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REVIEW

Hepatitis E virus: Current epidemiology and vaccine

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ABSTRACT

Hepatitis E virus infections have been continuously reported in Indian subcontinent, Africa, southeast and central Asia, posing great health threats to the public, especially to pregnant women. Hecolin® is the only licensed HEV vaccine developed by Xiamen Innovax Biotech Co., Ltd. Extensive characterizations on antigenicity, physicochemical properties, efficacy in clinical trials, and manufacturing capability have made Hecolin® a promising vaccine for HEV control. However, there are many obstacles in large scale application of Hecolin®. Efforts are needed to further evaluate safety and efficacy in HEV risk populations, and to complement HEV standards for quality control. Passing World Health Organization prequalification and licensing outside China are priorities as these are also hindering Hecolin® promotion. Multilateral cooperation among Chinese vaccine manufacturers, Chinese National Regulatory Authorization (NRA) and WHO will expedite the entrance of Hecolin® into international market, so that Hecolin® could play its due role in global hepatitis E control.

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Introduction

Hepatitis E virus is a nonenveloped virus with a positive-sense, single-stranded RNA genome and belongs to genus *Hepevirus* of the *Hepeviridae* family.[1,2] HEV infections are responsible for over 50% of acute viral hepatitis cases in areas like India and mainland China.[3-6] An estimated 35 million HEV infections occur annually worldwide, resulting in more than 70,000 deaths.[7,8] Average mortality rate is between 0.2%–4%, while it can reach to 10%–25% in pregnant women who are at higher risk for HEV.[9] Africa and Indian subcontinent, including Kenya, Sudan, India, Pakistan, Bangladesh and Nepal are the most commonly affected areas.[10] In 2004 and 2013, large HEV outbreaks were documented among refugees camps in Sudan and Kenya during humanitarian emergencies caused by internal conflicts, and pregnant women suffered disproportionately high mortality from hepatitis E.[11-15]

HEV can be divided into four genotypes I, II, III, IV.[16] Genome homology among four genotypes varies between 70–90%, and above 90% in the same genotype.[16] HEV genotypes I, II are restricted to humans, while genotypes III, IV primarily infect mammalian animals with occasional cross-species transmission to humans.[17] Despite of the genotypic differences, all known HEVs belong to the same serotype.[18] HEV RNA genome contains 3 open reading frames (ORF1–3), and ORF2 codes for the viral capsid protein which is the target of HEV neutralizing antibodies.[19]

Many HEV vaccine candidates have been under investigation for years, and most of them are based on antigenic HEV ORF2 protein: one recombinant HEV vaccine developed by GlaxoSmithKline achieved good safety and efficacy in volunteers from the Nepalese Army reported in a Phase II clinical trial study.[20] Unfortunately, following development of this vaccine was ceased. Another HEV vaccine with trade name as Hecolin®, a recombinant Virus-like particles (VLP) vaccine developed by Xiamen Innovax Biotech Co., Ltd (China), also showed good safety and efficacy in clinical trials and got successfully licensed in China in 2012.[21] To date, Hecolin® is the only known HEV vaccine on market. However, Hecolin® is now facing the dilemma in global marketing, and so far it is not able to play a fundamental role in global hepatitis E outbreaks and pandemics control. This review introduced the current epidemiology and vaccine development of HEV, with particular emphasis on obstacles in global application of Hecolin® and possible strategies to cope with these challenges.

Current epidemiology of HEV

Although HEV was first recognized during a waterborne hepatitis epidemic in Kashmir Valley of India in 1978,[22] the first documented hepatitis E pandemic could be traced back to New Delhi, India in 1955–1956 after the first direct experimental evidence of the existence of HEV had been founded in patients with hepatitis A-like disease in Tashkent, Uzbekistan in 1983.[23-25] Africa, Indian subcontinent and mainland China have been historically reported as areas with high HEV prevalence.[25-30,8,31] Geographic distribution of the 4 genotypes of HEV are distinct: genotype I,II are mainly circulating in developing countries and transmitted through contaminated food or water in younger adults, infections in pregnant women usually associated with high incidence of severe complications and

