

HBV vaccination in dialysis patients

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Vaccination in ESRD

- End stage renal disease (ESRD) patients are neither able to mount a sufficient immunologic response following vaccination, nor to maintain adequate antibody titers over time: response of these patients is at most 50–60%
- The second generation anti-HBV vaccine, produced in yeast, contains the S protein component of the HBV, but lacks the Pre-S1 and Pre-S2 components

- Numerous aspects of HBV vaccination have been studied in order to augment the immune response following HBV vaccination in ESRD
- Dosage multiplication and time schedule acceleration have already become a part of common practice, following official CDC recommendations
- Mode of injection (IM vs. ID) and adjuvant co-administration have been used in an attempt to improve seroconversion rates
- One of the most important aspects is the recognition of the correct timing for vaccination along the renal disease, taking to account the progressive character of CKD and the concurrent immunologic decline

Adjuvants

- The use of IFN as an immune adjuvant achieves an earlier and higher seroprotection rate
- Combined HBA and HBV vaccine
- GM-CSF may improve the immune response
- HB-AS02 is an adjuvant system consisting of MPL and QS21, a highly purified immunostimulant extracted from the bark of the South American *Quillaja saponaria* tree
- rHuEPO treatment improves the HBV vaccination response, and the immune response is positively correlated with the dose of rHuEPO

Effects of Oral Levamisole as an Adjuvant to Hepatitis B Vaccine in Adults With End-Stage Renal Disease: A Meta-Analysis of Controlled Clinical Trials Clinical Therapeutics, 2010

- 4 controlled clinical trials (328 pts), that weighted the seroprotection rate in patients with ESRD who received oral levamisole + HBV vaccine vs. those who received the HBV vaccine alone
- Patients received oral levamisole 80-120 mg for 2 weeks to 6 months + HBV vaccine
- The results from this meta-analysis suggest significant benefit in the administration of levamisole as an adjuvant to HBV vaccine to increase seroprotection in patients with ESRD

Novel vaccine

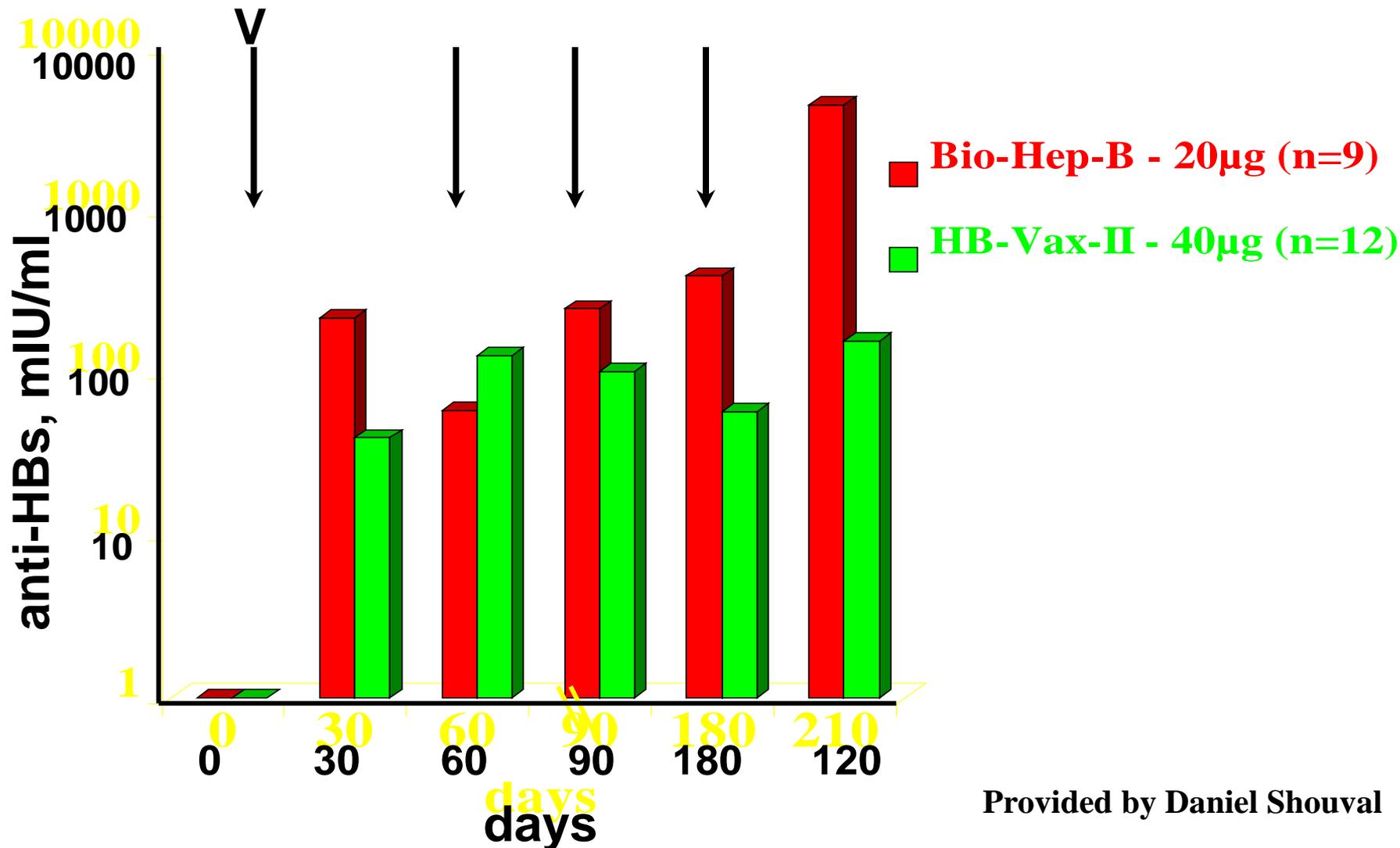
- Third generation recombinant vaccine, produced via expression of S, Pre-S and Pre-S2 protein components of HBsAg in mammalian Chinese hamster ovary (CHO) cell line which produce glycolysated antigens (e.g. “Bio-Hep-B®”, now Sci-B-Vac®)
- The two additional residues appear to have an enhancing effect on the T cell recognition of the S1 HBsAg

