Appendix A

Conducting a mixed comparison model between telbivudine and entecavir.

No RCT has conducted a head to head trial comparing telbivudine and entecavir. However there have been trials conducted between lamivudine and entecavir [1],[2],[3] and lamivudine and telbivudine.[4][5 We perform an indirect comparison in order to estimate the relative efficacies of telbivudine and entecavir in positive patients for the following measures:

- HBV DNA undetectability,
- Alt normalisation,
- HBeAg loss
- seroconversion of the 'e' antigen.

These analyses were conducted using version 1.4.2 of the Winbugs software (© Imperial College and MRC, UK). The Winbugs code for each comparison is contained at the end of this appendix. For each indirect comparison we provide the key statistics for the relative risk between entecavir and telbivudine and the density of the relative risk. The trace history, time series and autocorrelations are also provided to show that the models are stable and do not have repeatable patterns. In all cases 100,000 samples were taken after a burn-in period of 50,000 samples.

The data used in the indirect comparison are given in Table A1.1 For completeness HBeAg negative patients are included in the Table, however the analyses are conducted purely on HBeAg positive patients as this is the patient population where it is believed that telbivudine is cost-effective and, with particular focus on HBV detectability, there appears to be evidence of a difference in the relative risks between HBeAg positive patients and HBeAg negative patients

Since there are only 2 trials for both entecavir and telbivudine in HBeAg positive patients there is difficulty in estimating inter-trial variance and a fixed effects model was used. It is noted that this would underestimate the uncertainty when compared with a random effects model.

Conclusions from the indirect comparisons

Our indirect comparisons show that there is a significant difference in favour of entecavir for HBV undetectability. In addition, non-significant differences are seen in favour of entecavir for ALT normalisation, and in favour of telbivudine for both seroconversion of e antigen and HBeAg loss.

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[1] Chang TT, Gish RG, de Man R, Gadano A, Sollano J, Chao YC et al. A comparison of entecavir and lamivudine for HBeAg-positive chronic hepatitis B. N Engl J Med 2006; 354(10):1001-1010

Lai CL, Shouval D, Lok AS, Chang TT, Cheinquer H, Goodman Z et al. Entecavir versus lamivudine for patients with HBeAg-negative chronic hepatitis B. N Engl J Med 2006; 354(10):1011-1020

[3] Yao G, Chen C, Lu W, et al. Efficacy and safety of entecavir compared to lamivudine in nucleoside naïve patients with chronic hepatitis B: a randomized, double blind trial in China. *Hepatol Int* 2007; 1: 365-372

[4] GLOBE study NV-02B-007

[5] Hou J, Yin YK, Xu D, et al. Telbivudine versus lamivudine in Chinese patients with chronic hepatitis B: Results at 1 year of a randomized, double-blind trial. *Hepatology* 2008; 47 (2): 447-454.

Table A1.1 Relative risks in Study 007 and in the RCTs included in the indirect comparison

