

1 **Page 1: Title page**

2 **Immunogenicity and immunization costs of adjuvanted versus**

3 **non-adjuvanted hepatitis B vaccine in chronic kidney disease patients.**

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22 **Keywords:** chronic kidney disease, hepatitis B vaccine, AS04 hepatitis B vaccine,

23 immunogenicity, adjuvanted, costs

24

25 **List of abbreviations and acronyms:**

26 HBV - Hepatitis B virus; OR - Odds ratio; CI - Confidence interval; IU/ml-
27 International Units/ milliliter; HCB - Hospital Clinic of Barcelona; anti-HBs -
28 antibodies against the hepatitis B surface antigen; HBsAg - hepatitis B surface
29 antigen; SD - Standard Deviation.

30

31 **Abstract**

32 Hepatitis B virus (HBV) vaccination is recommended for all susceptible chronic pre-
33 hemodialysis and hemodialysis patients. This study assessed the immunogenicity
34 of HBV vaccines (adjuvanted and non-adjuvanted) in chronic kidney disease
35 patients vaccinated at the Hospital Clinic of Barcelona (Spain) between January
36 2007 and July 2012. In addition, the costs for the health system were evaluated
37 according to the proportion of vaccine responders after receiving either vaccine.
38 Patients receiving three doses of hepatitis B adjuvanted vaccine were three times
39 more likely to seroconvert than patients immunized with non-adjuvanted vaccines,
40 OR 3.56 (95% CI 1.84-6.85). This resulted in fewer patients requiring a second
41 course of HBV vaccination and fewer outpatient visits, saving more than €9,500
42 per 100 patients. The higher immunogenicity of the adjuvanted HBV vaccine would
43 counterbalance the lower costs associated with the non-adjuvanted vaccine.

44

45 **Introduction**

46 Chronic kidney disease patients are at high risk for hepatitis B virus (HBV) infection
47 due to increased exposure to blood products, shared hemodialysis equipment,
48 frequent skin breaches, and immunodeficiency.^{1,2} Despite preventive measures to
49 protect these patients against HBV infection, outbreaks continue to be reported in
50 dialysis units.^{3,4}

51

52 HBV vaccination is recommended for all susceptible chronic pre-hemodialysis and
53 hemodialysis patients, with regular monitoring of antibody levels to ensure they
54 remain above 10 IU/ml.⁵ Conventional HBV vaccines are poorly immunogenic in
55 patients with renal insufficiency,¹ with low response rates and suboptimal antibody
56 titers, and require frequent boosters to maintain protection.⁶ The efficacy of
57 conventional vaccines in chronic kidney disease patients has been reported as
58 55.4% one month after the third dose.⁷ To improve the immunological response to
59 HBV vaccination, patients should be vaccinated as soon as possible in the course
60 of the renal disease.⁸

61

62 A Hepatitis B vaccine adjuvanted with AS04 (Fendrix®, GlaxoSmithKline) has been
63 licensed for use in this population in Europe since 2005. In a comparative clinical
64 study in 165 pre-hemodialysis and hemodialysis patients, protective levels of
65 specific humoral antibodies (antibodies against the hepatitis B surface antigen
66 (anti-HBs) titers \geq 10 IU/ml) were observed in 74.4% of Fendrix recipients (N = 82)
67 one month after the third dose, compared with 52.4% of patients in the control
68 group who received a double dose of a commercially available HBV vaccine (N =

69 83).⁹ The adjuvanted vaccine has a good safety profile, with clinically-acceptable
70 reactions similar to those of non-adjuvanted HBV vaccines.¹⁰

71

72 In the region of Catalonia, Spain, the adjuvanted vaccine was acquired for the last
73 time in 2010, and only non-adjuvanted HBV vaccines (Engerix-B® 20 µg,
74 GlaxoSmithKline and HBVAXPRO® 40µg, Sanofi-Pasteur) have been acquired in
75 succeeding years (coinciding with the economic crisis) for chronic kidney disease
76 patients.

77

78 The objectives of this study were to assess the immunogenicity of HBV vaccination
79 with the adjuvanted and non-adjuvanted vaccines in chronic kidney disease
80 patients and to evaluate the economic costs for the health system according to the
81 immunogenicity achieved after receiving either vaccine.

