Chapter 7

Summary
7. SUMMARY

This study was conducted to evaluate the immunogenicity, reactogenicity and the efficacy of a new genetic recombinant hepatitis B vaccine called Genevac B in adults, adolescents and in infants born to HBsAg positive mothers. The study was carried out analysed with six major objectives.

I. Comparison of the immunogenicity and safety of a new recombinant hepatitis B vaccine, Genevac B, with commercially available hepatitis B vaccines, Engerix B and Shanvac B.

II. Comparative evaluation of immunogenicity and reactogenicity of the new recombinant hepatitis B vaccine, Genevac B at two different doses in healthy adolescents (11-19 years).

III. Comparison of the efficacy of recombinant hepatitis B vaccine, Genevac B, with commercially available hepatitis B vaccines in babies born to HBsAg positive mothers.

IV. To study the impact of CMI markers in hepatitis B vaccine high responders, hypo responders and non-responders involved in Genevac B clinical trials.

V. To analyze the persistence of antibody (anti-HBs) levels in vaccinees participated in Genevac B clinical trials.

VI To analyze the possible emergence of vaccine escape mutants in hepatitis B vaccinated adults, adolescents and in babies born to HBsAg positive mothers.
7.1 COMPARATIVE EVALUATION OF IMMUNOGENICITY AND SAFETY OF GENEVAC B IN ADULTS

420 healthy adult volunteers were enrolled in Genevac B vaccination trial. In prevaccination screening out of the 420 volunteers, 1.9% were positive for HBsAg, 1.4% were positive for antiHBs and 0.7% were positive for antiHBC IgM and 3 did not provide willingness to participate in the trial due to personal reasons.

400 healthy adult volunteers of both sexes were enrolled for the study and were analysed demographically, clinically, biochemically, serologically and by follow up studies.

7.1.1 Demographic details analysis

Age group analysis of the study volunteers revealed that the mean age of the volunteers who received Genevac B was 28.3 years, Engerix B was 25.1 years and 28.1 years in Shanvac B. The mean weight of the vaccinees who received Genevac B, Engerix B and Shanvac B was 57.7kgs, 57.8kgs and 59.2kgs and the mean height was 164cms, 166.1cms and 164.6cms respectively.

Of the 400 healthy volunteers, 240 volunteers were allotted for receiving Genevac B, 80 each for Engerix B and Shanvac B. All the volunteers were vaccinated by accelerated dosage regimen of 0,1 and 2-months schedule with the respective vaccine. After the third dose, follow up up to 4 months was achieved in 222 volunteers who were vaccinated with Genevac B, 68 who were vaccinated with Engerix B and 64 with Shanvac B. Of which 149, 41 and 40 were males and 73, 27 and 24 were females from Genevac B, Engerix B and Shanvac B group respectively.
7.1.2 Pattern of Immunogenicity in adult vaccinees involved in Genevac B clinical trials

- 100% of seroconversion was achieved in all the three vaccine groups.
- 99.5% of seroprotection was achieved with Genevac B compared with 98.5% with Engerix B and 98.4% with Shanvac B.
- The geometric mean titer of antiHBs achieved with Genevac B was 735.5 mIU/ml compared with 718.2 mIU/ml and 662.2 mIU/ml achieved with Engerix B and Shanvac B respectively.
- Thus the vaccine under study Genevac B was found to be equally effective compared with the other commercially available vaccines in India.

7.1.3 Sex wise correlation of immunogenicity in adults

- 100% of seroconversion was achieved in both males and females in all the three vaccine groups.
- 100% of seroprotection was achieved in females of Genevac B and Engerix B, whereas Shanvac B group females had 95.9% of seroprotection. The same was 99.4% in males of Genevac B group, 97.6% in Engerix B and 100% Shanvac B group. However this difference was statistically insignificant.
- Males had a high antiHBs response levels with Genevac B and Shanvac B (734.3 mIU/ml, and 709.1 mIU/ml) compared with females who were vaccinated with the same vaccine (428.8 mIU/ml with Genevac B and 443.3 mIU/ml with Shanvac B respectively).
- Engerix B group males had lower response levels (84 mIU/ml) when compared with 1373.3 mIU/ml in females.
7.1.4 Pattern of antibody titer in adult vaccinees

- An antiHBs titer greater than 1000mIU/ml was achieved in 37.5% of vaccinees who received Shanvac B while it was 30.18% and 32.3% in volunteers who received Genevac B and Engerix B respectively. However, this difference was statistically insignificant.