Improved Immunogenicity of a Novel Third-Generation Recombinant Hepatitis B Vaccine in Patients with End-Stage Renal Disease

Weinstein T, et al. *Nephron Clin Pract* 2004;97:c67–c72

- This case series describes our experience with a third-generation vaccine, Bio-Hep-B, (Sci-B-Vac) in ESRD patients who had not developed protective anti-HBs titers following a second-generation HBV vaccination protocol
- 29 ESRD patients were included in this series
- Patients received 10 µg of Bio-Hep-B IM at 0, 1 and 6 months
- Following immunization, 25 of 29 patients (86%) developed seroprotective anti-HBs levels
- Statistical analysis of the variables age, gender, diagnosis, dialysis mode, weight, hemoglobin, albumin, and KT/V failed to detect predictors of antibody response

Quantitative anti-HBs response to immunization of patients on hemodialysis – pilot study



Provided by Daniel Shouval

Liver Unit, Hadassah, Jerusalem

Comparison of 2nd and 3rd generation vaccine in dialysis patients

- Prospective, randomized, controlled study comparing Engerix[®] to Sci-B-Vac[®], performed at Tel Aviv Medical Center
- Assessed all 193 hemodialysis patients, of whom 62 (32.1%) were seropositive, and 8 (4.1%) were chronic HBV carriers
- 97 patients agreed to participate, and were randomized into non-previously vaccinated, and previously vaccinated groups
- Non-vaccinated received Engerix[®] 40 µg IM at 0,1,3,6 months, or Sci-B-Vac[®] **10** µg IM at time 0,1,6 months
- Previously vaccinated received Engerix[®] 40 µg IM at 0,1,3,6 months, or Sci-B-Vac[®] **20** µg IM at 0,1,6 months
- Anti-HBs antibodies were determined at 4, 7 months post-initiation of vaccination protocol