82

83 **Results**

84 *Characteristics of the study population*

85 A total of 267 patients with chronic kidney disease were included in the analysis, a
86 mean of 49 per year. The mean age of participants included was 68.1 years (SD
87 12.76) and 62.9% were male. Twenty patients presented immunocompromised
88 conditions, 13 had a cancer diagnosis, of which six were kidney-related cancers.
89 No patient presented HIV infection. Thirty-three patients were already in
90 hemodialysis at the beginning of the vaccination schedule, and two patients who
91 were not in hemodialysis started it before the administration of the third dose of

92 vaccine. Other demographic and clinical characteristics of subjects by type of HBV
93 received are shown in **Table 1**.

94

95 *Factors associated with response to the hepatitis B vaccine*

96 Our results show that 51.7% of patients presented an immunological response
97 after three doses. Proportion of immunogenicity shows differences between
98 adjuvanted and non-adjuvanted vaccines (see **Table 1**). Patients receiving three
99 doses of hepatitis B adjuvanted vaccine were three times more likely to
100 seroconvert than patients immunized with non-adjuvanted vaccines, OR 3.56 (95%
101 CI 1.84-6.85) (see **Table 2**). Only 43.3% of patients aged ≥ 65 years presented
102 levels of anti-HBs ≥ 10 IU/mL, and had a worse response than those aged <65 ,
103 ORa 0.35 (95% CI 0.21-0.60). There were no significant differences in the immune
104 response between immunocompromised and non-immunocompromised or
105 between patients on hemodialysis or not.

106

107 *Cost analysis*

108 The lowest probability weighted cost per patient was the one associated with
109 Fendrix® (€ 795.59), assessing the use of Fendrix® as the most convenient
110 (**Figure 1**). According to sensitivity analysis, EngerixX-B® or HBVAXPRO® would
111 be more convenient than Fendrix®, should Fendrix® price per dose increase from
112 the current value of 28.3 euros to about 48.11 or to 53 euros, respectively (**Figure**
113 **2**).

114

115 **Discussion**

116 To our knowledge, this is one of the few studies to evaluate the economic costs
117 associated with the type of HBV vaccine administered to chronic kidney disease
118 patients. It is nested within the context of a change in the type of HBV vaccine
119 acquired by the regional department of health, coinciding with the economic crisis
120 in Spain. The results suggest that the decision to use non-adjuvanted, less
121 immunogenic (and in this case, cheaper) HBV vaccines might also result in higher
122 costs for the health system and for patients.

123

124 The differing seroconversion rates found in patients vaccinated with the adjuvant
125 ASO4 vaccine and the non-adjuvanted HBV vaccines are consistent with
126 previously reported studies.¹¹⁻¹³ The benefits in the immune response resulting
127 from the use of the adjuvanted vaccine could also be augmented by including the
128 longer persistence of anti-HBs antibody titers,¹⁴ although this was not assessed in
129 our study. As previously reported, older patients presented lower seroconversion
130 rates, which were, however, higher with the adjuvanted vaccine.^{15,16} Unlike other
131 studies, we found no differences in the vaccine response according to the
132 creatinine level or the hemodialysis status. This might be explained by the limited
133 sample size of our study.

134

135 From an economic perspective, the differences translate into fewer patients
136 requiring a second course of HBV vaccination and fewer outpatient visits, with a
137 saving of more than €9,500 per 100 patients. Even with an increase of 70% in the

138 adjuvanted vaccine price, the costs associated with this strategy were lower than
139 those associated with non-adjuvanted vaccines.

140

141 Our study has some limitations. A higher sample size would have allowed us to
142 obtain more robust conclusions and, perhaps, to determine other factors
143 associated with the vaccine response. Secondly, there was no available
144 information on previously-administered doses of vaccine with the hepatitis B
145 component, although the age of the patients included suggests it is very unlikely
146 that they had been vaccinated according to the Spanish routine immunization
147 schedule. Thirdly, there was no patient follow-up, and therefore, the duration of
148 antibody levels could not be assessed: this would potentially have added to the
149 benefits of the adjuvanted vaccine. Fourthly, the cost per dose of vaccine and of
150 outpatient visits in our hospital may differ between health care centers and vaccine
151 prices may vary between countries and other time periods.