Histologic improvement	**lamivudine n/N**	**comparator* n/N**	**RR**	**95% CI**
Telbivudine, HBeAg-pos pts[a]	244/433	284/439	0.87	0.78, 0.97
Entecavir, HBeAg-pos pts[b]	195/314	226/314	0.86	0.77, 0.96
Study 007, HBeAg-neg pts[a]	144/218	141/212	0.99	0.87, 1.14
Lai et al, HBeAg-neg pts[b]	174/287	208/296	0.86	0.77, 0.97
HBV DNA undetectable (<300 copies/mL)	**lamivudine n/N**	**comparator* n/N**	**RR**	**95% CI**
Study 007, HBeAg-pos pts[a]	187/463	275/458	0.67	0.59, 0.77
Hou et al, HBeAg-pos pts[a]	38/143	67/147	0.58	0.42, 0.81
Chang et al, HBeAg-pos pts[b]	129/355	236/354	0.55	0.47, 0.64
Yao et al, HBeAg-pos pts[b]	83/221	166/225	0.51	0.42, 0.61
Study 007, HBeAg-neg pts[a]	160/224	196/222	0.81	0.74, 0.89
Hou et al, HBeAg-pos pts[a]	17/22	17/20	0.91	0.68, 1.22
Lai et al, HBeAg-neg pts[b]	225/313	293/325	0.80	0.74, 0.86
Yao et al, HBeAg-neg pts[b]	29/40	31/33	0.83	0.68, 1.00
ALT normalisation	**lamivudine n/N**	**comparator* n/N**	**RR**	**95% CI**
Study 007, HBeAg-pos pts[a]	334/446	340/440	0.97	0.90, 1.04
Hou et al, HBeAg-pos pts[a]	75/135	87/142	0.91	0.74, 1.11
Chang et al, HBeAg-pos pts[b]	213/355	242/354	0.88	0.79, 0.98
Yao et al, HBeAg-pos pts[b]	172/221	200/225	0.88	0.80, 0.95
Study 007, HBeAg-neg pts[a]	164/207	151/203	1.07	0.96, 1.19
Hou et al, HBeAg-pos pts[a]	17/22	20/20	0.77	0.62, 0.97
Lai et al, HBeAg-neg pts[b]	222/313	253/325	0.91	0.83, 1.00
Yao et al, HBeAg-neg pts[b]	31/40	31/33	0.83	0.68, 1.00
Seroconversion of e antigen	**lamivudine n/N**	**comparator* n/N**	**RR**	**95% CI**
Study 007, HBeAg-pos pts[a]	95/442	97/432	0.96	0.75, 1.23
Hou et al, HBeAg-pos pts[a]	20/138	31/138	0.65	0.39, 1.07
Chang et al, HBeAg-pos pts[b]	64/355	74/354	0.86	0.64, 1.16
Yao et al, HBeAg-pos pts[b]	39/221	33/225	1.20	0.79, 1.84
HBeAg loss	**lamivudine n/N**	**comparator* n/N**	**RR**	**95% CI**
Study 007, HBeAg-pos pts[a]	103/442	114/432	0.88	0.70, 1.11
Hou et al, HBeAg-pos pts[a]	18/138	25/138	0.72	0.41, 1.26
Chang et al, HBeAg-pos pts[b]	70/355	78/354	0.89	0.67, 1.19
Yao et al, HBeAg-pos pts[b]	44/221	41/225	1.09	0.75, 1.60

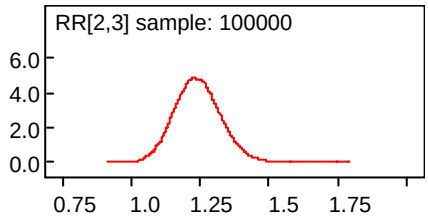
*Comparator ”a” = telbivudine; Comparator ”b” = entecavir.

Results for the HBV DNA undetectability indirect comparison.

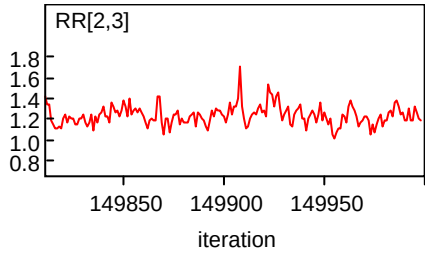
Descriptive statistics for the relative risk between entecavir and telbivudine

node	mean	sd	MC error	2.5%	median	97.5%	start	sample
RR[2,3]	1.242	0.08286	4.29E-4	1.088	1.239	1.413	50001	100000

