RESEARCH PAPER

Long-term Immunogenicity of Single Dose of Live Attenuated Hepatitis A Vaccine in Indian Children

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Objectives: To assess immunogenicity of a single dose of live attenuated hepatitis A vaccine in Indian children, ten years after immunization.

Methods: Of 143 children vaccinated in 2004, 121 children were evaluated in 2014, clinically and for anti-HAV antibodies.

Results: 13 children were early vaccine failures who received two doses of HAV vaccine subsequently. 106 (98%) of 108 remaining children had seroprotective levels with a geometric mean titer of 100.5 mIU/mL. On analysis of all 121 children, the immunogenicity was 87.6%.

Conclusion: Single dose of live attenuated hepatitis A vaccine provides long-term immunity in Indian children.

Keywords: *Immunization, Prevention, Protection, Hepatitis A vaccine*.

Hepatitis A (HAV) vaccine is now recommended by the World Health Organization (WHO) and Indian Academy of Pediatrics (IAP) in routine immunization of children, aged one year or above [1-3]. Both inactivated and live attenuated vaccines have been approved. The general recommendation for inactivated vaccine is to use two doses, 6 months apart. WHO and now, IAP, endorse a single dose schedule for live HAV vaccine [1,3]. However, IAP until recently recommended two doses, pending long term immunogenicity studies from India [2].

Single dose of live H2 strain HAV vaccines has been used in China for over 20 years, and shown remarkable safety, immunogenicity, and long-term protection [4,5]. The first study outside China to assess the safety and efficacy of single dose of live attenuated HAV vaccine (Biovac-A) was conducted at our center in Pune, India in 2004. It documented excellent immunogenicity (95.8%) two months after vaccination [6,7]. In this report, we present the results of immunogenicity in the children enrolled at Pune study center (in 2004) ten years after vaccination with a single dose of live HAV vaccine.

Methods

Children (age 1-12 y) who were enrolled at the start of the study in 2004 [6], and who participated in regular follow-up and immunogenicity assessments in 2007 and 2010, were re-valuated in 2014 (***Fig* 1**). Institutional ethics committee approval and informed consent were obtained. Participants were compensated for travel and loss of wages (where applicable). After routine clinical assessments, blood samples were collected and sent for estimation of total and IgM anti-HAV antibody analyses (Cobas anti-HAV electro-chemiluminescence immuno-assay, ECLIA, Roche Diagnostics Deutschland GmbH) [8] to an independent accredited laboratory (SRL Diagnostics, Mumbai, India). Seroprotection rate was defined as proportion of subjects with total anti-HAV antibody level ≥20 mIU/mL. Geometric mean titers (GMTs) were calculated as per standard method.

Accompanying Editorial: Pages 661-62.

Results

Of the original 143 children who received a single dose of live attenuated HAV vaccine in 2004, 121 subjects reported for 10 year follow-up assessment in 2014. Of these, four who had received two doses of licensed inactivated HAV vaccine (Havrix, GSK Biologicals) in 2004 (vaccine failures) and nine who had received a second dose of live HAV vaccine in 2007 for low titers (antibody levels <20 mIU/mL), were not evaluated in present analysis (***Fig.* 1**). Therefore, 108 children who received a single dose of the live vaccine were analyzed.

The clinical examination of the participants did not reveal any abnormal findings and none had a history of