7.1.5 Analysis of adverse events reported by Genevac B, Engerix B, and Shanvac B vaccinees

- No serious side effects were reported in our study.
- Pain at the site of injection was reported in 12.6% volunteers who received Genevac B, 13.2% in those received Engerix B, and 12.5% who received Shanvac B vaccine.
- Other haematological and biochemical safety parameters remained essentially normal before and after giving the vaccine in all the three groups of vaccinees.

7.2 COMPARATIVE EVALUATION OF IMMUNOGENICITY AND REACTOGENICITY OF GENEVAC B WITH TWO DIFFERENT DOSES IN HEALTHY ADOLESCENTS (11-19 YEARS)

- On prevaccination screening of 237 adolescents who consented to participate, 4.6% were HBsAg positive, 8.8% were found to be antiHBs positive, and 2.1% were unwilling to participate in the study.
- Of the effective 200 healthy adolescent volunteers who were eligible for trial participation, 100 volunteers each were assigned to be administered with 20μg and 10μg of Genevac B vaccine.
• Of the 100, in 1 ml of vaccine group, 58 were males and 42 were females, and in 0.5 ml of vaccine group, 57 were males and 43 were females.

• All the volunteers were administered with the standard vaccination regimen of 0.1 and 6 month dose schedule and given all the three doses of Genevac B vaccine.

7.2.1 Demographic data analysis of adolescent vaccinees.

• Adolescents between the age group of 11-19 years of both sexes were eligible for the study.

• Age group analysis of the study volunteers reveals that the mean age of the volunteers who received 1ml of Genevac B was 15.5 years while it was 15.4 years in the 0.5ml of the vaccine dose group.

• The mean of weight of the groups were 52.4 kg, 54 kg in 1ml and 0.5 dose of vaccine group. The mean height analysed were 158 cm, 154 cm in 1ml and 0.5 doses respectively.

• The dropout rates in the vaccine groups were 6% and 4% in 1ml and 0.5ml vaccine group respectively.

7.2.2 Evaluation of immunogenicity in adolescent volunteers.

• 100% of seroconversion and seroprotection was achieved with both the doses of vaccine.

• The anti HBs achieved in terms of GMT was 2628.9 mIU/ml in 1ml group of vaccinees when compared with 1372.8 mIU/ml in 0.5 ml of vaccinees.
1 ml of vaccine dose elicited a higher antibody response in females (2396.3 mIU/ml) than in males (1852 mIU/ml).

However the females of 0.5ml vaccine group had lower GMT of 1382.7 mIU/ml when compared with 1549.9 mIU/ml in males.

7.2.3 Range of antibody response in adolescent volunteers in both the group of vaccine

- Range of antibody was greater than 1000mIU/ml with 1ml of vaccine in 65.9% volunteers, however, it was 54% in 0.5 ml dose of vaccinees.

7.2.4 Adverse events associated with adolescent vaccinees in both the group of vaccine dose

- No serious side effects were reported in either group of vaccinees.

- Other hematological and biochemical safety parameters remained essentially normal in both the groups of vaccinees before and after vaccination.

- Fever was reported in 4.2% of volunteers of 1ml vaccine dose group compared with 2.1 % of vaccinees in 0.5ml of vaccine dose group.

7.3 COMPARITIVE EFFICACY OF RECOMBINANT HEPATITIS B VACCINE GENEVAC B WITH COMMERCIALY AVAILABLE HEPATITIS B VACCINE IN BABIES BORN TO HBsAg POSITIVE MOTHERS

Details of vaccination to children born to HBsAg positive mothers

Of the 158 babies born to HBsAg positive mothers, 118 were vaccinated up to 7th month. Pre vaccination and post vaccination samples were analyzed for HBs titers
to assess the efficacy of hepatitis B vaccination. Of the 118 babies followed up, 48 babies received Genevac B, 38 were administered Engerix B and 32 were administered Shanvac B with full course of vaccine dose. Out of 48 babies who were vaccinated with Genevac B, 28 were males and 20 were females while it was 20 males and 18 females in Engerix B group and 15 were males and 17 were females in Shanvac B group.

