Editor: High morbidity and mortality among pregnant women are characteristic identifiers of waterborne epidemic outbreaks of hepatitis E.1, 2 In the absence of effective treatment, vaccination offers a potential means to reduce the morbidity and mortality associated with pregnancy.3However, clinical studies are hampered by safety concerns, because vaccination during pregnancy is generally contraindicated. A review of the records of a recent phase 3 clinical trial of the recombinant hepatitis E vaccine3 identified 37 of 31,791 women in the vaccine group and 31 of 31,735 women in the placebo group who were pregnant at the time of enrollment or became pregnant during the course of the study and were inadvertently given one (n = 41 [22 vaccine, 19 placebo]), two (n = 23 [14 vaccine, 9 placebo]), or three (n = 4 [1 vaccine, 3 placebo]) doses of the HEV 239 vaccine or the control HBV vaccine. A total of 53 doses were received by the 37 pregnant women in the vaccine group, and 46 doses were received by the 31 pregnant women in the placebo group. Table 1 compares the adverse reactions observed in each of these subjects with that of two matched nonpregnant women. Only one subject in the vaccine group reported grade 1 pain at the site of inoculation. No serious adverse events were reported. The rates of adverse reactions to either vaccine were similar to those observed for the matched nonpregnant women. Nineteen (51.3%) of the women in the vaccine group and 14 (45.2%) in the placebo group underwent elective abortion. All the other women went on to give normal full-term

birth by vaginal delivery (seven in the vaccine group versus seven in the placebo group) or by cesarean section (11 in the vaccine group versus 10 in the placebo group). No spontaneous abortion occurred, and the babies were born without congenital anomalies. The weights ($3,573.5 \pm 356.7$ g versus $3,565.6 \pm 531.6$ g), lengths (50.7 ± 1.3 cm versus 50.8 ± 1.5 cm), and gestational ages (276.2 ± 7.6 days versus 276.6 ± 7.1 days) of the babies born to the mothers in the vaccine group and the placebo group, respectively, were comparable ($P > 0.05$). Blood samples from both month 0 and month 7 were available for one woman who received the third dose of HEV 239 vaccine during month 4 of her pregnancy. Her antibody level increased from undetectable to 34.7 Wu/mL, which is higher than that of 80% of subjects who received three doses of HEV 239 vaccine. None of the 68 pregnant women acquired hepatitis E. These preliminary observations suggest that the HEV 239 vaccine is safe for both mother and fetus and partially allay concerns regarding the safety of further clinical trials to substantiate this finding.

- **Wu T, et al. 2012b. Hepatitis E vaccine development: a 14 year odyssey. Hum Vaccin Immunother. 2012b; 8: 823-7.**

The first prophylactic vaccine, Hecolin®, against hepatitis E virus (HEV) infection and the HEV associated disease was approved by China's State Food and Drug Administration (SFDA) in December 2011. Key milestones during the 14-year HEV vaccine development are summarized in this commentary. After years of innovative research the recombinant virus-like particle (VLP) based antigen with virion-like epitopes was successfully produced in *E. coli* production platform on a commercial scale. Safety and efficacy of this vaccine was demonstrated in a large scale phase III clinical trial.

- **Wu T, et al. Immunogenicity and safety of hepatitis E vaccine in healthy hepatitis B surface antigen positive adults. Hum Vaccin Immunother. 2013; 9:2474-9.**

A recombinant hepatitis E vaccine, Hecolin, has been proven safe and effective in healthy adults. As hepatitis B surface antigen (HBsAg) positive individuals have a higher risk of poor prognosis after super-infection with hepatitis E virus (HEV), the safety and immunogenicity of Hecolin in this population should be assessed. The present study is an extending analysis of data from a large randomized controlled clinical trial of Hecolin. Healthy participants ($n = 14,065$) without current or previous evidence of chronic liver disease were randomized to receive Hecolin or placebo (hepatitis B vaccine) and donated their blood samples before vaccination and subsequently over 31 mo. Most of the adverse events were mild and comparable between participants with and without baseline hepatitis B surface antigen (HBsAg). No vaccine-related serious adverse events were reported. Rates of serious adverse events in HBsAg (+) or HBsAg (-) participants were also comparable between both groups. Almost all participants in the Hecolin group seroconverted to anti-HEV one month after full vaccination. The antibody response rates and levels were similar in HBsAg (+) and HBsAg (-) participants (98.38%, 19.32 Wu/mL vs. 98.69%, 19.00 Wu/mL). The two-year antibody dynamics of HBsAg (+) participants overlapped perfectly with those of HBsAg (-) participants. In conclusion, the safety and immunogenicity of Hecolin for HBsAg (+) adults is very similar to that for the general population.

- **Zhang J, et al. Development of the hepatitis E vaccine: from bench to field. Semin Liver Dis. 2013; 33:79-88.**

Along with the improvement of diagnostic techniques, hepatitis E has attracted increasing awareness in recent years. Hepatitis E virus infection leads to high mortality in pregnant women and patients with underlying liver disease. Several hepatitis E vaccine candidates have been designed and have proved their efficacy in animal models; two candidates have successfully undergone clinical trials. Having proved safe and effective in a large phase III trials,

an Escherichia coli expressed particulate protein, HEV 239, has been registered in China and is now available for use in China.