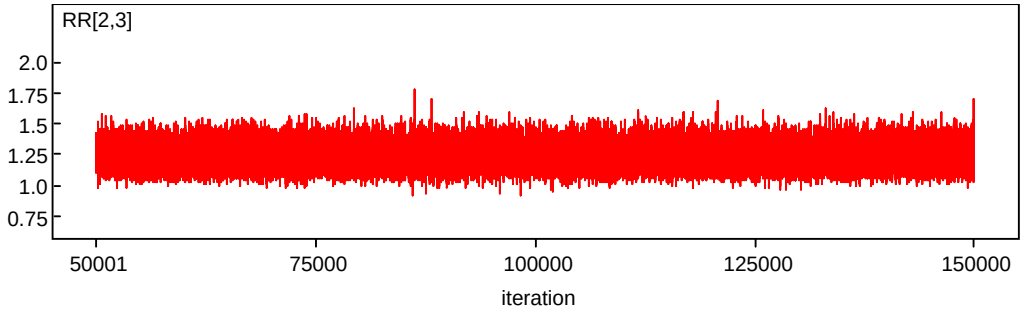
The density distribution of the relative risk



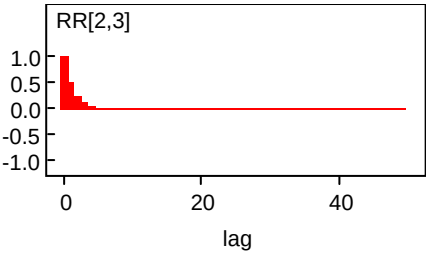
The trace history of the relative risk between entecavir and telbivudine.



The time series of the relative risk between entecavir and telbivudine.



The autocorrelation between the relative risk between entecavir and telbivudine



Conclusion.

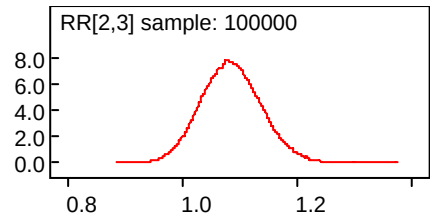
Entecavir produces a statistically significant improvement in HBV DNA undetectability compared with telbivudine. Telbivudine is at least as efficacious as entecavir in promoting HBV DNA undetectability in 0% of all simulations.

Results for the Alt normalisation indirect comparison.

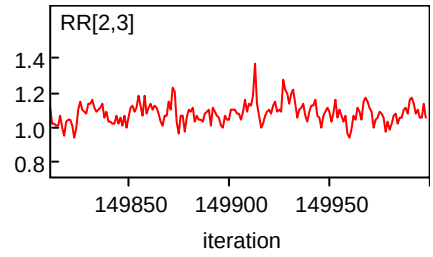
Descriptive statistics for the log relative risk between entecavir and telbivudine

node	mean	sd	MC error	2.5%	median	97.5%	start	sample
RR[2,3]	1.086	0.05195	2.863E-4	0.9883	1.085	1.192	50001	100000

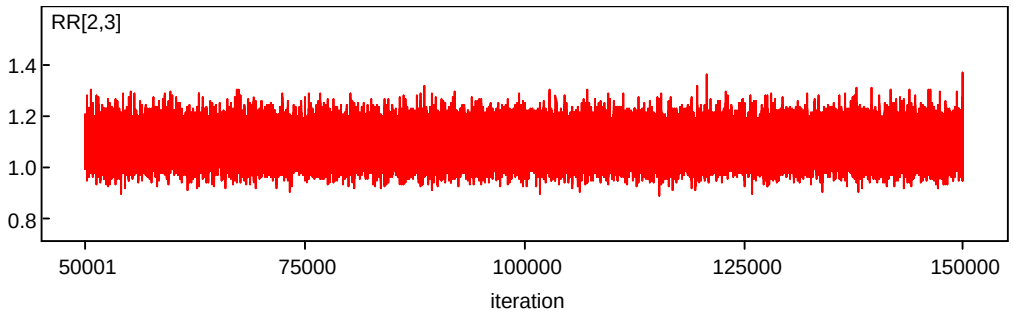
The density distribution of the relative risk



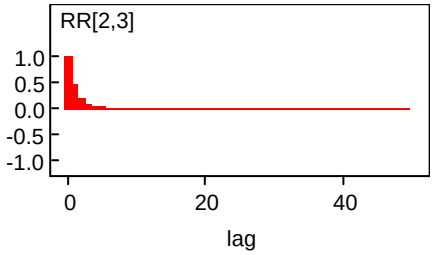
The trace history of the relative risk between entecavir and telbivudine.



