Appendix L:Network meta-analyses – results and input data for treatment of latent TB

This appendix contains details of the network meta-analyses (NMAs) that were conducted to support the GDG's decision making on which pharmacological treatment(s) should be recommended for people with latent TB infection. See section 8.2 of the full guideline for details of the evidence review and section 2.4.4 of the full guideline for a description of NMA methods.

All analyses were undertaken on 2 datasets:

- The full dataset of all included studies reporting data relevant to the outcome in question
- A restricted subgroup of evidence most applicable to NHS practice. This dataset excludes studies that were conducted in countries with TB incidence of greater than 50 per 100,000 and those that were conducted only in people with HIV.

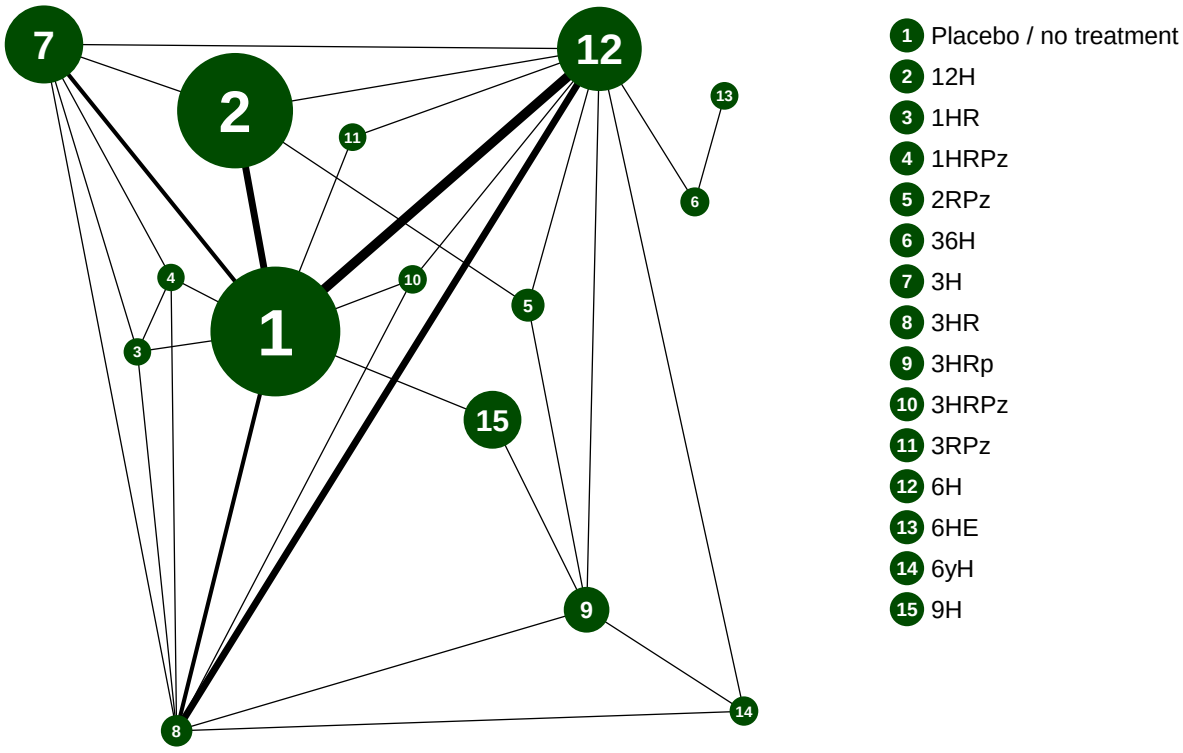
Results for the full dataset are presented in L.1; analyses on the restricted subgroup appear in L.2.