7.3.1 Evaluation of immunogenicity in infants administered with Genevac B, Engerix B and Shanvac B

- On completion of the standard regimen of vaccination in infants, 100% seroconversion and seroprotection rates were achieved in all the three groups.

- The anti-HBs titers achieved in terms of GMT were 90.3mIU/ml with Genevac B, 77.5mIU/ml with Engerix B and 61.9mIU/ml in Shanvac B group.

- The GMT achieved in females who belonged to Genevac B group and Shanvac B group was 94.1 mIU/ml and 70.9mIU/ml respectively. However, in males it was 87.1mIU/ml and 53.0mIU/ml. Engerix B showed a GMT of 77.5mIU/ml and 77.5mIU/ml in males and females respectively.

7.3.2 Range of antibody in infant vaccinees vaccinated with Genevac B, Engerix B and Shanvac B

- In Genevac B group, 45.7% of vaccinees had a high range of antiHBs titer between 101-300mIU/ml, while it was 38% in Engerix B group and 25% in Shanvac B group.
• In Shanvac B group, 75% of vaccinees had a range of antiHBs titer between 11-100mIU/ml. However, it was 54.2% in Genevac B group and 61.9% in Engerix B group.

7.4 FOLLOW UP ANALYSIS OF VACCINEES INVOLVED IN GENEVAC B CLINICAL TRIALS

7.4.1 Pattern of persistence of anti-HBs in adults involved in Genevac B clinical trial

• On completion of 36 months, follow up was achieved in 41% of adults in Genevac B group; 59% in Engerix B group and 82% in Shanvac B group.

• 100% of seroconversion was still seen after 3 years in Genevac B, Engerix B and Shanvac B group of volunteers.

• On completion of 3 years of follow up, the seroprotection achieved were 96% in Genevac B, 95% by Engerix B and 94% in Shanvac B.

• The GMT of antiHBs observed in the three groups of vaccinees was 524.5mIU/ml in Genevac B groups, 469.6 mIU/ml in Engerix B group and 443 mIU/ml in Shanvac B group.

• The GMT of anti-HBs observed in males and females in the three groups were 839.7 mIU/ml and 706.1 mIU/ml in Genevac B group, 617.6 mIU/ml and 642.5 mIU/ml in Engerix B group and 351.2 mIU/ml and 360.6 mIU/ml in Shanvac B group respectively.

• When the range of antibody response was analysed, a high response of > 1000mIU/ml was observed in 42.3% of Genevac B vaccinees when compared with 32.5% of Engerix B vaccinees and 18.8% of Shanvac B vaccinees.
7.4.2 Pattern of persistence of antibody (antiHBs) response after one year of followup in adolescents

- 100% of seroconversion and 100% of seroprotection was observed in both 1ml and 0.5 ml of vaccine dose group after one year of follow up.

- The sex wise analysis revealed that males elicited a higher GMT of antiHBs (2526.5 mIU/ml and 1236.9) compared to females (2083.3 mIU/ml and 829.1mIU/ml) in 1ml and 0.5ml vaccine dose group respectively.

- The range of antibody was >1000 mIU/ml in 71.2% of 1 ml dose of vaccinees compared with 54% of 0.5 ml dose of vaccinees.

- Males displayed >1000mIU/ml anti-HBs levels in 74.5% and 55.5% with 1ml and 0.5 ml of vaccine compared 16.6% and 52.3% respectively in females vaccinees.

7.4.3 Evaluation of immunogenicity in babies born to HBsAg positive mothers after one year of followup

- 100% of seroconversion and seroprotection was achieved in all the three groups of vaccinees.

- Babies who were followed up for 12\textsuperscript{th} month had a good antibody response with Genevac B (226.7mIU/ml), Engerix B (197.9mIU/ml) and Shanvac B (175.6 mIU/ml).

- High GMT response was observed in males (227.3mIU/ml, 202.8mIU/ml and 189.1mIU/ml with Genevac B, Engerix B and Shanvac B respectively) when compared with females (226.1mIU/ml, 193.3mIU/ml, 163.3mIU/ml) respectively.
• In all the vaccine group, high range of antibody response (101-300mIU/ml) was achieved.