The time series of the relative risk between entecavir and telbivudine.



The autocorrelation between the relative risk between entecavir and telbivudine



Conclusion.

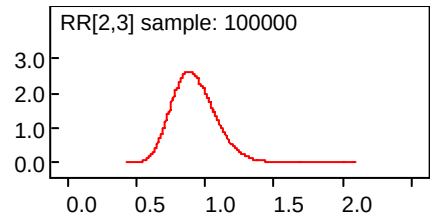
There is no statistically significant difference between entecavir and telbivudine in terms of Alt normalisation improvement, although the midpoint estimate is favourable to entecavir. Telbivudine is at least as efficacious as entecavir in promoting Alt normalisation in 4% of all simulations.

Results for the seroconversion of ‘e’ antigen indirect comparison.

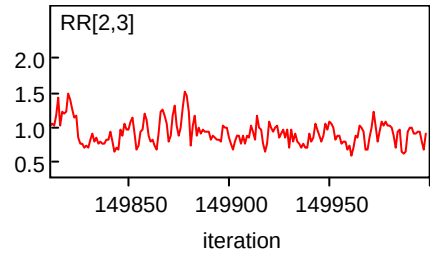
Descriptive statistics for the relative risk between entecavir and telbivudine

node	mean	sd	MC error	2.5%	median	97.5%	start	sample
RR[2,3]	0.923	0.1576	8.177E-4	0.6526	0.9103	1.267	50001	100000

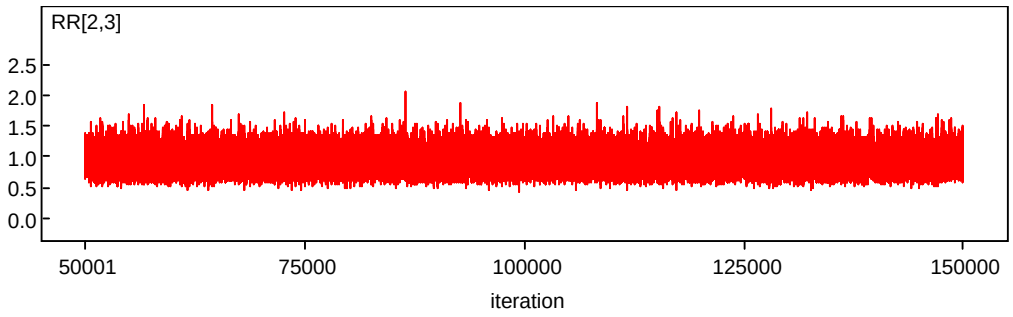
The density distribution of the relative risk



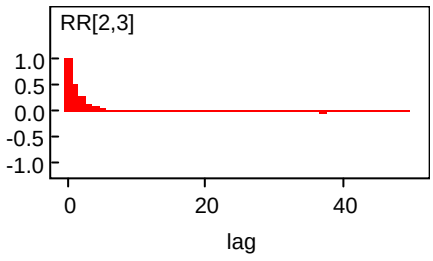
The trace history of the relative risk between entecavir and telbivudine.



The time series of the relative risk between entecavir and telbivudine.



The autocorrelation between the relative risk between entecavir and telbivudine



Conclusion.

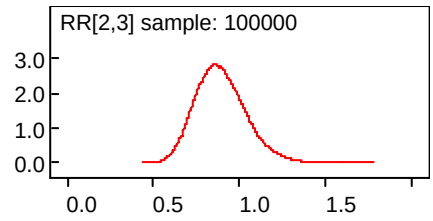
There is no statistically significant difference between entecavir and telbivudine in terms of seroconversion of the ‘e’ antigen, although the midpoint estimate is favourable to telbivudine. Telbivudine is at least as efficacious as entecavir in promoting seroconversion of the ‘e’ antigen in 71% of all simulations.

Results for the HBeAg loss indirect comparison.