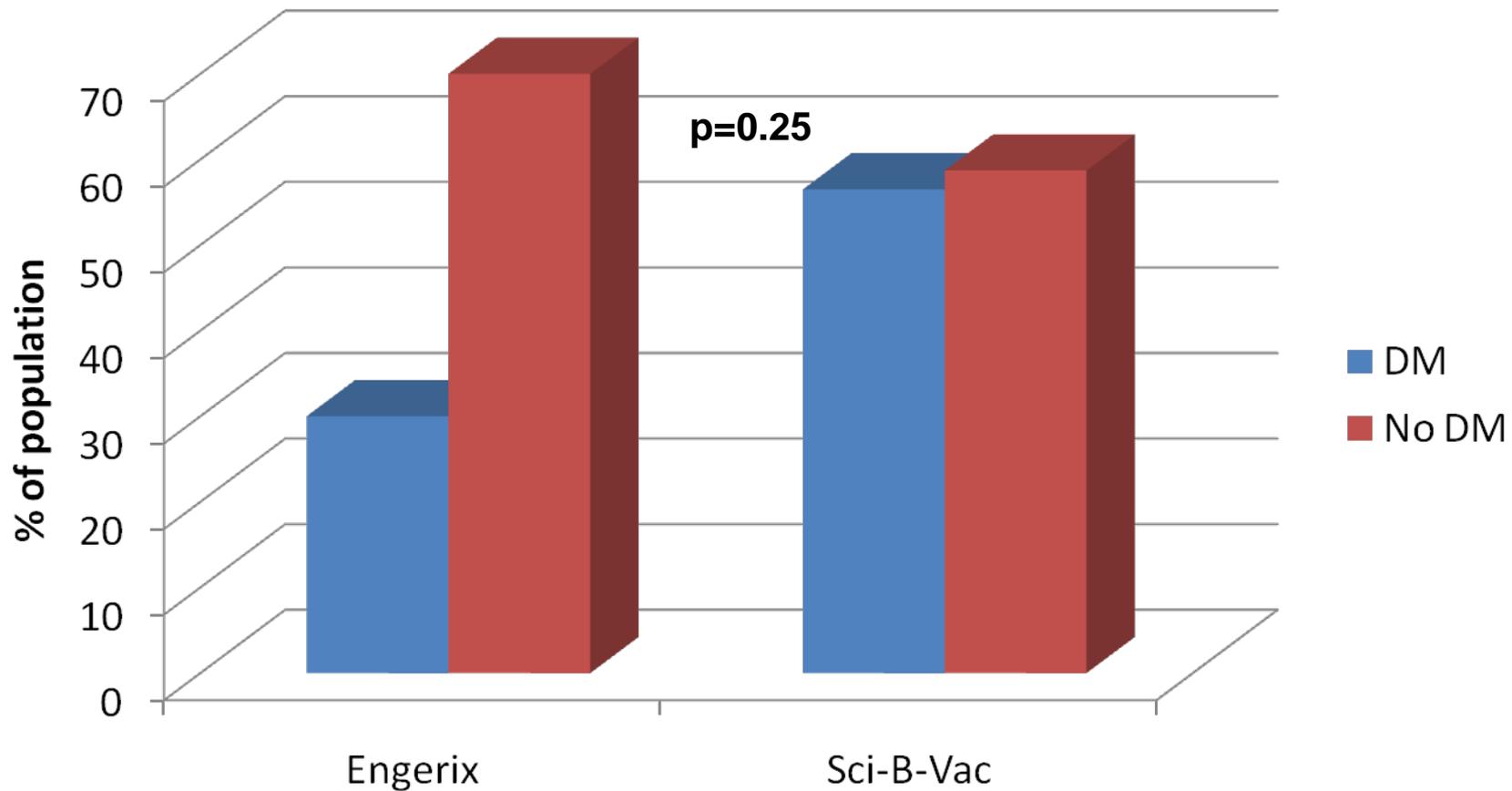
Data analysis

- Data were stored on spreadsheet and analyzed on SPSS v21 (IBM Inc. USA). Distributions of continuous variables were assessed for normality using the Kolmogorov-Smirnov test (cut-off at $p < 0.01$)
- Distributions of titer measures significantly deviated from normal so are presented as median (min-max)
- Other continuous variables had approximately normal distributions so are presented as mean \pm s.d
- Continuous variables were compared by vaccine type using the Mann-Whitney U (for titers) or the t-test for independent samples. Titers at 3 months were compared to those at 6 months using the Wilcoxon signed ranks test
- Categorical variables were assessed using frequency tables and are presented as n (%). Categorical variables were compared by vaccine type using the chi square test (Fisher's exact as appropriate)
- Qualitative response was compared at 3 months vs. 6 months using the McNemar test
- All tests are two-sided and considered significant at $p < 0.05$

