World Health Organization Approaches to Evaluating the Potential Use and Quality of Hepatitis E Vaccine

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In December 2011, the Chinese Food and Drug Administration licensed the first hepatitis E vaccine, with the trade name Hecolin, to be used in adults (16 years and above). The vaccine was shown to be safe and effective in a large phase 3 trial with a protective efficacy of 95.5% against hepatitis E disease among healthy adults (16–65 years old) of either gender over a 1-year period after the completion of immunization [1]. In addition, unpublished follow-up data from this trial indicate (1) an 87% protective efficacy on intention-to-treat basis and (2) 93% efficacy in those who had completed the full 3-dose schedule, over a period extending up to 4 years after completion of immunization.

In the light of this development and faced by large hepatitis E outbreaks, especially in camps of displaced persons, the World Health Organization (WHO) has recently developed a 3-pronged approach to the threat of hepatitis E infections.

1. Developing resources for responding to hepatitis E outbreaks.

WHO established a working group under the umbrella of the Global Hepatitis Network who published a manual in July 2014 for recognizing, investigating, and responding to waterborne hepatitis E outbreaks [2]. This manual is currently the only one of its kind.

2. Assessing evidence and developing evidence-based recommendations on the use of the hepatitis E vaccine.

The World Health Organization's Strategic Advisory Group of Experts (SAGE) on immunization established a working group to review the evidence on the safety, immunogenicity, efficacy, cost-effectiveness, and programmatic considerations of the licensed hepatitis E vaccine and identify potential indications and uses in the context of other preventive, control, and treatment strategies. The working group has prepared its recommendations for consideration by SAGE at its October 2014 meeting. The SAGE recommendations will lead to the publication of a WHO vaccine position paper on the use of the hepatitis E vaccine.

In addition to the SAGE, The Global Advisory Committee for Vaccine Safety (GACVS) has also examined the hepatitis E vaccine and concluded that the available safety data on Hecolin derived from phase 1, 2, and 3 clinical trials in healthy subjects are "reassuring." However, there are no safety data in children under 16 years of age, people over 65 years of age, pregnant women, and persons with underlying diseases or conditions (such as those who are immunosuppressed or have liver disease) or on coadministration with other vaccines. The Global Advisory Committee for Vaccine Safety recommended that studies be conducted in these subgroups. In addition, a phase 4 postmarketing study is also recommended for further assessment [3]. The assessment conducted by GACVS will be taken into consideration by SAGE during its review of the hepatitis E vaccine in October 2014.

3. Development of a framework for decision-making on vaccination in acute humanitarian emergencies.

In 2013, WHO published *Vaccination in Acute Humanitarian Emergencies: A Framework for Decision Making* [4]. This document was prepared by the SAGE working group and was endorsed by SAGE at its November 2012 meeting. Even with limited available information on the vaccine at the time, it was deemed important to include the hepatitis E vaccine in the report and allow for flexibility in decision-making by authorities in charge of such situations. This document states that: "*Vaccines being considered [for use in humanitarian emergencies] should meet international standards of*

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Table 1. Conditions for Accepting Vaccines for Evaluation for WHO Prequalification and the Current Status of the Hepatitis E Vaccine

Condition	Current Status of Hecolin
The candidate vaccine is on the current list of priority products for UN prequalification.	Hecolin is included in this list.
The candidate vaccine meets the mandatory characteristics for programmatic suitability [5].	Hecolin is currently presented in monodose, non-autodisable, prefilled syringes, which is not in line with WHO-UNICEF joint statement for vaccine safety.
The NRA responsible for the regulatory oversight of the product has been assessed by WHO as "functional" and has been found to meet all the critical indicators defined for prequalification purposes.	The Chinese NRA has been assessed by WHO as a "functional" NRA in 2013.
An MA has been granted by the relevant NRA, and the postmarketing regulatory oversight is under the responsibility of the NRA of the country of manufacture.	Hecolin has been available in the Chinese market since October 2012.

Abbreviations: MA, marketing authorization; NRA, National Regulatory Authority; UN, United Nations; WHO, the World Health Organization.

quality and safety and have obtained WHO prequalification. However, under certain circumstances, vaccines may be approved for use in a specific country while not having WHO prequalification status . . ."

In addition, this document also states "*The criteria for the exceptional case where a prequalified vaccine does not exist, are currently under revision by WHO. These criteria are intended as guidance. It is recommended that any modifications made on the basis of national benefit-risk considerations should ensure that if a non-prequalified vaccine is used, it is at least as safe and efficacious as one which would comply with these criteria.*"

The WHO Prequalification (PQ) Programme for vaccines is a service that WHO provides to UNICEF and other United Nations (UN) agencies that purchase vaccines. The purpose of the PQ assessment is to ensure that vaccines provided through the UN for use in national immunization services are safe and effective, are suitable for the target populations, and meet the necessary programmatic suitability criteria. The request for a WHO prequalification has to be initiated by the license holder. In addition to that, certain criteria (Table 1) must have been met even before initiating a request. However, it is important to note that although certain vaccines are not included in the list of prequalified vaccines, it does not mean that, if evaluated, they would not be found to comply with the required standards. Conditions for accepting vaccines for evaluation and the current status of the available hepatitis E vaccine, Hecolin, are presented in Table 1.

Hepatitis E infection is responsible for a significant burden in some parts of the world, and outbreaks can occur in conditions of humanitarian emergencies. Because no specific treatment exists, preventive measures are important. Vaccines are one of the best public health tools that exist, and careful consideration should be given to potential use of the available options. However, it is imperative that all possible safety, efficacy, and immunogenicity concerns are addressed before vouching for any medicinal intervention including vaccines.

The World Health Organization procedures aim to ensure safe and effective global public health advice based on the best available evidence. The final decision on whether to follow WHO recommendations always lies with sovereign states.

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