152

153 In conclusion, considering that patients not responding to the first three doses of
154 the first HBV vaccine course will required at least three more doses, with the
155 consequent outpatient visits, the accumulated costs of the non-adjuvanted and
156 adjuvanted vaccines differ widely. The higher immunogenicity achieved with the
157 adjuvanted HBV vaccine outweighs the lower costs associated with the non-
158 adjuvanted vaccine.

159

160 **Materials and Methods**

161 *Study characteristics*

162 We performed a retrospective study to assess the immunogenicity of adjuvanted
163 and non-adjuvanted HBV vaccines in chronic kidney disease patients vaccinated at
164 the Hospital Clinic of Barcelona (Spain) between January 2007 and July 2012.

165

166 *Laboratory methods*

167 Serological screening for HBsAg was made in all chronic kidney disease patients.

168 The response to HBV vaccination was detected by measuring anti-HBs and was

169 determined by enzyme immunoassay system using AUSAB AxSYM particles

170 (ABBOTT®). Seroprotection was defined as anti-HBs titers ≥ 10 IU/mL. Patients not

171 reaching this threshold were considered non-responders.

172

173 *Hepatitis B immunization protocol*

174 In non-immune patients (HBsAg negative), four doses of HBV vaccine were

175 recommended (0, 1, 2, 6 months regimen). The vaccines used during the study

176 period were Engerix-B® (GlaxoSmithKline (2 x 20 μ g)), HBVAXPRO® (Sanofi-

177 Pasteur (40 μ g)) and Fendrix® (GlaxoSmithKline (20 μ g)), which includes the AS04

178 adjuvant. Only patients who received three or more doses of HBV vaccine were

179 included in the analysis.

180 Approximately one month after the third dose, a blood sample was obtained. For

181 responders, a fourth dose was recommended six months after the first. For non-

182 responders, the immunization schedule was reinitiated with three further doses

183 followed by anti-HBs determination. If the patient again presented anti-HBs < 10

184 IU/mL, more doses were not recommended.

185

186 *Data collection and analysis*

187 Variables were limited to information recorded in the medical records, including
188 sex, creatinine level at initiation of the hepatitis B vaccination schedule, reported
189 immunocompromised conditions (cancer, chemotherapy treatment, HIV),
190 hemodialysis status, type of vaccine administered (adjuvanted or non-adjuvanted),
191 dates of administration of HBV vaccines, among others. The post-vaccination anti-
192 HBs level was the main endpoint. Vaccine safety-related variables were not
193 collected, since a safety assessment was not an objective of this study.
194 To evaluate factors independently associated with seroconversion after hepatitis B
195 vaccination, we performed univariate and multivariable logistic regression
196 analyses. The statistical analysis was made using the SPSS® v18.0 statistical
197 package. Statistical significance was established as a p-value <0.05.

198

199 For the cost analysis we compared costs per patient associated with the three
200 vaccination strategies by developing a decision tree (**Figure 1**). Costs associated
201 with each vaccination strategy were the price of each vaccine plus the cost of
202 outpatient visits. (For vaccines we used official prices for 2011-2012 in Catalonia
203 (Spain) of HBV vaccines. These were € 28.30 per dose for Fendrix®, € 26.09 per
204 dose for HBVAXPRO® and € 10.10 per dose for Engerix-B® (for which, two doses
205 were administered at each visit and thus the total comparable cost was € 20.20 per
206 visit).¹⁷ The cost of an outpatient medical visit at HCB was 137 €. ¹⁸ The three
207 strategies differed for the probability of needing a second vaccination course. Such

208 probability was given by the immunogenic response after the third doses of each
209 hepatitis B vaccine.

210 One way sensitivity analysis was performed on Fendrix price per dose.

211

212 *Ethical considerations*

213 Patient records/information were anonymized prior to analysis. The study was
214 approved by the HCB Clinical Research Ethics Committee (HCB/2015/0040).

215

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225 The remaining authors report no conflict of interest.

226

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Table 1. Immunogenic response after the third doses of hepatitis B vaccine was administered in patients with chronic kidney disease.