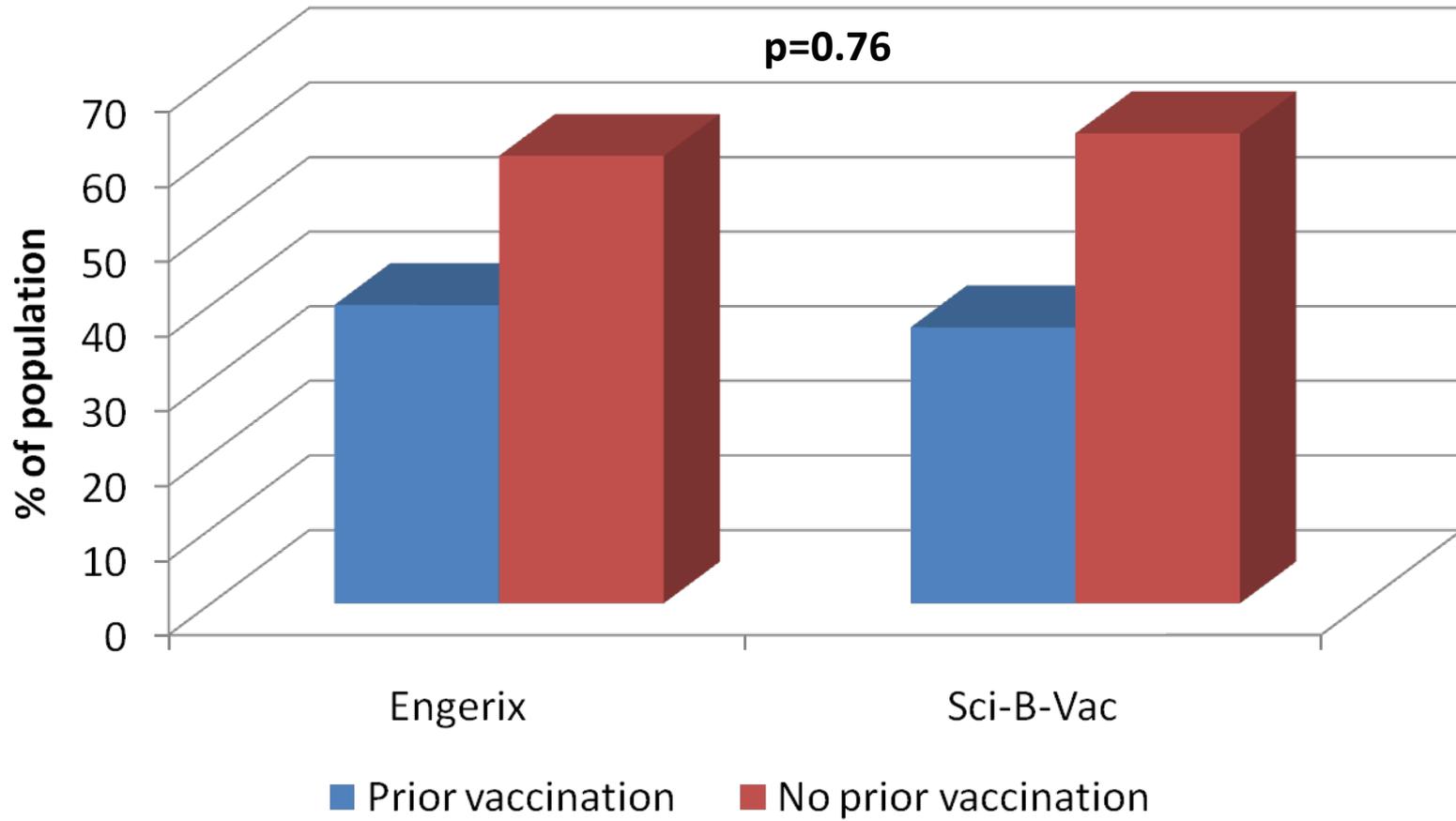
Results

- In the non-vaccinated group 53/60 completed the study, 6 died, 1 moved to another unit
- In the vaccinated group 33/37 completed the study, 4 died
- All deaths were from unrelated causes