L.1 Full dataset

Table 1: Model selection for NMAs – full dataset

Outcome	Model	DIC	Total residual deviance		SD	Preferred model
Active TB	FE	249.936	47.06	(42 datapoints)	–	RE
	RE	247.277	40.10		0.313 (95%CI: 0.055, 0.740)	
Adherence	FE	440.213	139.3	(48 datapoints)	–	RE
	RE	360.623	49.18		0.596 (95%CI: 0.361, 1.078)	
Hepatotoxicity	FE	230.447	53.63	(39 datapoints)	–	RE
	RE	221.826	38.95		0.822 (95%CI: 0.282, 1.673)	
Rash	FE	121.292	22.14	(23 datapoints)	–	FE
	RE	122.81	22.84		0.539 (95%CI: 0.023, 1.841)	
Nausea / vomiting	FE	99.159	18.41	(19 datapoints)	–	FE
	RE	100.317	18.85		0.711 (95%CI: 0.030, 1.894)	

L.1.1 Development of active TB



Size of nodes is proportional to total number of participants randomised to receive the treatment in question across the evidence-base. Width of connecting lines is proportional to number of trial-level comparisons available.

Figure 1: Development of active TB – evidence network

Table 2: Development of active TB – input data

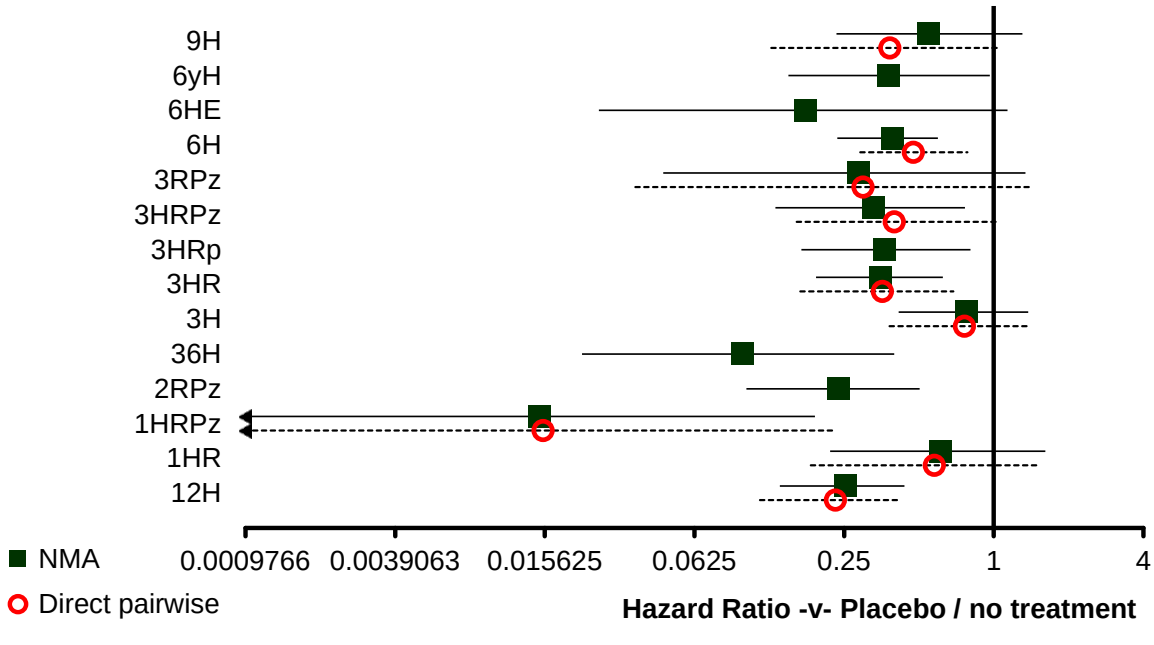
Study and duration of follow-up	Placebo / no treatment	12H	1HR	1HRPz	2RPz	36H	3H	3HR	3HRp	3HRPz	3RPz	6H	6HE	6yH	9H
Jimenez-Fuentes et al. (2013) - 5.00yr[a]								1/296				1/294			
Gupta et al. (1993) - 8.00yr[a]	17/85		9/83	0/80			10/82	4/85							
Swaminathan et al. (2012) - 3.00yr[b]						8/441.99							12/377.36		
Sterling et al. (2011) - 2.75yr[b]									7/10327						15/9619
Martinson et al. (2011) - 4.00yr[b]								24/1219.7	24/1187.5			8/561		22/1143.9	
Samandari et al. (2011) - 3.00yr[b]						4/701.75						12/585.37			
Schechter et al. (2006) - 2.72yr[b]					1/522				3/564						
Quigley et al. (2001) - 3.00yr[b]	9/98										2/74	2/88			
Gordin et al. (2000) - 3.08yr[b]		26/2428.8			19/2452.1										
Halsey et al. (1998) - 3.00yr[b]					14/824							19/1056			
Whalen et al. (1997) - 5.00yr[b]	42/1012							22/1151		15/800		34/1101			
Hawken et al. (1997) - 1.72yr[b]	10/125											7/125			
Pape et al. (1993) - 5.00yr[b]	6/61	2/118													
Anon. (1982) - 5.00yr[b]	97/33916	24/33333					76/33628					34/34000			
Debre et al. (1973) - 10.00yr[b]	24/9820														10/10372
Ferebee et al. (1963) - 3.45yr[b]	24/22523	5/22242													

