

Characterization of an age-response relationship to GSK's recombinant hepatitis B vaccine in healthy adults: An integrated analysis

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Abbreviations: anti-HBs, antibody to hepatitis B surface antigen; CI, confidence intervals

The immune system becomes less effective with age, and older age is associated with an increased susceptibility to diseases and reduced responses to vaccination. Furthermore, some adult populations, such as those with diabetes mellitus, are at increased risk of acute hepatitis B virus (HBV) infection. Decreasing responses to vaccination with advanced age have been described, but it is not known at what age immunogenicity starts to reduce, or until what age immunogenicity remains acceptable (for example $\geq 80\%$ seroprotection post-vaccination). We characterized the relationship between age and seroprotection rate induced by recombinant HBV vaccination by conducting a pooled analysis of clinical trial data. Healthy adults aged ≥ 20 y who had been vaccinated with 20 μ g HBV vaccine (*EngerixTM B*, GSK Vaccines, Belgium) in a 0, 1, 6 months schedule in 11 studies since 1996 were included. The observed seroprotection rate, defined as an anti-HBV surface antigen antibody concentration ≥ 10 mIU/ml was 94.5% in the whole population (N = 2,620, Total vaccinated cohort), ranging from 98.6% in adults vaccinated at age 20–24 years, to 64.8% in those vaccinated at age ≥ 65 y. A model on seroprotection rates showed a statistically significant decrease with age, and predicted that the anti-HBs seroprotection rate remains $\geq 90\%$ up to 49 y of age and $\geq 80\%$ up to 60 y of age. Individuals at risk of HBV infection should be vaccinated as early in life as possible to improve the likelihood of achieving seroprotection. Additional studies are needed to identify whether unvaccinated individuals older than 60 y would benefit from regimens that include additional or higher vaccine doses.

Introduction

The global population is aging, with the proportion of those aged 60 y and older expected to double between 2000 and 2050.¹ The immune system becomes less effective with age, and old age is associated with reduced responses to vaccination, increased susceptibility to infectious diseases, and an increased risk of developing severe or complicated illnesses as a result.² Age-related immune defects may also be exacerbated by co-existing morbidities and chronic diseases that can lead to immune dysfunction, such as chronic renal disease requiring hemodialysis,³ underlying liver disease⁴ and diabetes: adults with diabetes mellitus are at increased risk of acute hepatitis B infection and suffer 2–3-fold higher rates of complications including progression to cirrhosis and hepatocellular cancer, compared to non-diabetics.^{5–9}

Immune senescence is characterized by altered composition of bone marrow with reduced capacity to produce and nurture stem

cells, and atrophy of the thymus gland with reduced output of T-cells.¹⁰ The response to vaccination is impaired in the elderly due to functional defects at multiple levels in innate and adaptive immune responses. These include reduced capacity of antigen presenting cells to take up and present antigen, lower numbers of T-cells capable of responding to new antigen, reduced magnitude and quantity of the B-cell antibody response, and poor effector T-cell activation and signaling due to reduced numbers and loss of receptor diversity.^{11–13}

Decreasing responses to vaccination with increasing age have been described for numerous vaccines including those targeting seasonal influenza,¹⁴ diphtheria,¹⁵ tetanus,¹⁶ pertussis,¹⁷ pneumococcal disease,¹⁸ and others.¹⁹ Several studies describe decreased responses to hepatitis B vaccination in older adults, although the studied age ranges vary between 40 and 80 y.^{20–26} Indeed, it is not known at what age the magnitude of the immune response to hepatitis B vaccination starts to reduce, or until what age the immune response remains acceptable (for

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example ≥ 80 % seroprotection post-vaccination). In order to answer these questions for currently recommended doses and schedules, we undertook a pooled analysis of clinical trial data (E-track 201931). All GSK-sponsored interventional vaccine studies using hepatitis B vaccine (*EngerixTM* B, GSK Vaccines, Belgium) reported after 1996 were included. All studies were to be completed (published or unpublished), with a database and clinical study report available. Eligible study groups were those in which healthy adults aged ≥ 20 y received 20 μg of a licensed formulation of *EngerixTM* B according to a 0, 1 and 6 month immunization schedule. Data from subjects who received other hepatitis B vaccines, combination vaccines such as combined hepatitis A and hepatitis B vaccines, or who belonged to special populations (for example hemodialysis patients), or who were vaccinated according to an alternative schedule, were excluded from the analysis.