DM distribution by treatment assignment



Distribution of prior vaccination by treatment assignment



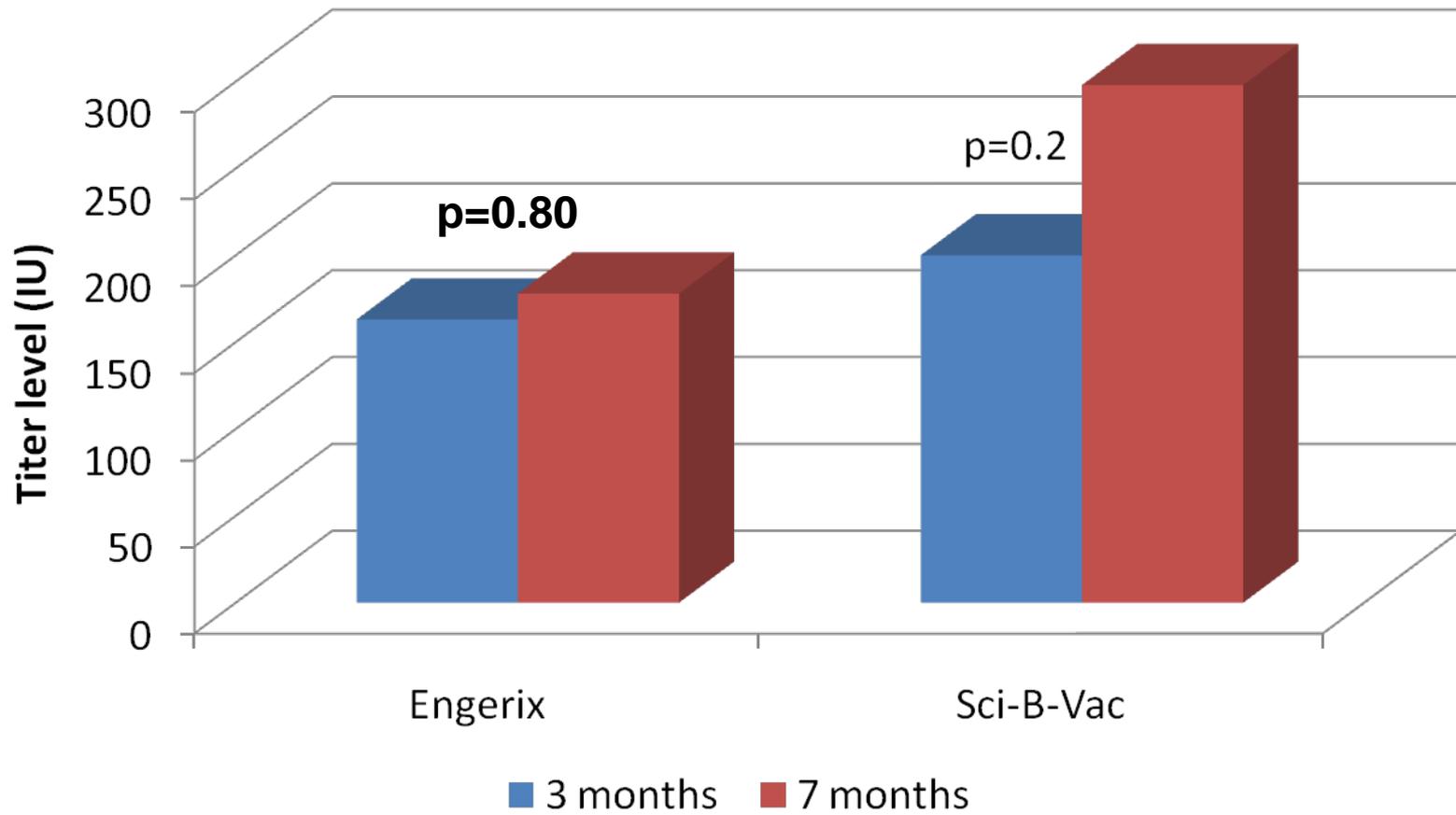
Results

	Engerix	Sci-B-Vac	p
responders	69.8%	73.2%	0.73
non-vaccinated	57.7%	60%	0.64
vaccinated	88.2%	87.5%	0.94