- **Zhang J, et al. Randomized-controlled phase II clinical trial of a bacterially expressed recombinant hepatitis E vaccine. Vaccine. 2009; 27:1869-74.**
The candidate recombinant hepatitis E vaccine, HEV 239, protect monkeys against infection by hepatitis E virus (HEV). The safety and immunogenicity of the vaccine for humans was assessed in a randomized controlled phase II clinical trial. The study was conducted in an endemic area of southern China and consisted of a dose scheduling, involving 457 adults and a dose escalation component involving 155 high school students. The results showed that the vaccine is safe and immunogenic for humans and suggest that it could prevent new HEV infection.
- **Zhang J, et al. Long term efficacy of a hepatitis E vaccine. N Engl J Med 2015;372:914-22.**
BACKGROUND: Hepatitis E virus (HEV) is a leading cause of acute hepatitis. The long-term efficacy of a hepatitis E vaccine needs to be determined. **METHODS:** In an initial efficacy study, we randomly assigned healthy adults 16 to 65 years of age to receive three doses of either a hepatitis E vaccine (vaccine group; 56,302 participants) or a hepatitis B vaccine (control group; 56,302 participants). The vaccines were administered at 0, 1, and 6 months, and the participants were followed for 19 months. In this extended follow-up study, the treatment assignments of all participants remained double-blinded, and follow-up assessments of efficacy, immunogenicity, and safety were continued for up to 4.5 years. **RESULTS:** During the 4.5-year study period, 60 cases of hepatitis E were identified; 7 cases were confirmed in the vaccine group (0.3 cases per 10,000 person-years), and 53 cases in the control group (2.1 cases per 10,000 person-years), representing a vaccine efficacy of 86.8% (95% confidence interval, 71 to 94) in the modified intention-to-treat analysis, rather than (95% confidence interval, 71 to 84) [corrected]. Of the participants who were assessed for immunogenicity and were seronegative at baseline, 87% of those who received three doses of the hepatitis E vaccine maintained antibodies against HEV for at least 4.5 years; HEV antibody titers developed in 9% in the control group. The rate of adverse events was similar in the two groups. **CONCLUSIONS:** Immunization with this hepatitis E vaccine induced antibodies against HEV and provided protection against hepatitis E for up to 4.5 years. (Funded by the Chinese Ministry of Science and Technology and others; ClinicalTrials.gov number, [NCT01014845](#).)
- **Zhang J, et al. Protection against hepatitis E virus infection by naturally acquired and vaccine-induced immunity. Clin Microbiol Infect 2014;20:O397-405.**
Immunity acquired from infection or vaccination protects humans from symptomatic hepatitis E. However, whether the risk of hepatitis E virus (HEV) infection is reduced by the immunity remains unknown. To understand this issue, a cohort with 12 409 participants randomized to receive the hepatitis E vaccine Hecolin[®] or placebo were serologically followed up for 2 years after vaccination. About half (47%) of participants were initially seropositive. A total of 139 infection episodes, evidenced by four-fold or greater rise of anti-HEV level or positive seroconversion, occurred in participants who received three doses of treatment. Risk of infection was highest among the baseline seronegative placebo group participants (2.04%). Pre-existing immunity and vaccine-induced immunity lower the risk significantly, to 0.52% and 0.30%, respectively. In conclusion, both vaccine-induced and naturally acquired immunity can effectively protect against HEV infection.

- **Zhu FC, et al. Efficacy and safety of a recombinant hepatitis E vaccine in healthy adults: a large-scale, randomised, double-blind placebo-controlled, phase 3 trial. Lancet. 2010; 376: 895-902.**

BACKGROUND: Seroprevalence data suggest that a third of the world's population has been infected with the hepatitis E virus. Our aim was to assess efficacy and safety of a recombinant hepatitis E vaccine, HEV 239 (Hecolin; Xiamen Innovax Biotech, Xiamen, China) in a randomised, double-blind, placebo-controlled, phase 3 trial. **METHODS:**

Healthy adults aged 16-65 years in, Jiangsu Province, China were randomly assigned in a 1:1 ratio to receive three doses of HEV 239 (30 microg of purified recombinant hepatitis E antigen adsorbed to 0.8 mg aluminium hydroxide suspended in 0.5 mL buffered saline) or placebo (hepatitis B vaccine) given intramuscularly at 0, 1, and 6 months. Randomisation was done by computer-generated permuted blocks and stratified by age and sex. Participants were followed up for 19 months. The primary endpoint was prevention of hepatitis E during 12 months from the 31st day after the third dose. Analysis was based on participants who received all three doses per protocol. Study participants, care givers, and investigators were all masked to group and vaccine assignments. This trial is registered with ClinicalTrials.gov, number NCT01014845. **FINDINGS:** 11,165 of the trial participants were tested for hepatitis E virus IgG, of which 5285 (47%) were seropositive for hepatitis E virus.

Participants were randomly assigned to vaccine (n=56,302) or placebo (n=56,302). 48,693 (86%) participants in the vaccine group and 48,663 participants (86%) in the placebo group received three vaccine doses and were included in the primary efficacy analysis. During the 12 months after 30 days from receipt of the third dose 15 per-protocol participants in the placebo group developed hepatitis E compared with none in the vaccine group. Vaccine efficacy after three doses was 100.0% (95% CI 72.1-100.0). Adverse effects attributable to the vaccine were few and mild. No vaccination-related serious adverse event was noted.

INTERPRETATION: HEV 239 is well tolerated and effective in the prevention of hepatitis E in the general population in China, including both men and women age 16-65 years. **FUNDING:** Chinese National High-tech R&D Programme (863 programme), Chinese National Key Technologies R&D Programme, Chinese National Science Fund for Distinguished Young Scholars, Fujian Provincial Department of Sciences and Technology, Xiamen Science and Technology Bureau, and Fujian Provincial Science Fund for Distinguished Young Scholars.