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mortality;[32] genotype III, IV are often founded in developed countries and adapt to a zoonotic transmission way, such as through consumption of uncooked or undercooked meat,[33] sporadic infections are often reported in older individuals or those with comorbidities such as chronic liver disease.[34] Transfusion transmission and vertical (maternal-fetal) transmission also occur and are well documented.[35,36]

From 1950 to 2000, Hepatitis E outbreaks have been reported in Indian subcontinent, Africa, Mexico, Southeast Asia and Central Asia.[25-30] Major documented Hepatitis E outbreaks are listed here chronologically (Fig. 1): New Delhi, India in 1955–1956 (30,000 cases);[23,25] Myanmar (20,000 cases) in 1976–1977;[37] Kashmir, India (52,000 cases) in 1978–1982;[22,38] Xinjiang, China (120,000 cases) in 1986–1988;[4] Kanpur, India (79,000 cases) in 1991;[28] Kitgum, Uganda(10,356 cases) in 2007–2009.[31,39] Since 2010, Africa and India Subcontinent are still highly endemic areas, though the numbers of outbreaks are reduced. Several outbreaks in refugees camps with high mortality rate in pregnant women have drawn the attention of the public.[40,41] In mainland China, hepatitis E occurs mainly as sporadic cases and occasional food-borne outbreaks in nursing homes.[5,42] In developed countries and areas, sporadic case or small scale outbreaks of HEV infection have been recorded in the USA, European countries (UK, France, the Netherlands, Austria, Spain, Greece and Germany), and developed Asian–Pacific countries (Japan, Korea, Australia and New Zealand).[43] The most recent outbreak reported was in France in 2013 caused by the consumption of undercooked piglet's liver and 12 were asymptomatic among the 17 cases infected with HEV genotype III.[44]

Indian subcontinent

The persistent high prevalence of HEV in Indian subcontinent has been a major issue for public health. Major hepatitis E outbreaks had been reported in Pakistan, Bangladesh, Sri Lanka, Nepal, etc.[8] More than 26 outbreaks in India had been reported in 1955–2012,[3] and at least 4 outbreaks were with more than 10,000 cases.[25,37,45] In 21st century, Indian subcontinent has still been HEV epidemic area: Pakistan (2005, 2006);[46] Nepal (2006, 2009, 2014);[47,48] Bangladesh (2010);[49,50] India (2012).

Africa

Hepatitis E outbreaks caused 11,759 cases and 346 deaths in Somali Republic in 1988–1989, while over 10,356 cases and 160 deaths in Uganda in 2007–2009.[31] The prevalence rate has remained high in these areas since 2010. Hepatitis outbreaks had been reported in Sudan (2010–2011),[12,13,51] South Sudan (5,080 cases, 2012–2013),[12] and Kenya (3,232 and 255 cases in 2 outbreaks, 2012).[11,13] Case fatality rate (CFR) in these outbreaks was astonishingly high: In Darfur of Sudan, reported CFR was 33%;[52] in South Sudan, CFR was 10% among pregnant women.[15] HEV genotype I and II have been the major circulating types,[1,53-57] while genotype III has also been reported in some cases.[58,59]

Mainland China

There were 9 hepatitis E outbreaks reported in 1982–1986,[4] and one hepatitis E pandemic of HEV genotype I happened in Xinjiang in 1986–1988 with over 120,000 persons infected.[60] After that, pandemics of HEV have been replaced with sporadic infections and small scale outbreaks. Since 1990, increasing cases in older population have been noticed as several outbreaks in nursing homes have been reported lately.[61-66] Along with economic growth and improvement in public health, HEV has been observed to adopt zoonotic transmission pattern with sporadic infections instead of previous waterborne or foodborne pattern in China.[67] Epidemiology surveillance based on a community of 400,000 population found that HEV genotype IV was the dominant type and occasional genotype I