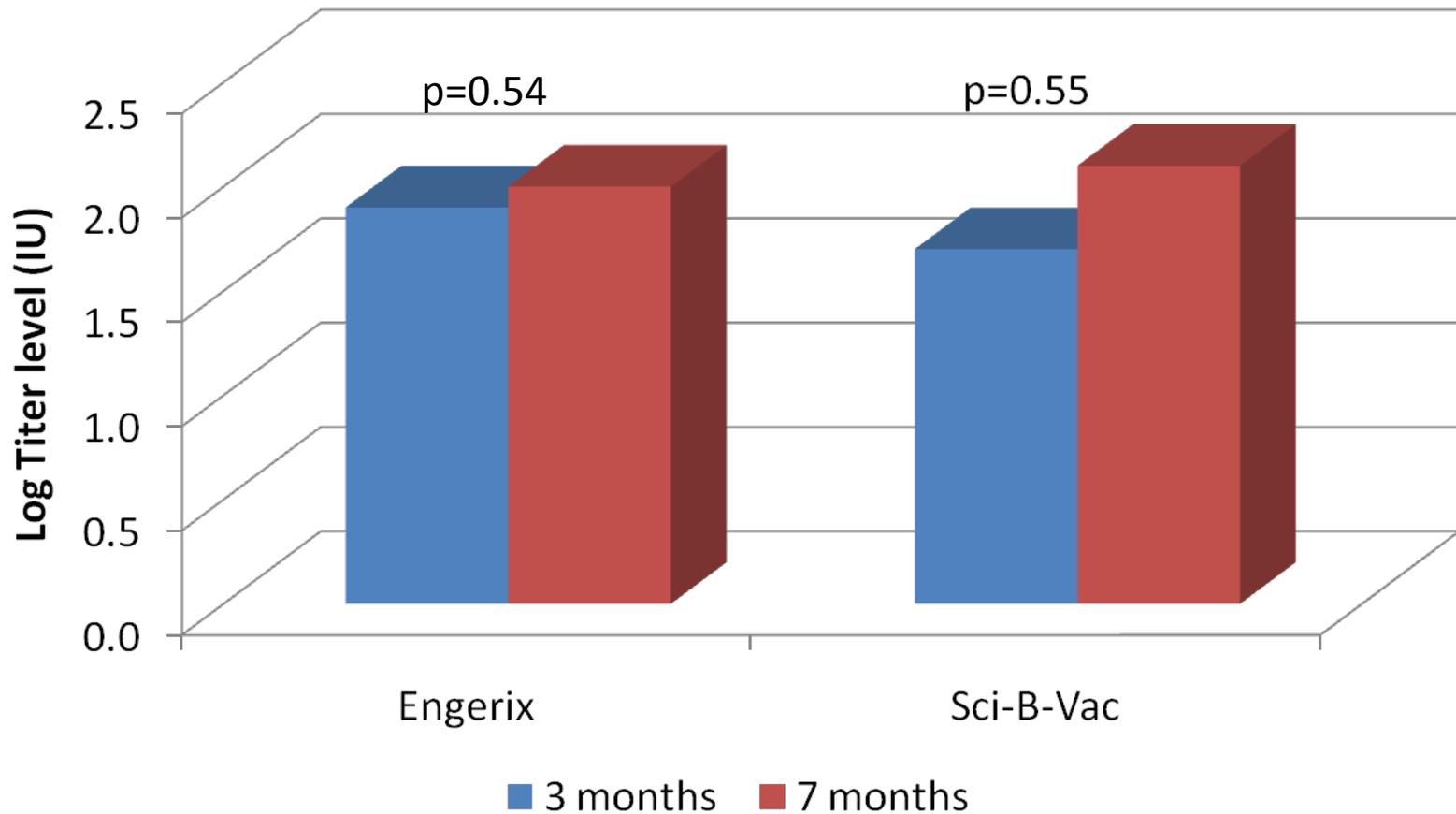
Titer levels at 7 months

	mean	standard deviation	median	min	max
Engerix	200.1	325.5	27.2	0	1000
Sci-B-Vac	297.7	394.0	78.6	0	1000

