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LETTER TO EDITOR

On the Comparison of Two HBV Recombinant Vaccines

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Dear Editor,

We would like to call your attention to our conviction that for a fair and balanced judgment of the article "Comparison of Two Recombinant Hepatitis B Vaccines" by Hasan Nikui Nejad *et al.* [1] published in your journal, the readers should consider a number of drawbacks, which in our opinion cast serious doubts upon the validity of the conduction, methods and conclusions of that trial. In this regard we judge it essential to take into account the following observations:

In order to ensure that vaccines used in national immunization services in different countries are safe and effective and to avoid having to constantly demonstrate the validity of vaccines, the World Health Organization (WHO) has compiled a list [2] of the available and proven vaccines it recommends for purchase by the United Nations (UN) agencies, without making any distinction between them [3]. The present comparison seems either untimely, or the reason for it unclear or undisclosed, since both vaccines are included in this list.

According to the results shown, the non-response levels (2.3 *vs.* 1.1, for the Cuban and Korean vaccines, respectively) mean that the proportion of responders are on the order of 97.7% *vs.* 98.9%, which is the usual seroconversion rate for this type of vaccine. This difference, which is slightly higher than 1%, is not significant from the statistical and clinical viewpoints, thus conferring the same level of success and benefit on both vaccines. Then the assertion that Hepavax-Gene vaccine provides more protection than Heberbiovac hepatitis B (HB) vaccine is not consistent, since from their own comparative results there is no difference between the two vaccines regarding non-responders (P = 0.439, see table 1). However, this small and irrelevant difference may be linked to one or several of the objections that follow.

The statistical hypothesis (to be proven or rejected) or the results to be expected from this study are not explicitly stated in the paper; and therefore, the sample size (N) estimation has not been appropriately justified (with the data shown in the article), so that it is impossible to ascertain the degree of significance or reliability for any claim based on these results.

The geometric mean is not adequately represented, since it refers to a standard deviation (SD) that by definition is calculated as a function of the arithmetic mean, and not of the geometric mean, which is a central

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trend measurement used to "alleviate" the extreme values of antibody titers. Therefore from the wording of the paper it is not clear whether the analysis has been done with the arithmetic or with the geometric mean (in which case the logarithmically transformed titers would have to be used for comparison).

There is no correspondence between the "P" value referred to in the comparison of the geometric mean titers (GMTs) and the estimated confidence intervals (CIs): 253.6±95.4 (95% CI: 0.9-310.8) *vs.* 315.7±163.5 (95% CI: 4.1-666.4) for the Heberbiovac HB Cuban vaccine group and the Hepavax-Gene Korean vaccine group, respectively. The CIs are non-excluding; on the contrary they are broadly overlapping and also have very low precision, so that the differences detected cannot be considered conclusive, neither in general, nor for the groups stratified according to sex and age. This proves the lack of repercussion on the percentages of protection.

The N distribution by age and sex was not shown for each vaccine group, although these factors have a well-known influence which may have affected one group differently from the other. Even assuming that the appropriate steps have been taken to ensure a random distribution, this source of bias would have to be checked, discarded and declared in the paper.

The Cuban Heberbiovac HB vaccine has been applied on Cubans under 29 years of age, which has led to the eradication of the acute hepatitis B virus (HBV) infection in the entire population of children and drastically lowered its prevalence in the general population [4], while being registered and/or distributed in more than 40 countries.

Finally, we consider that even if these results were absolutely faultless, and the authors were completely convinced of their validity, their direct recommendation to substitute one vaccine in favor of the other may prove inadequate, since such a proposal is beyond their capacity to judge. They should simply have published their findings objectively, and let the empowered authorities make their own decisions.

References

1. Nikui Nejad H, Ghorbani G, Razaghi R, Akbari H. Comparison of Two Recombinant Hepatitis B Vaccines. *Hepat Mon*. 2009;**9**(3):201-5.
2. World Health Organization. United Nations prequalified vaccines. WHO list of vaccines for purchase by UN agencies as of February 2010. Available from: http://www.who.int/entity/immunization standards/vaccine quality/pq suppliers/en
3. Procedure for assessing the acceptability, in principle, of vaccines for purchase by United Nations agencies, WHO/IVB/05.19. Department of Immunization, Vaccines and Biologicals, June 2006. Available from: http://whqlibdoc.who.int/hq/2006/WHO IVB 05.19 eng.pdf.
4. Castaneda C, Delgado G, Galindo MA. Impact of Vaccination in the Elimination of Hepatitis B in Children <5 Years.(1992-04): 102. *J Pediatr Gastroenterol Nutr*. 2005;**41**(4):524.