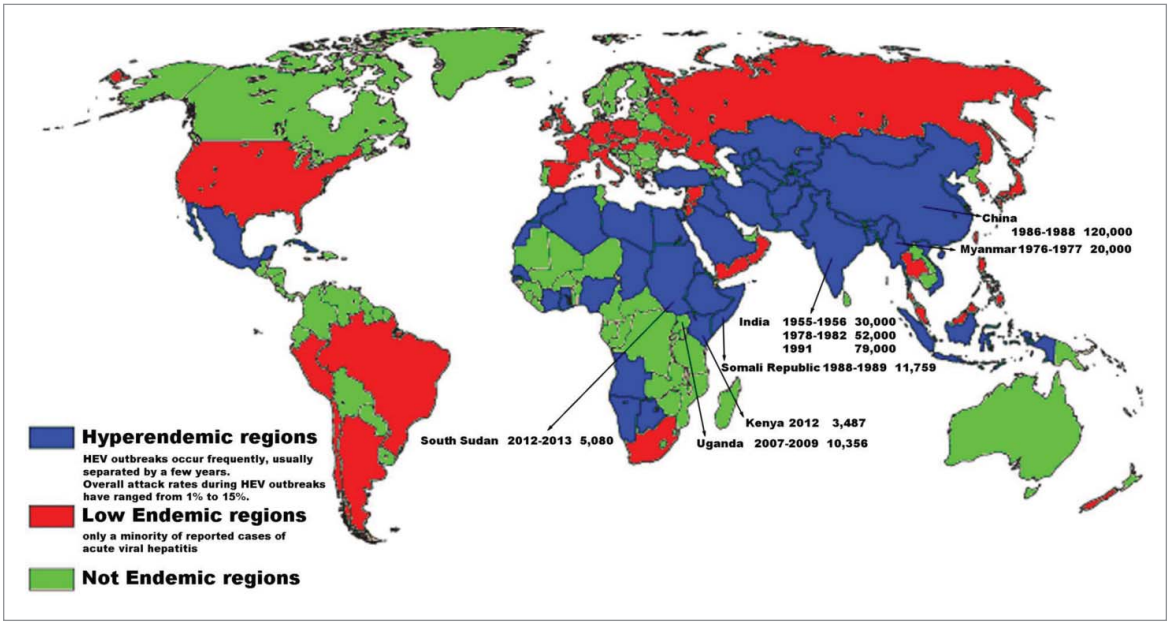

Figure 1. Global distribution of HEV infection 43.

infections were also revealed, indicating that both genotype I, IV were both circulating in mainland China.[67]

Licensing and availability of HEV vaccine

HEV vaccine development

For the lack of *in vitro* culture system, HEV vaccine design strategies using inactivation or attenuation are not feasible.[68] So HEV vaccine development has been focused on HEV capsid protein ORF2 (Open reading frame2). ORF2 is 660 aa in length. X-ray crystal structure analysis shows that ORF2 protein monomer contains 3 distinct domains: the shell(S), middle (M), and protruding (P) domains.[4,69] Recombinant antigens, DNA vaccine or other new recombinant vaccines candidates have been proposed: various subunit vaccines based on truncated ORF2 purified in E.coli expression system;[70-74] VLP vaccines expressed either in E.coli, insect cells (Sf9) or Chinese hamster ovary cell (CHO) expression systems;[75-78] DNA vaccine consisting expression vector encoding full length ORF3 or (and) ORF2.[79]

HEV vaccines that have undergone clinical trials

Currently, there are 3 vaccines have entered into clinical trials. One developed by GSK have finished phase II clinical trial; another developed by Changchun Institute of Biological Products Co., Ltd (China) is now in phase I clinical trial (Clinical trial NO. CXSL1000041); the third one is the previously mentioned Hecolin® which has finished phase III clinical trial and been licensed in China. Hecolin® is based on recombinant HEV ORF2 truncated protein HEV 239 (aa368-aa606) expressed in E.coli expression system. After purification and refolding, HEV 239 can efficiently self-assemble into VLPs particles, which have high structural similarity with the capsid of mature HEV virions.[80-82] Notably, HEV 239 has good immunoreactivity with patient serum samples from acute and convalescent phase of hepatitis E patients.[75,83] Hecolin® has shown good protection of rhesus monkey from HEV infection in animal challenge studies. In completed phase III clinical trial, the efficacy of Hecolin® has reached to 96%, and the geometric mean antibody titer levels induced by the 3 dose regimen is 15.9 World Health Organization units (Wu)/ml (95% CI:13.8–18.2).[84,85] Efficacy after 4.5 y is 86.8% and seropositivity is over 50% in a follow-up study.[86] Clinical data have proven good short-term and long-term protection efficacy of Hecolin® in 16–65 y old healthy Chinese people.