(a) dichotomous data – proportion of participants developing active TB over duration of follow-up
(b) rate data – number of cases of active TB per patient-year

Table 3: Development of active TB (random effects) – relative effectiveness of all pairwise combinations

	Placebo / no treatment	12H	1HR	1HRPz	2RPz	36H	3H	3HR	3HRp	3HRPz	3RPz	6H	6HE	6yH	9H
Placebo / no treatment		N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A
12H	0.25 (0.14,0.44)		N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A
1HR	0.61 (0.22,1.61)	2.40 (0.81,7.29)		N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A
1HRPz	0.01 (0.00,0.19)	0.06 (0.00,0.80)	0.02 (0.00,0.35)		N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A
2RPz	0.24 (0.10,0.50)	0.93 (0.44,1.93)	0.39 (0.11,1.29)	15.88 (1.10,12020)		N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A
36H	0.10 (0.02,0.40)	0.39 (0.08,1.72)	0.16 (0.03,0.88)	6.75 (0.35,3977.00)	0.42 (0.08,1.94)		N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A
3H	0.78 (0.41,1.38)	3.05 (1.51,6.37)	1.28 (0.45,3.50)	52.12 (4.03,37640)	3.27 (1.35,8.33)	7.87 (1.77,36.70)		N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A
3HR	0.35 (0.19,0.62)	1.38 (0.67,3.00)	0.58 (0.20,1.66)	24.11 (1.77,17090)	1.48 (0.63,3.68)	3.54 (0.83,16.59)	0.45 (0.22,0.96)		N/A	N/A	N/A	N/A	N/A	N/A	N/A
3HRp	0.36 (0.17,0.81)	1.42 (0.59,3.70)	0.60 (0.18,2.04)	24.97 (1.70,19490)	1.53 (0.59,4.34)	3.68 (0.82,18.37)	0.47 (0.19,1.24)	1.04 (0.49,2.33)		N/A	N/A	N/A	N/A	N/A	N/A
3HRPz	0.33 (0.13,0.77)	1.30 (0.47,3.53)	0.54 (0.15,1.93)	22.84 (1.50,16040)	1.39 (0.46,4.31)	3.33 (0.67,17.53)	0.42 (0.15,1.17)	0.95 (0.37,2.31)	0.92 (0.29,2.59)		N/A	N/A	N/A	N/A	N/A
3RPz	0.29 (0.05,1.34)	1.11 (0.17,6.02)	0.46 (0.06,2.99)	19.40 (0.72,20160)	1.20 (0.17,7.06)	2.89 (0.28,25.92)	0.37 (0.06,1.97)	0.81 (0.12,4.14)	0.79 (0.11,4.37)	0.87 (0.12,5.16)		N/A	N/A	N/A	N/A
6H	0.39 (0.23,0.60)	1.54 (0.82,2.84)	0.64 (0.22,1.81)	26.57 (1.97,19080)	1.65 (0.79,3.56)	3.93 (1.02,16.13)	0.50 (0.26,0.96)	1.11 (0.61,1.94)	1.08 (0.47,2.24)	1.19 (0.49,2.86)	1.38 (0.28,8.54)		N/A	N/A	N/A
6HE	0.18 (0.03,1.14)	0.69 (0.10,4.80)	0.29 (0.03,2.27)	12.31 (0.51,8373)	0.74 (0.10,5.45)	1.77 (0.54,5.94)	0.23 (0.03,1.54)	0.50 (0.07,3.30)	0.48 (0.07,3.35)	0.53 (0.07,4.09)	0.60 (0.05,8.91)	0.45 (0.07,2.85)		N/A	N/A
6yH	0.38 (0.15,0.96)	1.48 (0.55,4.31)	0.62 (0.17,2.36)	26.17 (1.68,19910)	1.59 (0.54,5.06)	3.84 (0.77,20.09)	0.49 (0.17,1.43)	1.08 (0.45,2.64)	1.04 (0.41,2.54)	1.14 (0.35,3.86)	1.34 (0.21,10.17)	0.97 (0.41,2.43)	2.16 (0.29,16.24)		N/A
9H	0.55 (0.23,1.30)	2.16 (0.82,6.16)	0.90 (0.26,3.27)	37.24 (2.51,25520)	2.32 (0.80,7.55)	5.63 (1.16,29.17)	0.70 (0.26,2.02)	1.57 (0.63,4.08)	1.51 (0.63,3.67)	1.66 (0.54,5.74)	1.92 (0.32,14.53)	1.41 (0.59,3.63)	3.18 (0.43,23.69)	1.45 (0.47,4.60)	

