RESEARCH BRIEF

Immunogenicity of Single Dose Live Attenuated Hepatitis A Vaccine

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A long-term immunogenicity study of a single dose live attenuated H2 strain hepatitis A vaccine is being conducted in healthy Indian children at KEM Hospital, Pune. 131 of the original 143 children vaccinated in 2004, were evaluated for anti-HAV antibodies 30 months post vaccination (2007). Seroprotective antibody levels ≥20 mIU/mL were demonstrated in 87.8% subjects with an overall GMT of 92.02mIU/mL. No hepatitis like illness was recorded in any of the subjects since vaccination

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Live attenuated Hepatitis A vaccines derived from H2 strains were licensed for human use in 1992. Since then, these vaccines have been used successfully in the Chinese population in the primary prevention of Hepatitis A infections as well as in the control of epidemics [1-5].

The first study of this vaccine outside China was conducted at Pune, India in 2004, and showed an immunogenicity of 95.8% by the end of 2 months after a single dose of the vaccine [6]. The high immunogenicity of the single dose schedule in Indian children was corroborated in 2008 by a larger multicentre study, showing seroconversion of 95.1% and 97.9% at 6 weeks and 6 months, respectively [7]. The original Pune cohort has been under regular follow up since vaccination, and this report refers to the immunogenicity data of this cohort at 30 months after vaccination.

METHODS

All children who completed the first phase of the study are called regularly to our centre for a follow up clinical visit once a year. At each visit, the children are evaluated with: (*i*) detailed medical history, especially enquiring about jaundice, and (*ii*) physical examination including size of liver and spleen.

At 30 months (after vaccination), their blood samples were collected and sent for estimation of anti-HAV IgG antibodies (HAVB 2.0; Abbott Axsym, ELISA) to an independent accredited laboratory (Super Religare Laboratories, Mumbai). Seroprotection was defined as anti-HAV antibody (IgG) level ≥20mIU/mL and immunogenicity was defined as the percentage of seroprotected subjects. The study was conducted after the approval of the Institutional Ethics Committee.

RESULTS

Of the original 143 subjects, 131 came for the 30 month immunogenicity study. Of the 12 'dropouts' 9 have transferred to other towns/ countries and 3 were refusals. Of the 131 subjects enrolled for follow up study, 8 subjects with sampling errors were excluded from immunogenicity analysis. Six

WHAT THIS STUDY ADDS?

- Immunogenicity at 30 months following single dose of live attenuated Hepatitis A vaccine in Indian children is 87.8%.

of the remaining 123 subjects were 'vaccine failures' from initial study and hence antibody titers were analyzed in 117 subjects (73 boys) with a mean age of 7.2 ± 2.6 years (range 3.5 - 15 years).

The number of children seen at each yearly clinical review were 139 (2005), 136 (2006), and 131 (2007). No reports of hepatitis like illnesses were recorded in any of the subjects since vaccination. 30 months after vaccination, protective antibody levels (≥20 mIU/mL) persisted in 108 of the 117 evaluable subjects (92.3%). By including the 6 vaccine failures from the Initial study, long term immunogenicity over 30 months was calculated as 87.8%. The geometric mean titre (GMT) of anti-HAV antibodies of all 117 evaluable subjects was 92.02 mIU/mL, while that of the 108 seroprotected subjects was 111.16 mIU/mL. The distribution of the subjects as per their antibody titres in comparison with the Initial study is seen in ***Fig.* 1**. The number of subjects with titers >100 mIU/mL had increased significantly in the Follow up study ($P < 0.001$).

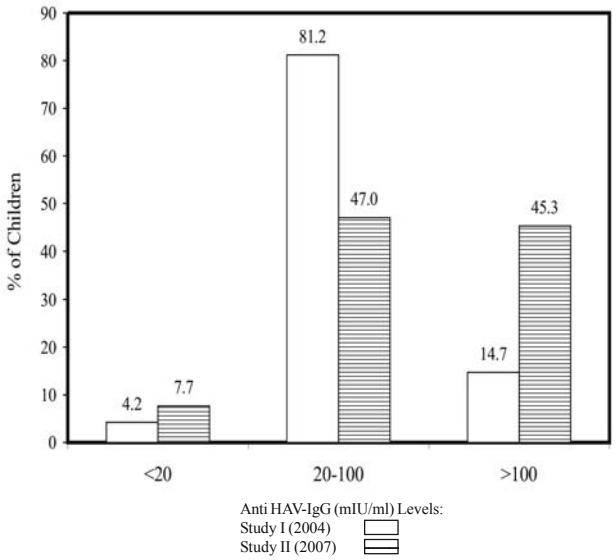

FIG. 1 *Percent distribution of subjects in the Initial study and the Follow up Study as per their antibody titres.*

DISCUSSION

The current follow up study demonstrates an immunogenicity of 87.8% with a GMT of 92.02mIU/mL, 30 months after a single dose of live attenuated Hepatitis A vaccine (Zhepu, Zhejiang Pukang Biotechnological Company Ltd, China). The results compare well with long term immunogenicity data following mass vaccination programs in various centres in China [4,5,8]. The Shanghai study reported seroprotective levels of 94.9% at 8 weeks falling to approx 80% by 3 years [4]. Cohort studies by Zhuang, *et al.* [5] recorded seroprotective levels in 98.6 % at 2 months, falling to 83.3% at 6 years and 80.2% at 10 years with GMTs of 287 mIU/mL**,** 173 mIU/mL and 145 mIU/mL, respectively.

Wang, *et al*. [9] compared immunogenicity data of two doses of live versus two doses of inactivated hepatitis A vaccine (Havrix, GSK Biologicals) at 12 and 24 months post vaccination. At 12 months, the reported GMT levels were 448 mIU/mL for live vaccine versus 1063 mIU/mL for inactivated vaccine whereas the corresponding values for 24 months were 218 mIU/mL versus 655 mIU/mL, respectively. At 24 months, seroprotection in this study was 92% for live vaccine and 100% for inactivated vaccine. Although seroprotective levels and GMTs achieved by a two dose schedule (inactivated or live attenuated vaccines) are somewhat higher [8-10], the excellent efficacy of a single dose schedule in prevention of symptomatic hepatitis A in epidemics has been demonstrated convincingly [1-5]. It has been suggested that exposures to natural infections (after vaccination) may act as 'booster doses', a phenomena of considerable significance in developing countries like India, which are endemic for Hepatitis A [8]. This may also explain the increased titres of HAV antibodies in our study at 30 months despite no further vaccination.

There have been no cases of hepatitis A like illness in study subjects till date, but the efficacy of the single dose schedule in our children will be elucidated by the long term follow up of our cohort.

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Contributors: ShB and AB were responsible for designing of the study. AS was primarily responsible for day to day conduct of the study. AB carried out statistical analysis. ShB, AB and SB coordinated the study and drafted the paper. AP supervised all aspects of the study. ShB will act as guarantor for the manuscript.
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