Availability of Hecolin®

Hecolin® is a VLP vaccine developed by genetic engineering. The encoding gene is from the ORF2 of a HEV genotype I strain. Innovax Biotech has optimized the manufacturing technique of 50 L fermentation tank for fermentation cultivation. Recombinant proteins are refolded and self-assembled into VLP particles.[87] Finished products are available as a pre-filled syringe containing aluminum hydroxide-adsorbed antigen suspended in buffered saline. The complete vaccination series consists of 3 doses (30μg/0.5ml/dose) on a schedule of 0, 1, and 6 months. This manufacturing technique can be easily to scale up and has advantages in quality control.[88] Although actual manufacturing output of Hecolin® in Innovax Biotech is about 200,000 doses/year currently, Innovax Biotech has great potential to produce 5000,000 doses/year according to manufacturing capacity planning, so Hecolin® will have the availability to meet HE vaccination need worldwide in the future.

Bottlenecks in the application of HEV vaccine

Bottlenecks of Hecolin® application in mainland China

Although China is the first country that has licensed HEV vaccine, the reported cases of hepatitis E since 2012 have only declined by 7.58% (29,202 cases in 2011, 26,988 cases in 2014).[89] According to data released by China Notifiable Disease Reporting System (CNDRS) in 2014, hepatitis E still consisted about 50% of the reported acute hepatitis cases, and the ratio had been increasing annually, the number of HE cases reported after Hecolin® licensing had remained at similar high level. Hecolin® has not been fully exploited its protective potential in hepatitis E outbreaks control in China. Inadequate clinical data and insufficient public awareness of HEV related diseases are the main reasons on account for this difficult situation. Current clinical trial data on efficacy and safety are limited to 16–65 y old healthy people, and no data are available in children under 16 y old, adults over 65 y old, or HEV high risk groups (pregnant women and persons combined with other diseases). Moreover, for the lack of studies in disease burden and cost-benefit of HEV related diseases, the public are currently unaware of the importance of the HEV vaccine and show poor acceptance to this rather new vaccine.

Bottlenecks in the worldwide application of Hecolin®

Hepatitis E has been recognized as a public health problem in many developing countries and Hecolin® is considered as a promising HEV vaccine.[90-92] However, worldwide application of Hecolin® is also hindered and HEV risk groups are in the dilemma.

As the only available data are from clinical trials conducted in China where overall hepatitis E incidence is low and genotype IV is the major type, efficacy of Hecolin® in worldwide areas needs further verification, especially in HEV endemic areas where genotype I, II are the prevailing types, like Africa, India subcontinent. Also, the current recommended Immunization Schedule of 3 doses at 0, 1 and 6 months is not suitable for controlling hepatitis E outbreaks in emergencies, especially in refugees camps. Limited data showed that 2 doses (at 0 and 6 months or at 0 and 1 month) could also lead to a high rate of seroconversion and conveyed good protection.[20,84,93] In a Phase IIa study of Hecolin® conducted in healthy seronegative persons aged 16–55 y old, seroconversion rates were 98% in the 2-dose group (at 0 and 6 month) compared with 100% in the 3-dose group (at 0, 1 and 6 month) and 8% in the control group; however, the geometric mean concentrations (GMCs) of antibody in 3-dose group were 2-fold higher than those in 2-dose group.[93] In a Phase III study of Hecolin®, Vaccine efficacy after first 2 doses (at 0 and 1 months) was 100%