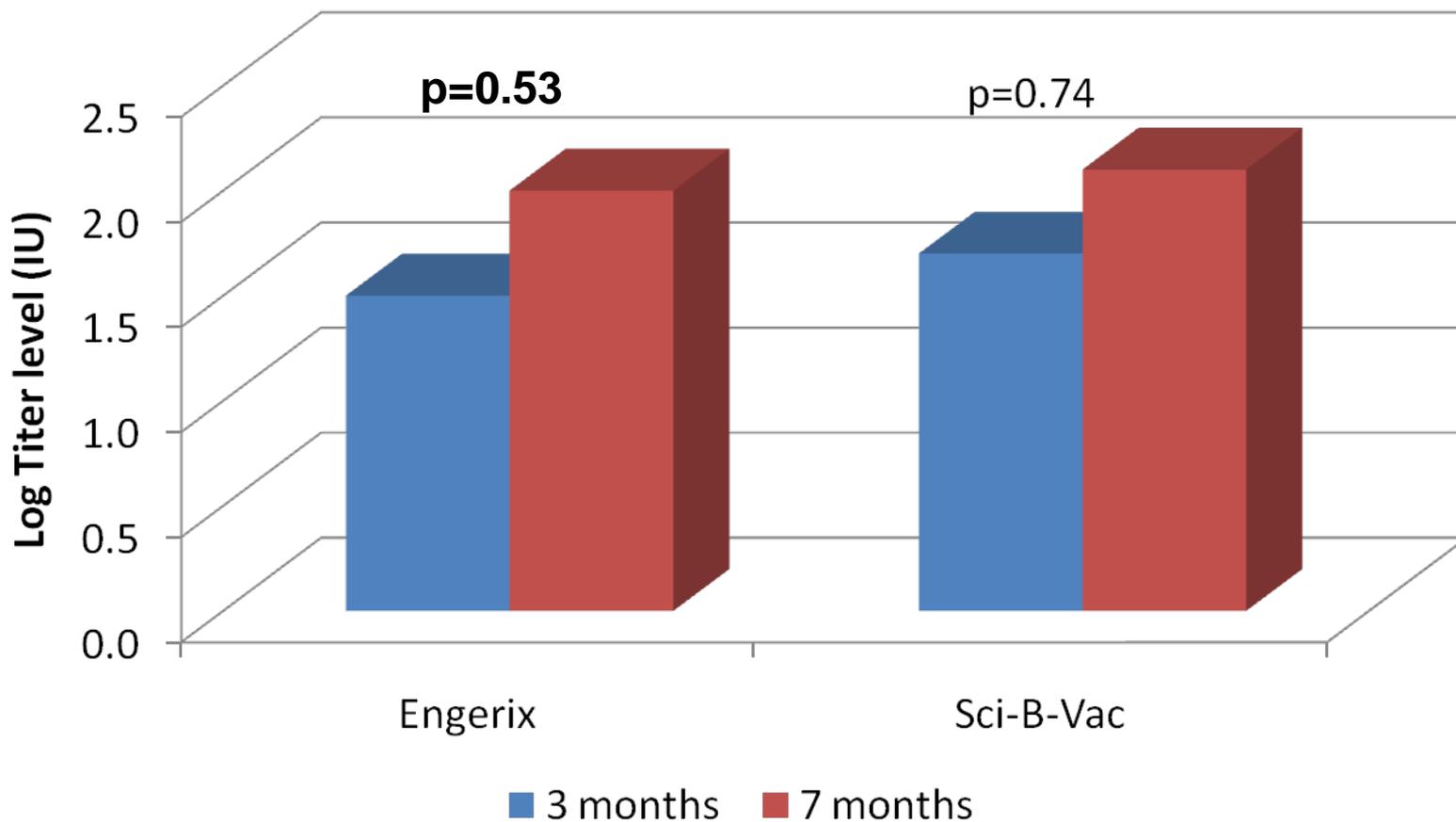
Titer levels at 3 and 7 months by treatment assignment