Values given are hazard ratios.
The segment below and to the left of the shaded diagonal is derived from the network meta-analysis, reflecting direct and indirect evidence of treatment effects (row versus column). The point estimate reflects the mean of the posterior distribution, and numbers in parentheses are 95% credible intervals. Because it is not easily possible to pool dichotomous and rate data and derive analogous estimates of hazard ratios from a single frequentist analysis of direct data only, the segment above and to the right of the shaded diagonal is left blank



Values less than 1 favour the comparator treatment; values greater than 1 favour placebo. Error bars are 95% credible intervals. Direct pairwise estimates are drawn from inconsistency model.

Figure 2: Development of active TB (random effects) – relative effect of all options versus common comparator

Table 4: Development of active TB (random effects) – rankings for each comparator

	Probability best	Median rank (95%CrI)
1HRPz	0.853	1 (1, 4)
36H	0.087	2 (1, 8)
3RPz	0.028	6 (1, 15)
6HE	0.026	4 (1, 15)
2RPz	0.003	5 (2, 11)
12H	0.001	5 (3, 10)
3HRPz	0.001	8 (3, 13)
6yH	0.001	9 (3, 14)
3HR	0.000	8 (4, 12)
3HRp	0.000	8 (4, 13)
6H	0.000	9 (6, 12)
1HR	0.000	12 (5, 15)
9H	0.000	12 (5, 15)
3H	0.000	13 (10, 15)
Placebo / no treatment	0.000	15 (13, 15)