All adults vaccinated with *EngerixTM* B and whose immune results were available one month after the third vaccine dose were included in the analysis (Total vaccinated cohort). Seroprotection results with exact 95% confidence intervals (CI) were summarized by age in 5-y intervals. All studies measured antibodies to hepatitis B surface antigen (anti-HBs) one month post-dose 3 using either an enzyme-linked immunosorbent assay or chemiluminescence immunoassay. An anti-HBs threshold of 10 mIU/ml defined seroprotection. The 10 mIU/mL threshold is accepted as a serological correlate of protection for HBV infection and was used in our study as indicative of immunogenicity.^{27,28}

A logistic model on seroprotection rate was used to assess whether age influenced the seroprotection rate. A 2-sided p-value < 0.05 for the null hypothesis, that there is no age effect, was used to indicate a statistical significant effect of age. With $\geq 2,300$ subjects aged between 20 and 83 years, and an expected seroprotection rate at ages 35 and 45 y of 90% and 87.8%, respectively (corresponding to a 0.8 odds ratio for a decennial age increase), the analysis had 89% power to identify a statistically significant age effect on the hepatitis B seroprotection rate (PASS 2005, logistic regression with a normally distributed covariable, 2-sided alpha = 5 %). If a significant age effect was observed, a piecewise linear model was used to determine whether an age cut-off exists for the seroprotection rate decrease. The age cut-off was estimated from the best fitted piecewise model based on the Akaike Information Criterion (a measure of the relative quality of a statistical model for a given set of data).

The analysis included 2,620 eligible adults (Total vaccinated cohort) who participated in 11 studies conducted in 10 countries (Table 1). The mean age was 34.3 y (standard deviation 12.3 years), 57.7% of subjects were female and 91.8% were Caucasian. The seroprotection rate in the whole population was 94.5% (95% CI 93.5; 95.3), ranging from $\geq 98.6\%$ in adults 20–24 y of age to 64.8% in those aged ≥ 65 y (Fig. 1A).

The best model fit was achieved using a log-linear curve with an age effect beginning at 20 y of age where $\text{Ln}(P/1-P) = 4.23 - 0.07 \cdot \text{age}$ (Fig. 1B). The model predicted that the anti-HBs

Table 1. Summary of subject characteristics by age group (total vaccinated cohort)