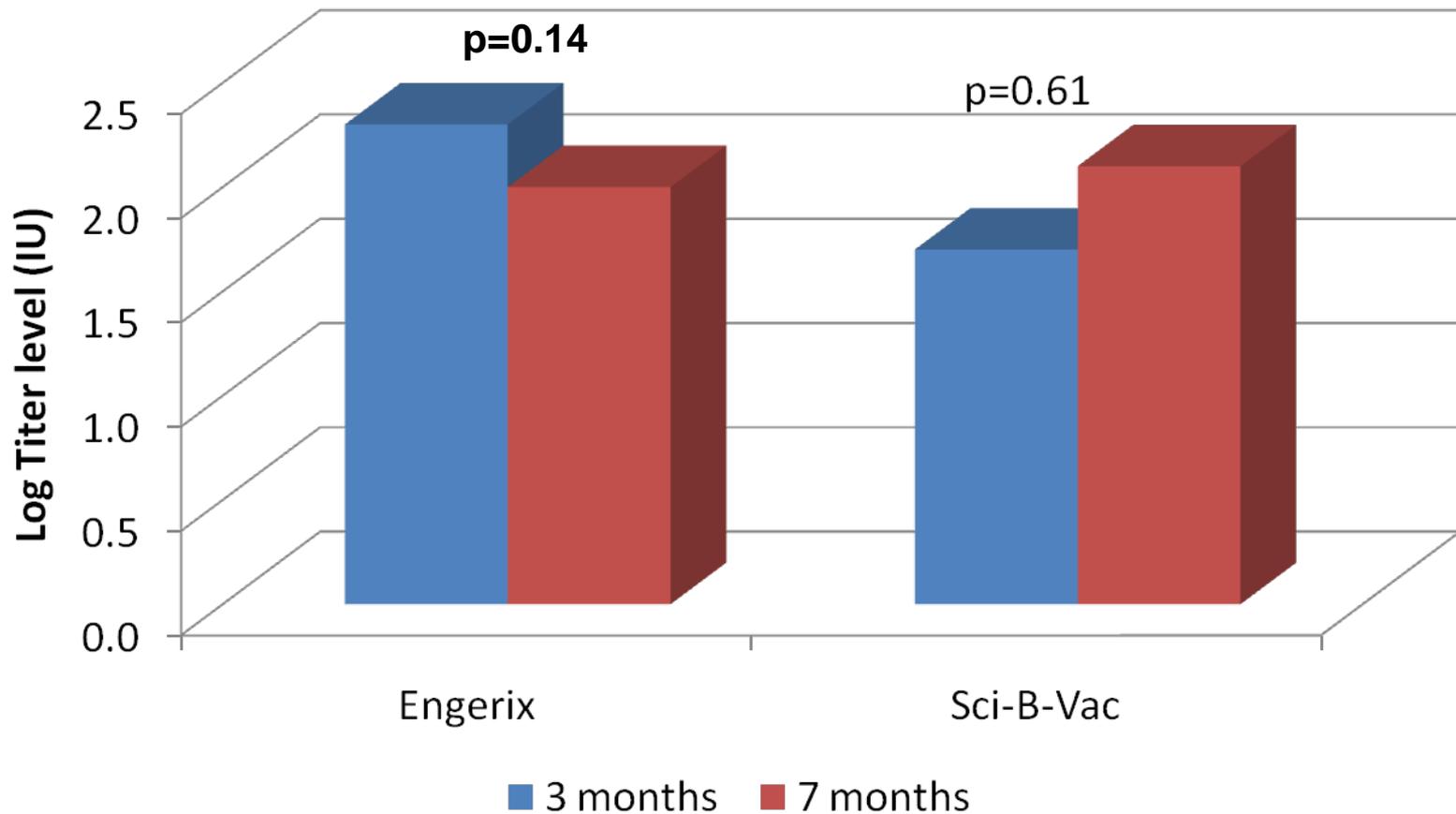
Log-transformed titer levels at 3 and 7 months by treatment assignment



Log-transformed titer levels at 3 and 7 months by treatment assignment in patients with no prior vaccine



Log-transformed titer levels at 3 and 7 months by treatment assignment in patients with prior vaccine



- Both at 3 and 7 months, previously vaccinated patients had significantly higher titers than non-previously vaccinated patients ($p < 0.003$)
- This was regardless of the type of vaccine the patients received

Summary

- In dialysis patients, a 3rd generation vaccination protocol achieved similar seroprotection to a 2nd generation vaccine
- In non-previously vaccinated patients, 3 doses of 10 μg Sci-B-Vac were comparable to 4 doses of 40 μg Engerix, and achieved 70% seroprotection
- In previously vaccinated patients, 3 doses of 20 μg Sci-B-Vac were comparable to 4 doses of 40 μg Engerix, achieving 88% seroprotection

Conclusion

- In dialysis patients, it is feasible to achieve high levels of seroprotection with both vaccines, providing careful timing and administration are carried out
- Based on the results of this study, it seems that previously vaccinated patients are able to mount a very high response rate, with both vaccines
- This pilot study will be followed by a large multicenter study in the USA

Thank you