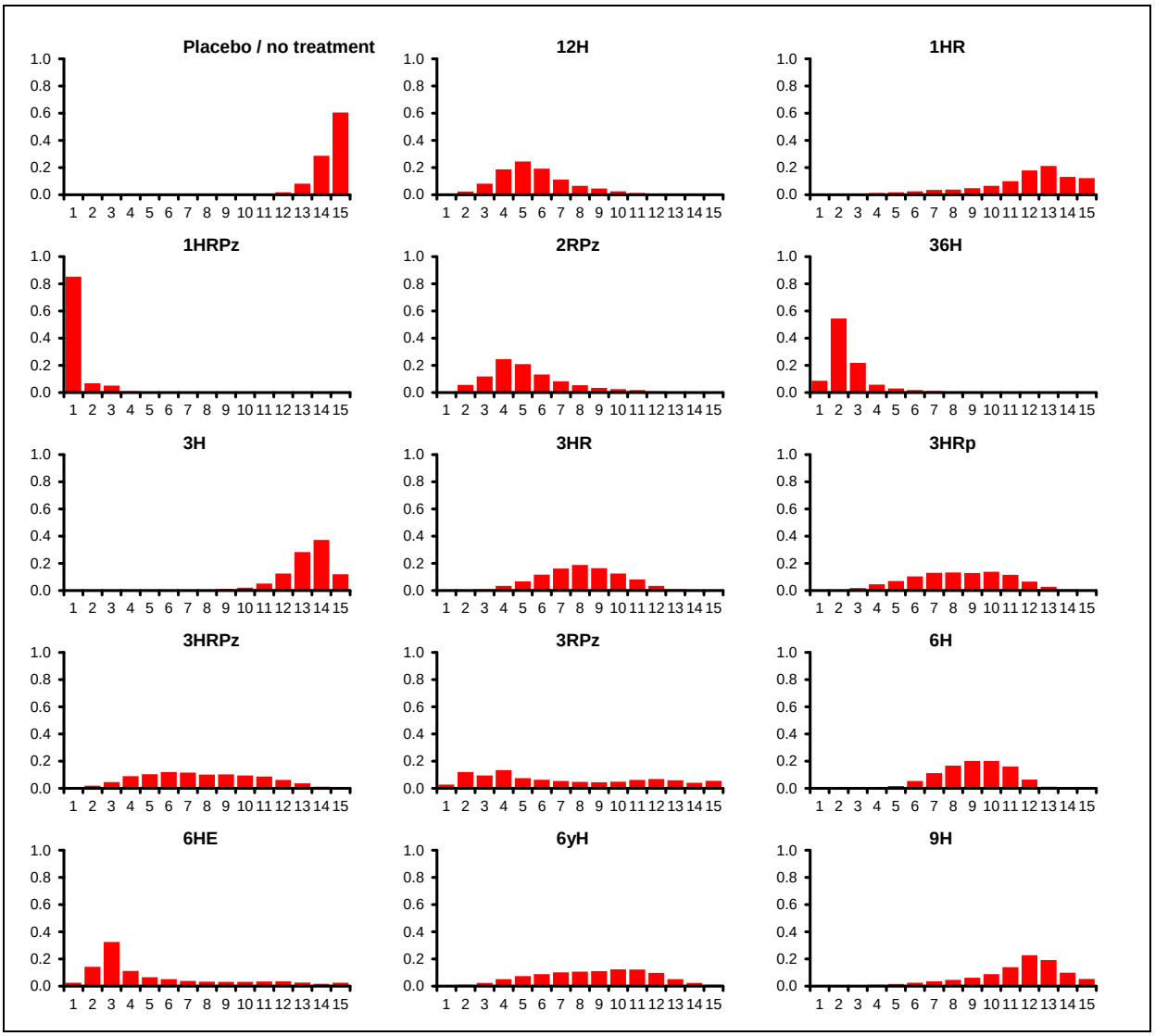


Figure 3: Development of active TB (random effects) – rank probability histograms

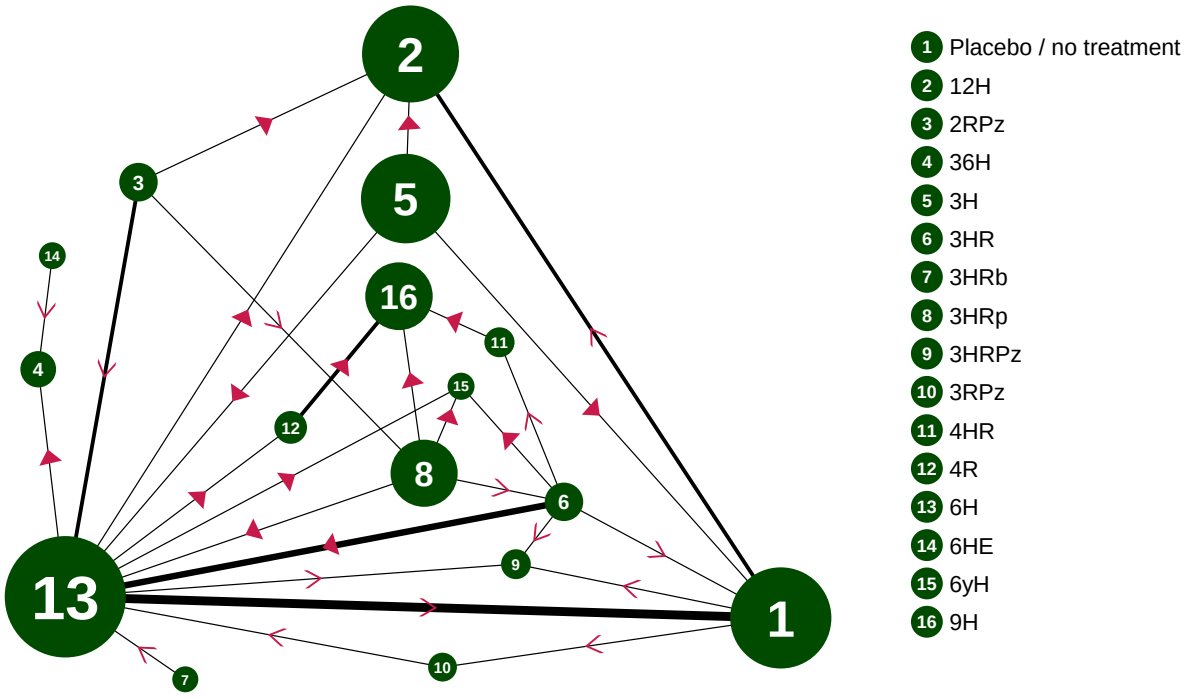
Table 5: Development of active TB (random effects) – model fit statistics