Category	Age (years)										Total n (%)	
	20–24 n (%)	25–29 n (%)	30–34 n (%)	35–39 n (%)	40–44 n (%)	45–49 n (%)	50–54 n (%)	55–59 n (%)	60–64 n (%)	≥ 65 n (%)		
Study												
	HAB-056 ³³	15 (2.0)	5 (1.1)	2 (0.7)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	22 (0.8)
	HAB-061 ³⁴	35 (4.6)	29 (6.5)	38 (14.1)	73 (24.0)	80 (27.5)	55 (20.5)	35 (30.4)	17 (28.3)	13 (23.6)	6 (10.9)	381 (14.5)
	HAB-166 ³⁵	20 (2.6)	37 (8.4)	20 (7.4)	11 (3.6)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	88 (3.4)
	HBV-269	195 (25.7)	136 (30.7)	71 (26.4)	63 (20.7)	64 (22.0)	72 (26.9)	7 (6.1)	1 (1.7)	0 (0.0)	0 (0.0)	609 (23.2)
	HBV-270	312 (41.1)	115 (26.0)	45 (16.7)	38 (12.5)	7 (2.4)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	517 (19.7)
	HBV-274	7 (0.9)	5 (1.1)	1 (0.4)	9 (3.0)	8 (2.7)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	30 (1.1)
	HBV-275	19 (2.5)	9 (2.0)	10 (3.7)	14 (4.6)	1 (0.3)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	53 (2.0)
	HBV-282 ³⁶	54 (7.1)	57 (12.9)	23 (8.6)	34 (11.2)	46 (15.8)	50 (18.7)	5 (4.3)	0 (0.0)	0 (0.0)	0 (0.0)	269 (10.3)
	HBV-283	28 (3.7)	16 (3.6)	15 (5.6)	20 (6.6)	22 (7.6)	16 (6.0)	4 (3.5)	4 (6.7)	0 (0.0)	2 (3.6)	127 (4.8)
	HBV-308	68 (8.9)	26 (5.9)	19 (7.1)	18 (5.9)	31 (10.7)	40 (14.9)	27 (23.5)	11 (18.3)	15 (27.3)	11 (20.0)	266 (10.2)
	HBV-323	7 (0.9)	8 (1.8)	25 (9.3)	24 (7.9)	32 (11.0)	35 (13.1)	37 (32.2)	27 (45.0)	27 (49.1)	36 (65.5)	258 (9.8)
	Total	760 (29.0)	443 (16.9)	269 (10.3)	304 (11.6)	291 (11.1)	268 (10.2)	115 (4.4)	60 (2.3)	55 (2.1)	55 (2.1)	2620 (100)
Gender												
	Female	476 (62.6)	222 (50.1)	147 (54.6)	171 (56.3)	164 (56.4)	158 (59.0)	71 (61.7)	33 (55.0)	35 (63.6)	34 (61.8)	1511 (57.7)
	Male	284 (37.4)	221 (49.9)	122 (45.4)	133 (43.8)	127 (43.6)	110 (41.0)	44 (38.3)	27 (45.0)	20 (36.4)	21 (38.2)	1109 (42.3)
Country												
	Australia	2 (0.3)	1 (0.2)	1 (0.4)	3 (1.0)	3 (1.0)	4 (1.5)	3 (2.6)	3 (5.0)	3 (5.5)	3 (5.5)	26 (1.0)
	Belgium	398 (53.4)	213 (48.6)	122 (45.7)	122 (40.1)	106 (36.4)	112 (41.8)	34 (29.6)	12 (20.0)	15 (27.3)	11 (20.0)	1145 (44.1)
	Canada	1 (0.1)	2 (0.5)	7 (2.6)	7 (2.3)	11 (3.8)	9 (3.4)	12 (10.4)	7 (11.7)	9 (16.4)	11 (20.0)	76 (2.9)
	Czech Republic	54 (7.2)	57 (13.0)	23 (8.6)	34 (11.2)	46 (15.8)	50 (18.7)	5 (4.3)	0 (0.0)	0 (0.0)	0 (0.0)	269 (10.4)
	Germany	117 (15.7)	54 (12.3)	9 (3.4)	9 (3.0)	4 (1.4)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	193 (7.4)
	New Zealand	1 (0.1)	0 (0.0)	1 (0.4)	4 (1.3)	3 (1.0)	3 (1.1)	4 (3.5)	3 (5.0)	2 (3.6)	4 (7.3)	25 (1.0)
	Philippines	28 (3.8)	16 (3.7)	15 (5.6)	20 (6.6)	22 (7.6)	16 (6.0)	4 (3.5)	4 (6.7)	0 (0.0)	2 (3.6)	127 (4.9)
	Russian Federation	20 (2.7)	37 (8.4)	20 (7.5)	11 (3.6)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	88 (3.4)
	Spain	86 (11.5)	24 (5.5)	15 (5.6)	11 (3.6)	1 (0.3)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	137 (5.3)
	United States	38 (5.1)	34 (7.8)	54 (20.2)	83 (27.3)	95 (32.6)	74 (27.6)	53 (46.1)	31 (51.7)	26 (47.3)	24 (43.6)	512 (19.7)
	Missing	15	5	2	0	0	0	0	0	0	0	22

n (%) = number (percentage) of subjects in the indicated category.

