

## CORRESPONDENCE



## Hepatitis E Vaccine

**TO THE EDITOR:** The study by Shrestha et al. (March 1 issue),<sup>1</sup> which evaluated a vaccine for hepatitis E virus (HEV), represents a major advance but continues to raise ethical concerns. The trial of the HEV recombinant protein (rHEV) vaccine, conducted by the U.S. military and GlaxoSmithKline, was forced out of a Nepalese community after protests about whether residents would have access to the vaccine after the trial.<sup>2</sup> The study was subsequently relocated to the Nepalese Army. The consent of soldiers may be “unduly influenced . . . by fear of disapproval or retaliation if they refuse,”<sup>3</sup> which is why research involving soldiers should take place only if it “could not be carried out equally well with less vulnerable subjects.”<sup>3</sup> Indeed, the subjects may have been placed at needless risk, because the vaccine may not be developed. GlaxoSmithKline stated that a third party would need to develop the vaccine, given its low profit value.<sup>4</sup> It is crucial that phase 3 trials take place soon and that thereafter any viable vaccine be made accessible, particularly to communities that undertook the risk of testing.

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1. Shrestha MP, Scott RM, Joshi DM, et al. Safety and efficacy of a recombinant hepatitis E vaccine. *N Engl J Med* 2007;356:895-903.
2. Stevenson P. Nepal calls the shots in hepatitis E virus vaccine trial. *Lancet* 2000;355:1623.
3. Bankowski Z, Levine RJ, eds. International ethical guidelines for biomedical research involving human subjects. Geneva: Council for the International Organization of Medical Sciences, 1993.
4. Jack A. GSK is criticized for army drug test. *Financial Times*. February 28, 2006.

**TO THE EDITOR:** Challenges posed by the rHEV vaccine trials conducted in Nepal should not be overlooked. Original plans to test the vaccine in the civilian population were aborted after opposition from the local community leadership.<sup>1</sup> The leadership's failure to honor ethics approvals for the trial, issued by concerned authorities, raised unique ethical and operational dilemmas. Investigators resolved the dilemmas by testing the vaccine among Nepalese soldiers — a decision that has been debated.<sup>2</sup> In Nepal, hepatitis E is common, and recently even the prime minister and a number of ministers were taken ill by the virus. Prevention and control strategies are urgently needed.

The effectiveness of the rHEV vaccine generates hopes for prevention of disease among high-risk populations. But will the population at risk in Nepal benefit from this vaccine? Experience shows otherwise. International travelers benefit from the parenteral Vi capsular polysaccharide typhoid vaccine, which was tested among natives of Kathmandu.<sup>3</sup> However, Nepalese natives do not benefit from the vaccine, probably owing to the vaccine's high cost and short-term protective efficacy. Such

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examples discourage community support for research. The rationale of medical research cannot be justified if the population in which the research was carried out does not benefit from the results of the research.<sup>4</sup> In this regard, the investigators need to clarify the usefulness of the rHEV vaccine in preventing and controlling disease in the native population of Nepal.

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1. Stevenson P. Nepal calls the shots in hepatitis E virus vaccine trial. *Lancet* 2000;355:1623.
2. Andrews J. Research in the ranks: vulnerable subjects, coercible collaboration, and the hepatitis E vaccine trial in Nepal. *Perspect Biol Med* 2006;49:35-51.
3. Acharya IL, Lowe CU, Thapa R, et al. Prevention of typhoid fever in Nepal with the Vi capsular polysaccharide of *Salmonella typhi*: a preliminary report. *N Engl J Med* 1987;317:1101-4.
4. World Medical Association. Declaration of Helsinki: ethical principles for medical research involving human subjects: basic principles for all medical research. Article 19. 2007. (Accessed May 17, 2007, at <http://www.wma.net/e/policy/b3.htm>.)

**THE AUTHORS REPLY:** Our research established that the rHEV vaccine provides highly effective protection and generated a hypothesis that hepatitis E, an underrecognized disease, is so burdensome in places where it is endemic that vaccination could be cost-effective. Nevertheless, since the vaccine is being developed for the developing world, access will define its impact on health.

Basu and Lurie question whether volunteers in our trial were coerced because they were soldiers. We note that the trial began after a decade of capacity building and documenting the high risk of hepatitis E in Nepalese civilians and in the military. Our trial was responsive to a national health need and adhered to international guidelines for informed consent. The trial was approved by ethics review panels in Nepal and the United States and was monitored by independent experts. In particular, we took measures to remove the influence of military commanders over participation by their subordinates. Of more than 40,000 soldiers

who were informed about the trial, only 5323 gave informed consent to be screened; of 3023 soldiers with the lowest screening levels of antibody, only 1885 agreed to undergo randomization. The high proportion that declined to participate in the study at each stage of enrollment belies coercion.

GlaxoSmithKline, along with U.S. government agencies, has supported rHEV vaccine research, because the company recognized the value of developing vaccines and medicines against diseases in the developing world — efforts it has undertaken for more than 20 years. Bhattarai asks about access to the vaccine after the trial. We affirm that GlaxoSmithKline embraces the principle of distributive justice and is committed to continue development of the rHEV vaccine so that it can be available in Nepal. Nevertheless, since control of infectious diseases is a global public good, we call for international financing for the introduction of the rHEV vaccine through partnerships similar to those developed for rotavirus and pneumococcal conjugate vaccines.

We emphasize that GlaxoSmithKline is seeking public-sector partners who also are committed to the long and challenging endeavor to add the rHEV vaccine to immunization programs in high-risk countries. Despite competing public health priorities, we remain optimistic that the 95% protective efficacy of the rHEV vaccine can attract support. Adoption of rHEV vaccination programs in Nepal would be a fitting outcome for our trial's volunteers and our many colleagues who since 1987 have examined options to identify and control hepatitis E.

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## Improving the Management of Chronic Disease

**TO THE EDITOR:** The Special Article by Landon and colleagues (March 1 issue)<sup>1</sup> on improving the management of chronic disease at community health centers illustrates the importance of identifying

appropriate outcomes when measuring the effectiveness of interventions to improve processes of care. Establishing a more realistic schedule than that used in this study for assessing the effect of