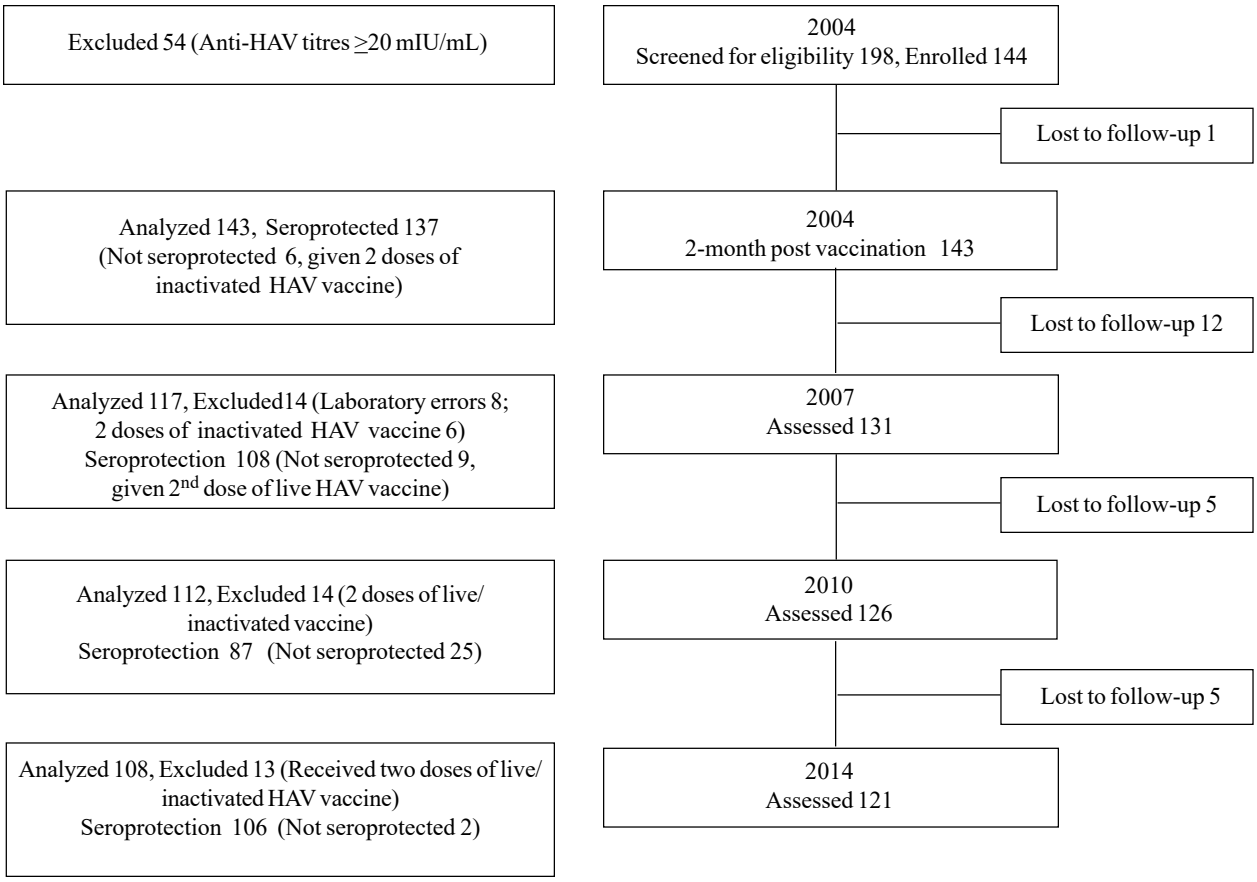


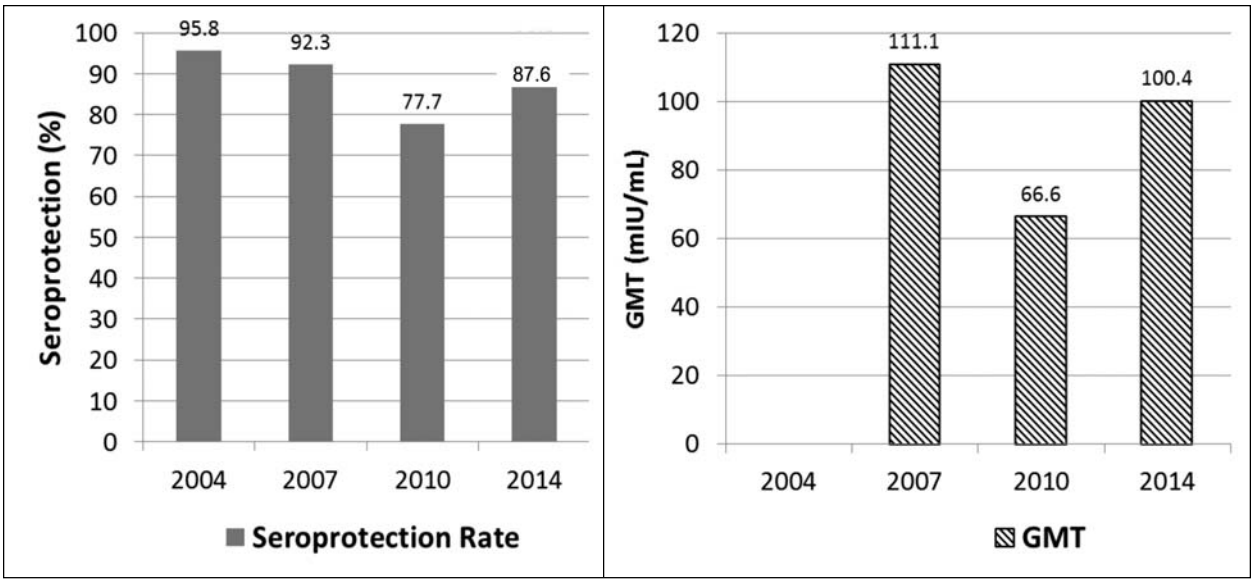
FIG.1 *Flow chart of 10-year study (2004-2014).*