	HBVAXPRO®		ENGERIX-B®		FENDRIX®		Vaccinated population		
	Total	Anti-HBs ≥ 10	Total	Anti-HBs ≥ 10	Total	Anti-HBs ≥ 10	Overall	Anti-HBs ≥ 10	p-value¶
	n (%)*	n (%)**	n (%)*	n (%)**	n (%)*	n (%)**	n (%)*	n (%)**	
Overall	152 (100)	70 (46.1)	56 (100)	25 (44.6)	59 (100)	43 (72.9)	267 (100)	138 (51.7)	
95% CI		(38.1 - 54.0)		(31.6 - 57.7)		(61.5 - 84.2)		(45.7 - 57.7)	
Sex									0.767
Female	49 (32.2)	19 (38.8)	24 (42.9)	11 (45.8)	26 (44.1)	20 (76.9)	99 (37.1)	50 (50.5)	
Male	103 (67.8)	51 (49.5)	32 (57.1)	14 (43.8)	33 (55.9)	23 (69.7)	168 (62.9)	88 (52.4)	
Age (years)									0.001
18 - 44	9 (5.9)	4 (44.4)	2 (3.6)	2 (100)	5 (8.5)	4 (80.0)	16 (6.0)	10 (62.5)	
45 - 64	47 (30.9)	31 (66.0)	20 (35.7)	11 (55.0)	13 (22.0)	12 (92.3)	80 (30.0)	54 (67.5)	
≥65	96 (63.2)	35 (36.5)	34 (60.7)	12 (35.3)	41 (69.5)	27 (65.9)	171 (64.0)	74 (43.3)	
Creatinine (mg/dL)									0.620
< 2	24 (15.8)	12 (50.0)	16 (28.6)	5 (31.3)	4 (6.8)	3 (75.0)	44 (16.5)	20 (45.5)	
2 - 4	77 (50.7)	36 (46.8)	29 (51.8)	15 (51.7)	37 (62.7)	26 (70.3)	143 (53.6)	77 (53.8)	
> 4	51 (33.6)	22 (43.1)	11 (19.6)	5 (45.5)	18 (30.5)	14 (77.8)	80 (30.0)	41 (51.3)	
Immunocompromised									0.836
Yes	9 (5.9)	4 (44.4)	9 (16.1)	4 (44.4)	2 (3.4)	1 (50.0)	20 (7.5)	8 (45.0)	
No	143 (94.1)	66 (46.2)	47 (83.9)	21 (44.7)	57 (96.6)	43 (73.7)	247 (92.5)	129 (52.2)	
Hemodialysis									0.965
Yes	21 (14.5)	11 (52.4)	8 (14.8)	3 (37.5)	4 (6.8)	3 (75.0)	33 (12.8)	17 (51.5)	
No	124 (85.5)	54 (43.5)	46 (85.2)	21 (45.7)	55 (93.2)	40 (72.7)	225 (87.2)	115 (51.1)	

* = columns percentage

** = row percentage, values of non acceptable immunogenicity (Anti-HBs < 10 UI/mL) were omitted.

95% CI= confidence interval 95% of the proportion of acceptable immunogenicity to each vaccine (Anti-HBs ≥ 10 UI/mL)

¶ = chi-square test of distribution of total vaccinated population

296
297

298 **Table 2. Factors potentially associated with an immunogenic response after hepatitis B immunization in**
 299 **patients with chronic kidney disease.**
 300

	OR	(95% CI)	p-value	ORa	(95% CI)
Sex					
Female	1	-			
Male	1.12	(0.71 - 1.79)	0.767		
Age (years)					
< 65	1	-		1	-
≥ 65	0.38	(0.23 - 0.64)	< 0.001	0.35	(0.21 - 0.60)
Creatinine (mg/dL)					
< 2	1	-			
2 - 4	1.38	(0.72 - 2.83)	0.364		
> 4	1.32	(0.57 - 2.61)			
Immunocompromised					
No	1	-			
Yes	0.71	(0.33 - 1.87)	0.534		
Hemodialysis					
No	1	-			
Yes	1.02	(0.54 - 2.12)	0.965		
Hepatitis B Vaccine					
non- adjuvanted†	1	-		1	-
adjuvanted	3.24	(1.66 - 5.97)	<0.001	3.56	(1.84 - 6.85)

301

OR: odds ratio.

