Hepatitis E Vaccine to Prevent Morbidity and Mortality During Epidemics

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Recurrent, large, waterborne epidemics of hepatitis E virus (HEV) occur regularly after monsoon rains contaminate water supplies in Asia or during humanitarian crises in Africa. These epidemics commonly affect thousands of persons, and it has a high mortality in pregnant women who become infected. Although a subunit HEV vaccine has been developed by Chinese investigators and was found to be highly effective and safe in a large clinical trial, this vaccine is only available in China. Until it is prequalified by the World Health Organization, the vaccine may not be available for use outside of China in low-income countries that lack national vaccine regulatory agencies. In this manuscript, we explore possible strategies for providing access to this potentially important vaccine for international use in responding to epidemics of HEV in low-resource countries.

Keywords. hepatitis E virus; humanitarian emergencies; waterborne epidemics; World Health Organization.

The recent epidemic of hepatitis E virus (HEV) infections, which involved more than 5000 cases with over 100 deaths among refugees in South Sudan in 2012–2013, presented a major ethical dilemma for the international public health community [1]. Similar to previous large outbreaks, over half of the fatal cases occurred among pregnant women. However, in contrast to epidemics of HEV before January 2012, a highly effective HEV vaccine was available and licensed in China after a trial involving more than 90 000 Chinese subjects. The results showed a 95% efficacy rate in preventing clinical hepatitis among the subjects who received the vaccine [2]. Although pregnant women were not enrolled in the trial per protocol, the vaccine was immunogenic and safe among 37 pregnant women who inadvertently enrolled in this trial [3]. The continuing need for an effective HEV vaccine for use during humanitarian crises is underscored by an ongoing outbreak of HEV in the Napak region of northern Uganda, where 635 cases were reported and 19 deaths occurred, 13 of which were pregnant women. In addition, a new outbreak of HEV involving over 6000 cases and 9 deaths has been reported recently in the Biratnagar Municipality of Nepal [4]. Since these outbreaks have often persisted for several months, prompt administration of an effective vaccine could be useful in preventing morbidity and mortality.

Although it is highly desirable to perform additional trials to determine the immunogenicity and safety of the HEV vaccine, in 1–3 dose schedules among pregnant women in all trimesters of their pregnancy and in children under age 16 in countries where genotype 1 HEV epidemics occur, this subunit HEV vaccine is not infectious and almost certainly effective and safe for pregnant women, their fetuses, and young children. If the current World Health Organization (WHO) regulations were amended to accept, in certain situations, the approval and licensure of a vaccine by a national regulatory authority that had been certified previously by the WHO for procurement and use in an emergency by a United Nations (UN) agency or a nongovernmental organization in a low-resource country, the HEV vaccine might have been available for use in the epidemics in the Sudan or Nepal. HEV continues to contribute to a substantial global burden of disease, with an estimated 20 million infections, 3.4 million cases, and 70 000 deaths from genotypes 1 and 2 annually [5]. We and others have also shown that HEV is most likely a major contributor to maternal and neonatal mortality worldwide, especially in low-resource,

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highly endemic countries such as Bangladesh [6, 7].

The HEV vaccine is distributed by Innovax and sold under the trade name Hecolin. It contains a 239-amino acid polypeptide that is encoded by HEV open-reading frame 2 and represents the viral-capsid protein. This polypeptide, produced in *Escherichia coli*, forms virus-like particles that are free of HEV genomic RNA and are highly immunogenic. This vaccine was under development for 14 years and has been tested extensively in primates and humans before the large phase 3 trial. It is currently licensed for use in humans by the Chinese Government Food and Drug Authority (CFDA). Production and distribution are rigorously regulated by the CFDA, which reviews each vaccine lot for adherence to quality manufacturing standards. Innovax maintains cGMP certification by the CFDA. This regulatory agency has been certified by the WHO as meeting international standards for vaccine production oversight and regulation [8].

Purchase of vaccines through the UN system for use during such emergencies requires that the vaccine be prequalified by the WHO. The prequalification, although a valuable resource for low-resource countries, is time-consuming and involves some expense. Consequently, only 1 vaccine produced in China is presently prequalified by the WHO—a vaccine to prevent Japanese encephalitis virus (JEV) infection. The economic incentive for the manufacturer for prequalification licensure of the JEV vaccine differs substantially from the HEV vaccine, because the JEV vaccine is included in the routine immunization schedule of all infants and children in Asia, where JEV infections are endemic. In contrast, an HEV vaccine might be used episodically in humanitarian crises, in low-resource populations during flooding conditions, and possibly in patients prior to solid-organ transplantation, because these patients are particularly at risk for chronic and severe HEV.

It is almost certain that another humanitarian crisis or disaster event will trigger an outbreak of HEV, when a safe water supply is disrupted, such as the 1200 cases that occurred after the 2005 Pakistan earthquake [9]; the 2012 outbreak in Maharashtra, India, with over 5100 cases and 36 deaths [10]; or the current outbreaks in Uganda and Nepal [4]. It is likely that an HEV vaccine could have been an important public health intervention measure during these epidemics. The protracted and often seasonal nature of these massive outbreaks offers a unique possibility to prevent unnecessary mortality among pregnant women and others who are infected with HEV.

So what are the options for the future? An expert advisory committee of the WHO has listed several options for the use of a vaccine that has not been prequalified in an emergency [11]. First, a vaccine could be used internationally if the national vaccine agency has developed another vaccine, which is prequalified by WHO. Second, a vaccine that has been licensed by the vaccine regulatory agency of more than 1 country can be used internationally in an emergency. Third, a country could purchase a licensed vaccine from another country for use during an emergency. Unfortunately, the Chinese HEV vaccine is not likely to be available for international use because its current status does not meet the first 2 criteria. Moreover, many nations where these epidemics continue to occur cannot afford the Chinese HEV vaccine.

Therefore, what strategies can now be pursued to make this very effective, safe, valuable vaccine available to countries where it would be extremely useful in the future? First, it seems obvious that another country that has had recurrent waterborne epidemics should step forward to evaluate, approve, and purchase the vaccine when it is needed. There are many countries in South Asia and Africa where recurrent massive epidemics with high mortality occurred, and these countries have sophisticated and functional national drug and vaccine review agencies. Second, additional pragmatic strategies to provide global access to the HEV vaccine, and other similar vaccines in the future, should be developed by UN agencies or other global organizations. This procedure could include providing funding and resources to assist in prequalifying critical vaccines by the WHO. Third, the WHO should re-evaluate the current exceptions to the international access to vaccines, which have been found to be highly effective and safe and are qualified and licensed by the vaccine regulatory agency of a single country, when that agency is known to have effective oversight of vaccine production and safety.

Hopefully, serious morbidity and mortality among pregnant women during the next major outbreak of HEV can be reduced, without the global health community being paralyzed by measures intended to protect the public from harm. To achieve this urgent necessity, the current barriers to the international deployment of this effective vaccine need to be removed to allow access to the HEV vaccine in a cost-effective and timely way, when needed to control future epidemics.

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