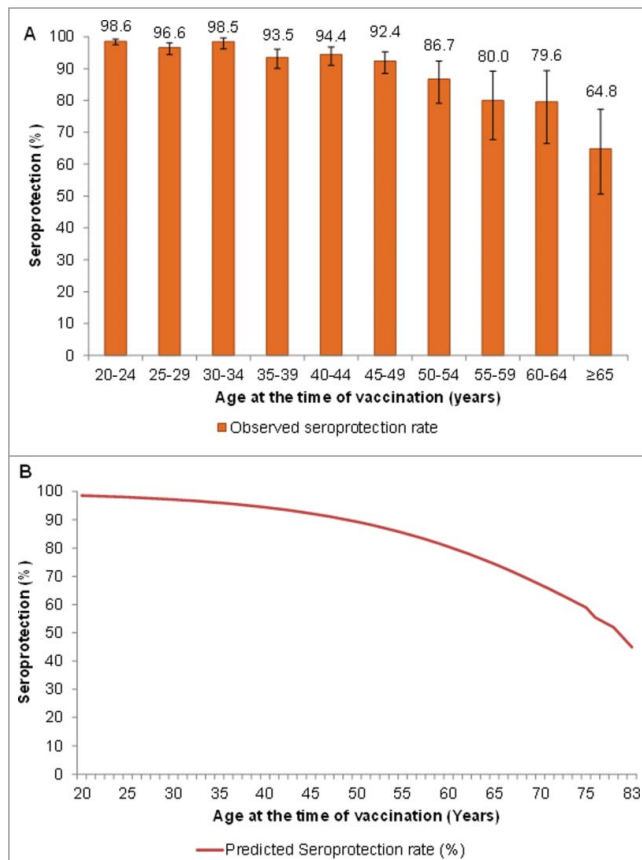


Figure 1. Observed (A) and predicted (B) seroprotection rates with 95% CI (Total vaccinated cohort). Predicted seroprotection rate (%) = Predicted percentage of subjects with anti-HBs concentration ≥ 10 mIU/ml evaluated from the best fit logistic regression model where $\ln(P/1-P) = 4.23 - 0.07 \times \text{age}$ and P represents seroprotection rate. Vertical lines indicate 95% confidence intervals.

seroprotection rate remains $\geq 90\%$ up to 49 y of age and $\geq 80\%$ up to 60 y of age (Fig. 1B).

This pooled analysis of clinical trial data allows robust assessment of the effect of age upon the immune response to hepatitis B vaccination in a large population. The clinical trials were conducted in healthy adults without underlying disease or known immune deficiencies, allowing assessment of the effect of age alone on the immune response. The decline in anti-HBs seroprotection rate with age followed a log linear curve, indicating that the decrease in hepatitis B seroprotection progresses throughout all age groups. Our study suggests that immune senescence starts in early adulthood, but accelerates after 50–60 y of age.

The thymus gland has a pivotal role in immune functioning and produces diverse populations of naïve T-cells necessary for humoral and cellular immune responses.^{10,29} Thymic involution is one of the most important events that contributes to immune dysfunction in the elderly.^{10,29} Evidence of early and continual decreases in vaccine responses with age is broadly consistent with

the process of thymic involution, which begins in early adulthood. By 50 y of age around 80% of functional thymus tissue has been lost.¹⁰

Our model predicts that the hepatitis B seroprotection rate remains $\geq 90\%$ up to 49 y of age, and above 80% until 60 y of age in adults who are otherwise healthy. While we did not investigate interactions between gender and immune senescence, our results are comparable to results of a modeling study of anti-HBs concentrations in more than 11,000 healthy adults in the Netherlands.²⁶ In the Netherlands study the response rate (anti-HBs ≥ 10 mIU/ml) was also predicted to be 90% until approximately 40 y of age and 80% at around 60 y of age.²⁶ This information has implications for vaccination policy. Individuals at risk of hepatitis B infection should be vaccinated as early in life as possible to improve the likelihood of achieving seroprotection, and because of the ease of identifying an at-risk individual before exposure occurs. This is particularly relevant for at-risk older populations, including patients with co-morbidities such as chronic renal or liver disease, and patients with diabetes, who have higher rates of acute hepatitis B and are at greater risk of developing complications of hepatitis B than healthy individuals.³⁻⁸ Further investigations are needed to identify if unvaccinated individuals over 60 y of age, in whom hepatitis B vaccination is recommended, would benefit from regimens that include additional or higher doses, as adopted for patients on hemodialysis,^{30,31} in order to improve seroprotection rates.³²

Engerix is a trademark of the GlaxoSmithKline group of companies.

Disclosure of Potential Conflicts of Interest

All authors are employees of the GlaxoSmithKline group of companies. MDR, BC and OVDM declare to be in receipt of GSK stocks.

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