ORa: odds ratio adjusted by multiple logistic regression model

†= HBVAXPRO and Engerix-B were grouped together

p-value= chi-square test

302

303

304 **Figure 1. Decision tree and associated costs for each HBV vaccine.**

305

p1, p2 and p3 = immunogenicity of HBAXPRO, Engerix-B and Fendrix, respectively.

306

307

308

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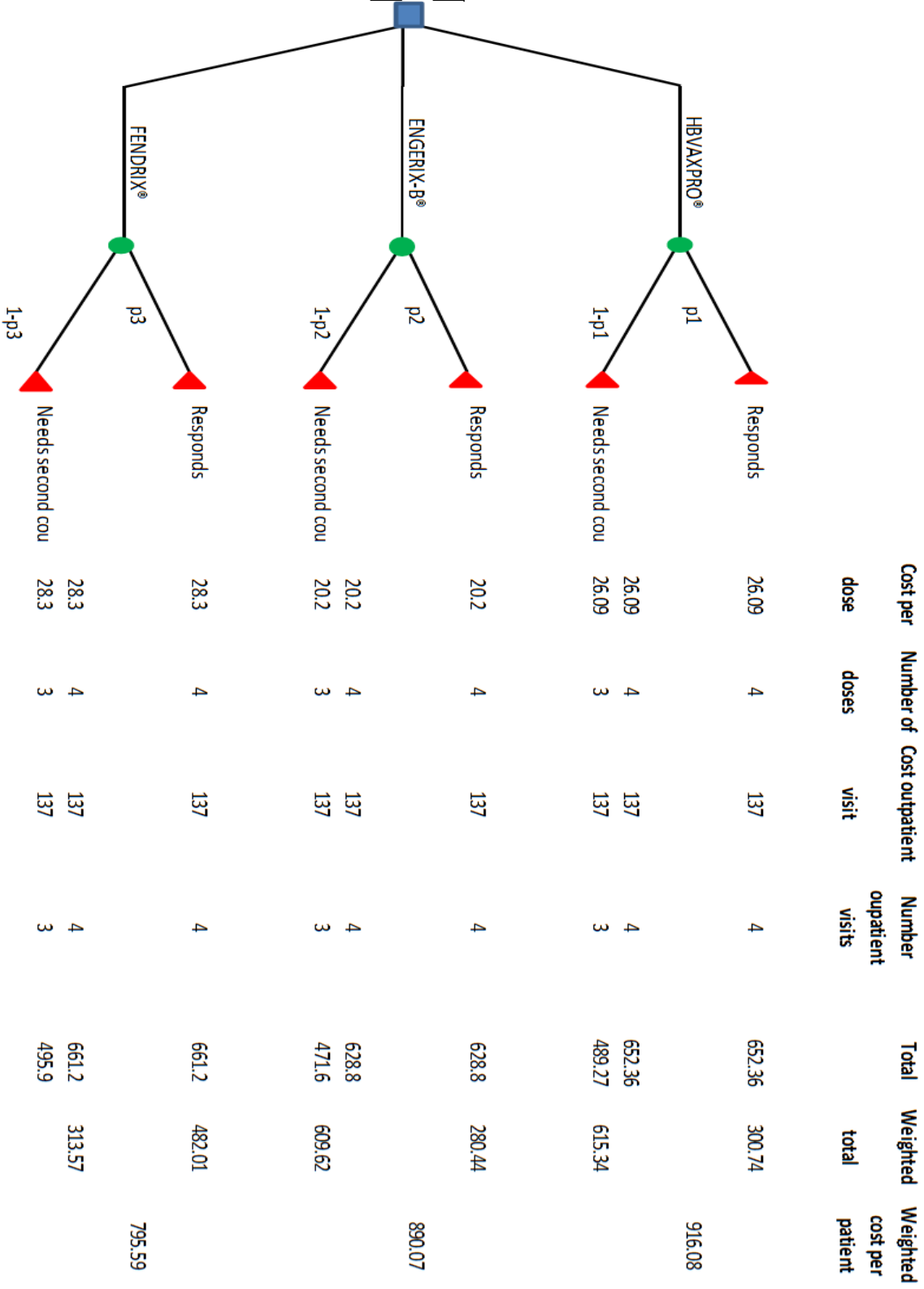