Residual deviance	Dbar	Dhat	pD	DIC	tau
40.1 (compared to 42 datapoints)	27.089	22.344	4.745	31.833	0.313 (95%CrI: 0.055, 0.740)

Table 6: Development of active TB (random effects) – notes

- Hybrid cloglog--Poisson model for count/dichotomous data; random effects
- Prior distribution for between-study heterogeneity: uniform (Min=0; Max=2)
- 50000 burn-ins; 10000 recorded iterations

L.1.2 Adherence



Size of nodes is proportional to total number of participants randomised to receive the treatment in question across the evidence-base. Width of connecting lines is proportional to number of trial-level comparisons available. Arrowheads indicate direction of effect in pairwise data (a > b denotes a is more effective than b) – filled arrowheads show comparisons where one option is significantly superior (p<0.05); outlined arrowheads show direction of trend where effect does not reach statistical significance.

Figure 4: Adherence (random effects) – evidence network

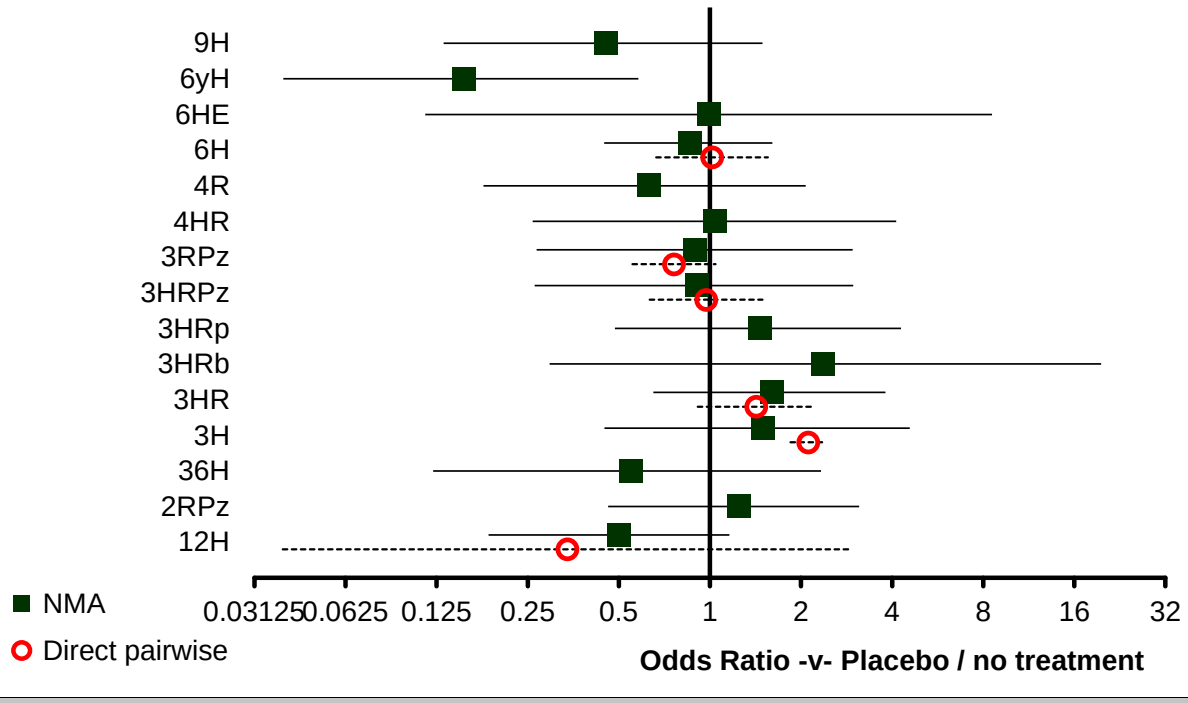
Table 7: Adherence (random effects) – input data