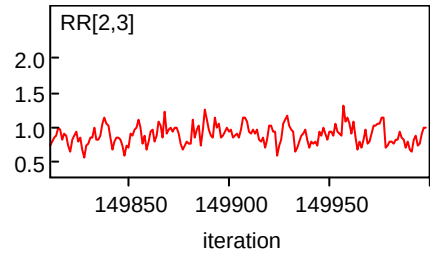
Descriptive statistics for the relative risk between entecavir and telbivudine

node	mean	sd	MC error	2.5%	median	97.5%	start	sample
RR[2,3]	0.8929	0.1456	8.43E-4	0.6417	0.8817	1.212	50001	100000

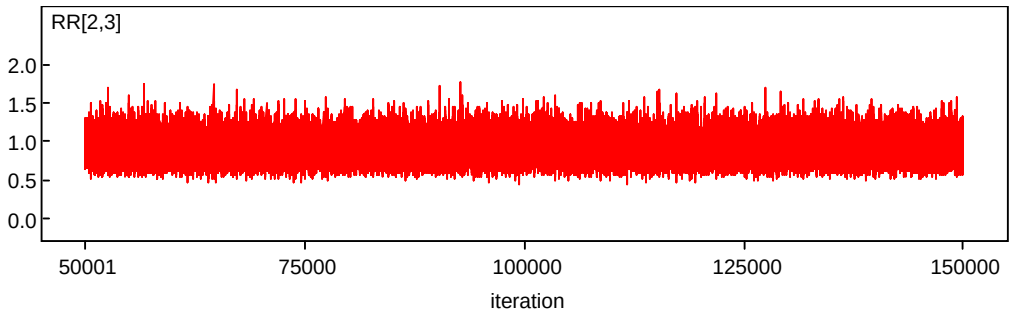
The density distribution of the relative risk



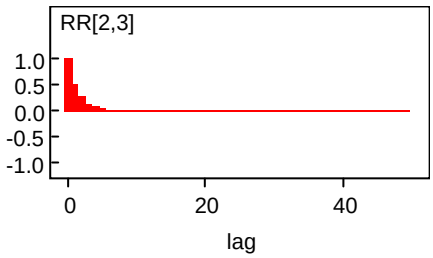
The trace history of the relative risk between entecavir and telbivudine.



The time series of the relative risk between entecavir and telbivudine.



The autocorrelation between the relative risk between entecavir and telbivudine



Conclusion.

There is no statistically significant difference between entecavir and telbivudine in terms of seroconversion of the ‘e’ antigen, although the midpoint estimate is favourable to telbivudine. Telbivudine is at least as efficacious as entecavir in promoting HBeAg loss in 78% of all simulations.

Winbugs Code for the fixed effects model for HBV dectectability *

```
model
{

 for (i in 1:N) {
#N is the total number of study ARMS

r[i] ~ dbin(p[i],n[i])

logit(p[i])<-mu[s[i]] + d[t[i]] - d[b[i]]

}

for (j in 1:NS) { mu[j]~dnorm(0,.0001)}

d[1] <- 0

for (q in 2:3){

d[q] ~ dnorm(0,0.001)}

for (i in 1:N) {mu1[i] <- mu[s[i]] * equals(t[i],1) }

for (k in 1:NT) { logit(T[k])<- sum(mu1[])/Nbase1 +d[k]}


for (c in 1:(NT-1)) { for (k in (c+1):NT)
                        { RR[c,k] <-  T[k]/T[c]

}
}

Telbbetter <- step(1-RR[2,3])

}

###data

list(N=8, NS=4, NT=3, Nbase1 = 4,
s = c(1,1,2,2,3,3,4,4),
t = c(1,2,1,3,1,3,1,2),
r = c(187,275,129,236,83,166,38,67),
n = c(463,458,355,354,221,225,143,147),
b = c(1,1,1,1,1,1,1,1)

)

 #initial 1

list(
d=c(NA,0,0), mu=c(0,0,0,0),

 )
```

**** Note that for other outcome measures the relevant number of successes and relevant number of population associated with each trial would be inserted into the 'r =' and the 'n =' lines within the data section.***