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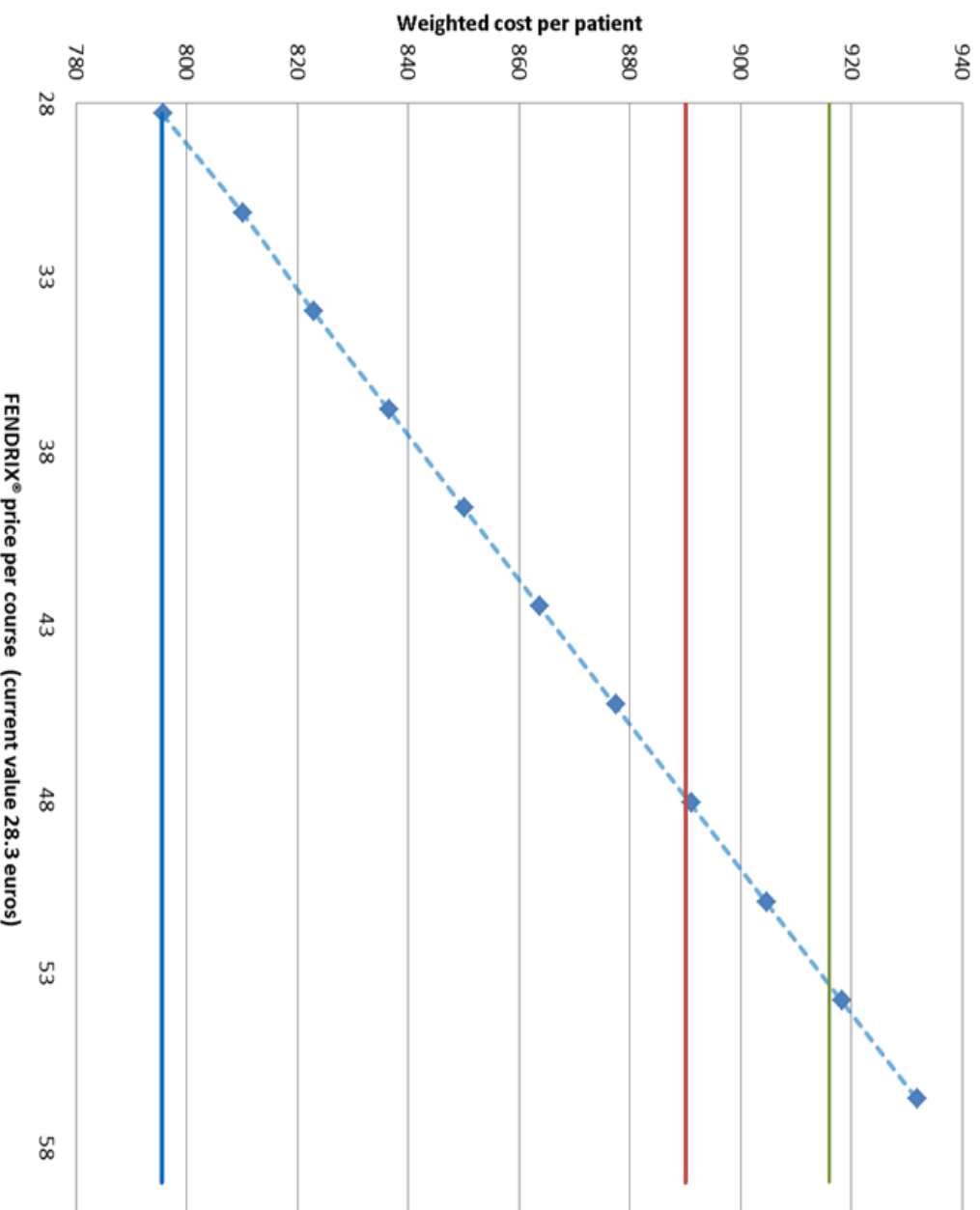
311 **Figure 2. One way sensitivity analysis on Fendrix® price per dose versus costs associated with other**

312 **vaccines.**

HBV vaccination in chronic
kidney disease patients

p1=0.46
p2=0.45
p3=0.73





---◆--- Cost associated with FENDRIX® for hypothetical increase of price per dose

— Costs associated with ENGERIX-B®

— Costs associated with HBVAXPRO®

— Current costs associated with FENDRIX