(95% CI 9.1–100.0).[84] It is absolutely necessary to establish an accelerated vaccination schedule for those who face imminent HEV exposure. Additionally, Hecolin® is a white suspension with each dose of vaccine supplied in a non auto-disable prefilled syringe (one per package, with a package volume of 100 cm^3, 13.2×3.7×2.15 cm); so the package of Hecolin® needs to meet some general requisites for transportation and storage to facilitate centralized procurement of vaccines; improvements on multiple doses, large package, suitable preservative(s) addition are also necessary. The last but the most important reason is that Hecolin® have not received WHO prequalification (PQ) or licenses outside of China yet, so it is not available to HEV endemic countries receiving vaccine through United Nations International Children's Emergency Fund supply division or other United Nations procurement agencies, especially to the refugees at high risk.[94]

Current status and bottlenecks in commercial scale production and quality control of HEV vaccine

Efforts have been made to implement reliable production and quality control of HEV vaccine. First of all, production and quality control of Hecolin® have met the general requirements of WHO and Chinese Pharmacopoeia (3rd edition). Then, by establishing a series of in-house references and utilizing a toolbox combining biophysical, biochemical, and immunochemical methods, Innovax Biotech have showed that antigen characteristics was comparable from a bench scale to a manufacturing scale, ensuring process reproducibility and product consistency in the vaccine production process.[88] National Institutes for Food and Drug Control, China (NIFDC) have analyzed the potency consistency among 14 released batches of Hecolin® in animal models; the average potency was 0.05 and all analyzed batches showed consistent potency (unpublished data). As the size of released batches of Hecolin® is still small, the quality consistency of mass production still needs further assessment.

Although WHO guideline on Hecolin® production and quality control has not been issued, some HEV related standards have already been established: the first WHO HEV IgG standard was established in 2002 (NIBSC code: 95/584);[95] the first WHO HEV RNA standard was established in 2013 (NIBSC code: 6329/10, HEV genotype IIIa) and can be used in quality control of diagnostic reagents and quantification of HEV RNA in serum; Chinese national anti-HEV IgG linear standard calibrated against WHO anti-HEV IgG reference was established by NIFDC in 2008, and it has been used for quantification of anti-HEV IgG in serum samples from clinical trials. But both WHO and Chinese national standards for antigen quality control and potency evaluation of HEV vaccine are still lacking.

Strategies to overcome the bottleneck on HEV vaccine application

WHO, NIFDC and Innovax Biotech have carried out the work from different aspects to promote the worldwide application of HEV vaccine for HEV control.

WHO have issued several guidelines for the prevention and control hepatitis E epidemics. Technique report "Waterborne Outbreaks of Hepatitis E: Recognition, Investigation and Control" issued by WHO (Jun, 2014) providing knowledge on epidemiology, diagnosis, clinical symptoms of hepatitis E, assisting public health authorities to cope with hepatitis E outbreaks;[96] in the same year, recommendations of HEV working group on the use of hepatitis E vaccine was released by WHO (Dec, 2014).[97] In May, 2015, WHO issued a regularly position paper on HEV vaccine;[98] in this paper, WHO asked for further investigation on safety and efficacy of Hecolin® in expanded populations (including the elderly, children, pregnant women, etc.) and when co-administered with another vaccines, as well as the cross-protection efficacy against different genotypes other than genotype I. These issued documents and related initiatives by WHO have laid the groundwork for global promotion and application of HEV vaccine.

NIFDC has been conducting the research to establish HEV standards for vaccine evaluation. NIFDC has recently launched the development of national HEV antigen standard and vaccine potency standard. Besides, for the lack of HEV infection mouse model, a competitive ELISA method has been developed to evaluate vaccine potency *in vitro*. 8G12, a well-characterized mouse broad neutralizing monoclonal antibody developed by Innovax Biotech, can recognize the dominant neutralizing epitope on HEV capsid protein. Previous studies have shown that 8G12 can strongly compete the binding of human and Macaques rhesus HEV convalescent sera as well as Hecolin® vaccinated sera to HEV ORF2 protein,[99] indicating that most neutralizing antibodies elicited by HEV natural infection or Hecolin® vaccination might recognize similar epitope as 8G12.[99-101] Thus, the feasibility to use 8G12 as a probe to analyze the correlation between protection efficacy and 8G12-like antibodies elicited by HEV vaccine immunization was explored. Preliminary data have suggested that 8G12 can be used as substitute standard for serum samples from preclinical animal studies and clinical trials in vaccine evaluation (unpublished data). This would greatly facilitate the preclinical evaluation of other new HEV vaccines and post-license surveillance of Hecolin®.