hepatitis-like illness in the past. In the present analysis, 106 of the 108 included children had anti-HAV titres ≥20 mIU/mL; seroprotection rate of 98.1% (95% CI 93.5%, 99.8%); 10 years after a single dose of the live attenuated vaccine. Only two participants had anti-HAV titres <20 mIU/mL (11.5 mIU/mL and 13.5 mIU/mL). Anti-HAV IgM was negative in all the children studied. The GMT of anti HAV antibodies of seroprotected children was 100.5 mIU/mL (95% CI 87.4 mIU/mL, 115.4 mIU/mL). On analysis of all 121 children (including 4 'vaccine failures' and 9 with low titres at 30 months post-vaccination), the immunogenicity was 87.6%. The comparison of 10 year immunogenicity data with previous assessments (2004, 2007 and 2010) is presented in ***Fig. 2.***

DISCUSSION

This long term follow-up of a cohort of children vaccinated with a single dose of live attenuated HAV vaccine in 2004 demonstrated a seroprotection rate of 98.1% (anti – HAV GMT of 100.46mIU/mL.), 10 years after vaccination, in those who showed adequate seroprotection in earlier studies. The seroprotection rate would be 87.6%, on inclusion of 13 participants who had to be given additional hepatitis A doses because of poor immunogenicity documented in earlier evaluations [6,7]. None reported hepatitis-like illness.

The strength of this study is that 85% of the cohort enrolled in 2004 reported regularly for follow-up. Differences in the kits used for evaluation of titers is one of the limitation of this study. In the first three follow-ups, immunogenicity was assessed using quantitative Axsym HAVB 2.0 ELISA from Abbott Laboratories (Abbott Park, Illinois, USA). These kits were not available in 2014, and hence different kits had to be used for the present analysis. AxSYM HAVB 2.0 uses microparticle enzyme immunoassay (MEIA) whereas present kits were based on ECLIA technology [8]. Some reports have shown higher sensitivity of ECLIA as compared to ELISA-based immunoassays [9], and this could be a reason for the higher titers of antibodies observed in this analysis. Cross validation of immunogenicity data between the two kits was not possible as sera from previous analyses were not available. Another limitation was the cohort contamination with second dose of the vaccine. Due to ethical reasons, children who remained seronegative after vaccination in 2004 were given 2 doses of inactivated (licensed) HAV vaccine; in 2007 those who remained seronegative



** GMT of 2004 not presented as anti HAV titres >100mIU/mL were not quantified in 2004.*

FIG. 2 *(a) Serial Seroprotection Rates (2004-2014); (b) Serial GMTs (2004-2014).*

received a second dose of now licensed live HAV vaccine, In 2010, however, in view of the encouraging reports of persisting immunological memory despite low titres [10,11], no revaccination was done in seronegative children. The contribution of asymptomatic infections towards immunogenicity also cannot be ruled out as there was no control group in our study.

Our results are consistent with earlier reports from China [4,5], which showed seroprotection levels of 98.6%, 93.6%, 83.3% and 80.2% at 2 months, 12 months, 6 years and 10 years, respectively. Although studies have reported higher seroprotection and GMT levels with two dose schedule of live HAV vaccine, long-term efficacy studies with a single dose have uniformly demonstrated complete protection against the disease suggesting anamnestic response despite low titers [10]. Similarly, anamnestic response (immunological memory) is also the basis for recently proposed single dose schedule even for inactivated HAV vaccine [1,11,12]. The long-term results of the other Indian study (multicentric) of a single dose live HAV vaccine [13], are awaited.

In conclusion, a single dose of live attenuated HAV vaccine continues to show excellent immunogenicity 10 years after immunization, in Indian children. A single dose of live HAV vaccine will cut costs considerably, while providing long-term protection.

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Contributors: SB, AS, AB**:** designed the study, recruited patients, analyzed results and wrote the manuscript; VK, AM: provided technical help needed for the study. All authors approved the final version of manuscript.

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WHAT THIS STUDY ADDS?

- A single dose of live attenuated HAV vaccine is immunogenic in 87.6% of children at 10 years after vaccination.

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