• In Genevac B vaccinees high range (101-500mIU/ml) of anti-HBs was seen in 80% volunteers, 66.6% with Engerix B and 58.3% with Shanvac B.

7.5 PATTERN OF VACCINE RESPONDERS VS. NON-RESPONDERS IN ADULTS, ADOLESCENTS AND BABIES BORN TO HBSAG POSITIVE MOTHERS

• In adult vaccinees with the accelerated vaccination regimen, 0.5% in Genevac B group, 1.5% in Engerix B group and 1.6% in Shanvac B group were found to be non-responders.

• In adolescents, non-responsiveness of vaccine was not observed. However, 3.1% and 4% of low responsiveness was observed in 1ml and 0.5 ml of vaccine dose respectively.

• Non-responsiveness was not seen in infants vaccinated with any of the vaccines. However, hypo response was seen in 60.4% of Genevac B vaccinees, 68.4% and 84% of vaccinees in Engerix B and Shanvac B group respectively.

7.6 ANALYSIS OF CYTOKINE RESPONSE IN NON-RESPONDERS, HYPO RESPONDERS AND HIGH RESPONDERS

7.6.1 Analysis of cytokine in adult vaccinees

• In adults vaccinees high protection with CMI markers like TNF-α and IL-12 was detected.
Measurable amounts of IL-12 were detected in high responders which in terms of mean was 582.4 pg/ml, 573.6 pg/ml, and 549 pg/ml in Genevac B, Engerix B and Shanvac B respectively.

Measurable amounts of TNF-α were detected in high responders which in terms of mean were 695.4 pg/ml, 518.8 pg/ml, and 508 pg/ml in Genevac B, Engerix B and Shanvac B respectively.

Measurable amounts of IL-12 were detected in hypo responders which in terms of mean were 104.8 pg/ml, 102.4 pg/ml, and 104.8 pg/ml in Genevac B, Engerix B and Shanvac B respectively.

Measurable amounts of TNF-α were detected in hypo responders, which in terms of mean were 122.8 pg/ml, 126 pg/ml, and 136.2 pg/ml in Genevac B, Engerix B and Shanvac B respectively.

However hypo responders of Genevac B and Engerix B vaccine group displayed a significant protection with IFN-γ whereas it is not detected in hypo responders of Shanvac B group.

In non-responders, IFN-γ was detected in all the volunteers. Measurable amounts of IFN-γ were detected in non-responders, which in terms of mean was 10.4 IU/ml.

7.6.2 Analysis of cytokines in adolescent group volunteers

High responders in the adolescent vaccinees displayed a higher production of IL-12 and TNF-α.

The mean IL-12 and TNF-α response observed were 1075.7 pg/ml, 1034.2 pg/ml and 1118.5 pg/ml, 998 pg/ml with 1ml and 0.5 ml of vaccinees respectively.
• The levels of IL-12 and TNF-α produced by hypo responders was 146.7 pg/ml and 141.7 pg/ml with 1ml and 0.5ml dose of vaccine group respectively.

• Hypo responders displayed comparatively low levels of IL-12, TNF-α.

7.6.3 Analysis of cytokine response in babies born to positive mothers

• High responder infants vaccinated with Genevac B, Engerix B and Shanvac B produced IL-2 and IFN-γ.

• Measurable amounts of IL-2 were detected in high responders which in terms of mean was 3.6U/ml, 4.6U/ml, and 4.6U/ml in Genevac B, Engerix B and Shanvac B respectively.

• Measurable amounts of IFN-γ were detected in high responders which in terms of mean was 5.6IU/ml, 4.8IU/ml, and 4.8IU/ml in Genevac B, Engerix B and Shanvac B respectively.

• In Hypo responders measurable amounts of IL-2 and IFN-γ was detected. The amount of IL-2 detected in terms mean was 3.4U/ml, 4.6U/ml and 5.4U/ml in Genevac B, Engerix B and Shanvac B group respectively.

• Measurable amounts of IFN-γ were detected in hypo responders which in terms of mean was 4.4IU/ml, 5.6IU/ml, and 4.4IU/ml in Genevac B, Engerix B and Shanvac B respectively.