Innovax Biotech has been further evaluating Hecolin® in clinical trials, as well as stability assessment in Hecolin® large-scale production. After Phase III clinical study for Hecolin®, Innovax Biotech has continued a 4.5-year follow-up study in the original cohorts of vaccine group (56302 subjects) and control group (56302 subjects). 60 cases of hepatitis E were identified: 7 cases were confirmed in the vaccine group (0.3 cases/10,000 person-years), and 53 cases in the control group (2.1 cases/10,000 person-years), representing a vaccine efficacy of 86.8% (95% CI: 71–94%). 87% of those who received 3 doses of Hecolin® maintained anti-HEV antibodies positive for at least 4.5 y compared with 9% in control group.[86] Another phase IV clinical study have been conducting to determine the safety and immunogenicity of Hecolin® in people older than 65 years, and evaluate the efficacy of hepatitis E vaccine in this population(Clinical trial: NCT02189603). For scale-up production, stability and product consistency of Hecolin®, multiple methods including differential scanning calorimetry (DSC), surface plasma resonance (SPR), analytical ultracentrifugation (AUC), mAb binding profiling were applied in the comprehensive characterization of the recombinant hepatitis E VLP in

Hecolin®. Data showed consistency of vaccine products from different batches in particle size, thermo stability, and immunogenicity, proving that antigen production process was robust and scalable during the manufacturing of Hecolin®. Furthermore, effects of aluminum containing adjuvant on structural characteristics, biological activity and stability of Hecolin® have also been analyzed. Both vaccine bulk and product with aluminum adjuvant showed good thermo stability measured by DSC (Tm = 70–72°C).[88] As antigenicity or the binding activity to various antibodies is a critical attribute, Innovax Biotech have produced a panel of mouse monoclonal antibodies with different epitopes, like 8C11, 8H3, 13D8,12A10 and 16D7. Base on these mAbs, one-site binding and label-free assay (SPR) and 2-site binding assay (sandwich ELISA) have been carried out to evaluate the antibody binding activity of Hecolin®. These mAbs provides a convenient toolbox for HEV vaccine antigenicity control of different batches.[88]

Summary

In 2013, Chinese NRA passed the assessment in 2010 and the reassessment in 2014 by WHO. NIFDC became the seventh WHO Collaborating Center for standardization and evaluation of biologics in 2013. Since then, Chinese vaccines are added to the WHO international vaccine purchase list. This paves the road for vaccines produced by Chinese manufacturers to enter into international market.[102] So far, Chinese live attenuated Japanese encephalitis vaccine and influenza vaccine have already passed WHO prequalification, showing that China is contributing to worldwide disease prevention and control. For Hecolin®, top priorities need to be done, including further verification on the safety and efficacy on HEV risk groups, optimization of immunization schedule, passing WHO prequalification, licensing in HEV endemic countries, and development of vaccine reference materials for quality control. Collaborative efforts from vaccine manufacturers, Chinese NRA and WHO will bring Hecolin® to the world and confer benefits to people with high HEV infection risk.

Abbreviations

AUC	Analytical ultracentrifugation
CFR	Case fatality rate
CNDRS	China Notifiable Disease Reporting System
DSC	differential scanning calorimetry
GMCs	geometric mean concentrations
HEV	hepatitis E virus;
NIFDC	National Institutes for Food and Drug Control, China
NRA	Chinese National Regulatory Authorization;
PQ	prequalification
SPR	surface plasma resonance
VLP	Virus-like particles
WHO	World Health Organization

Disclosure of potential conflicts of interest

No potential conflicts of interest were disclosed.

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