Nikui Nejad *et al.* reply:

We are thankful to Dr. Cinza Estévez *et al.* for their attention to our study.

While it is true that the WHO approved each of these two vaccines, and that they diminished the prevalence of hepatitis B virus infection in vaccinated populations and that this has also been seen in IRAN [1], evaluation of the efficacy of any vaccine is warranted for any group of users in different countries, because vaccination with each vaccine may induce varying immunity in different ages, sexes, races and populations with varying background diseases; and about 5% of the population does not respond to vaccine [2].

In our country, all children and military families were vaccinated for HBV, and the discovery of unvaccinated groups is difficult; therefore we cannot consider a large sample size. However, calculation of the sample size is dependent on the prevalence of vaccine response, so that if we take a minimum estimated prevalence of vaccine response, P = 95% and Q = 5% and $\alpha = (1.96)^2$ and d=0.03, the sample size needed for evaluation is calculated according to this formula, $n = (1.96)^2 \times 95\% \times 0.05 \div (0.03)^2 = 202$, but here, 347 persons were recruited for study and seemed to be a sufficient sample size.

The levels of antibody to hepatitis B surface antigen (HBsAb) were different between these two vaccines, although nonresponders are not significantly different. This fact is important to health managers [3], because even if coverage of vaccination is 100%, after vaccination about 1-2% and more than this number shown in the other study, will be susceptible to hepatitis B virus infection.

The possible primary failure of any vaccine must always be kept in mind, but it may vary, depending on the race, sex and age of recipients: here, the mean age of vaccinees is 32.3±7 and responses may be diminished, resembling the findings of the other study [4]. Also, the other study confirmed that the titer of the vaccine is higher in females than in males, and in our study it was higher in males than in females; and in those subjects less than 40 years old and above 40 years old: each vaccine was evaluated [5, 6].

Here the seroprotection titer was evaluated as different between these vaccines, although the lower mean titer and the CI of each of the two vaccines were similar, whereas the high mean and high CI of the titer were significantly lower in the Cuban

vaccine; and this is important because a high titer may induce prolonged protection [7, 8].

Ultimately, we recommend further investigation of the fact that some people do not respond to hepatitis B vaccine.

References

1. Alavian SM. Immunization: An Important Strategy to Control Hepatitis B. *Hepat Mon*. 2006;**6**(1):3-5.
2. Rendi-Wagner P, Shouval D, Genton B, *et al*. Comparative immunogenicity of a PreS/S hepatitis B vaccine in non- and low responders to conventional vaccine. *Vaccine*. 2006;**24**(15):2781-9.
3. Ghorbani GH, Alavian SM, Esfahani AA. Long-Term Protection of Hepatitis B Vaccine in Adult. *J Med Sci*. 2007;**7**(7):1214-7.
4. Scott PT, Niebuhr DW, McGready JB, Gaydos JC. Hepatitis B immunity in United States military recruits. *J Infect Dis*. 2005;**191**(11):1835-41.
5. Vos GH, Rose EF, Marimuthu T. Hepatitis B antigen and antibodies in rural and urban Southern African blacks. *S Afr Med J*. 1980;**57**(21):868-70.
6. Mansour-Ghanaei F, Fallah MS, Jafarshad R, *et al*. The Immunologic Response to Anti-Hepatitis B Vaccination Among Medical Students of Guilan University of Medical Sciences, Guilan, Iran. *Hepat Mon*. 2006;**6**(2):63-6.
7. Ghorbani GA, Alavian SM, Ghadimi HR. Long term effects of one or two doses of hepatitis B vaccine in adults after five years. *Pak J Biol Sci*. 2008;**11**(4):660-3.
8. Burgess MA, Rodger AJ, Waite SA, Collard F. Comparative immunogenicity and safety of two dosing schedules of a combined hepatitis A and B vaccine in healthy adolescent volunteers: an open, randomised study. *Vaccine*. 2001;**19**(32):4835-41.