	Placebo / no treatment	12H	2RPz	36H	3H	3HR	3HRb	3HRp	3HRPz	3RPz	4HR	4R	6H	6HE	6yH	9H
Jimenez-Fuentes et al. (2013)						213/296							154/294			
Swaminathan et al. (2012)				116/132										131/141		
White et al. (2012)												60/180				47/184
Chan et al. (2012)												142/190	163/183			
Sterling et al. (2011)								3273/3986								2585/3745
Martinson et al. (2011)						312/329		314/328					274/327		99/164	
Samandari et al. (2011)				763/1006									821/989			
Menzies et al. (2008)												328/420				255/427
Spyridis et al. (2007)											220/238					200/232
Spyridis et al. (2007)						209/220					221/236					
Schechter et al. (2006)			181/193					192/206								
Leung et al. (2003)			22/40										23/36			
Quigley et al. (2001)	259/360									238/360			221/360			
Gordin et al. (2000)		544/792	636/791													
Matteelli et al. (1999)							26/30						10/14			
Halsey et al. (1998)			264/380										173/370			
Whalen et al. (1997)	418/464					516/556			415/462				491/536			
Hawken et al. (1997)	143/342												138/342			
Anon. (1982)	6291/6990	6089/6919			6608/6956								6477/6965			
Byrd et al. (1977)	59/60	50/60														

Table 8: Adherence (random effects) – relative effectiveness of all pairwise combinations

	Placebo / no treatment	12H	2RPz	36H	3H	3HR	3HRb	3HRp	3HRPz	3RPz	4HR	4R	6H	6HE	6yH	9H
Placebo / no treatment		0.34 (0.04,2.94)	-	-	2.11 (1.85,2.41)	1.42 (0.91,2.21)	-	-	0.97 (0.63,1.49)	0.76 (0.55,1.04)	-	-	1.02 (0.66,1.55)	-	-	-
12H	0.50 (0.19,1.16)		1.87 (1.48,2.36)	-	2.59 (2.27,2.95)	-	-	-	-	-	-	-	1.81 (1.61,2.03)	-	-	-
2RPz	1.25 (0.46,3.11)	2.50 (0.99,6.78)		-	-	-	-	0.91 (0.41,2.02)	-	-	-	-	0.69 (0.19,2.51)	-	-	-
36H	0.55 (0.12,2.33)	1.09 (0.23,5.88)	0.44 (0.10,2.12)		-	-	-	-	-	-	-	-	1.56 (1.25,1.94)	1.81 (0.79,4.14)	-	-
3H	1.51 (0.45,4.57)	2.98 (0.94,10.58)	1.20 (0.32,4.48)	2.75 (0.46,15.67)		-	-	-	-	-	-	-	0.70 (0.61,0.81)	-	-	-
3HR	1.61 (0.65,3.80)	3.21 (1.13,10.24)	1.28 (0.47,3.77)	2.93 (0.64,13.41)	1.07 (0.30,4.23)		-	1.22 (0.59,2.52)	0.68 (0.44,1.06)	-	0.78 (0.35,1.73)	-	0.48 (0.27,0.84)	-	0.08 (0.05,0.15)	-
3HRb	2.36 (0.30,19.62)	4.84 (0.56,45.70)	1.91 (0.23,17.63)	4.34 (0.40,48.16)	1.59 (0.16,16.80)	1.47 (0.18,12.75)		-	-	-	-	-	0.38 (0.08,1.84)	-	-	-
3HRp	1.47 (0.48,4.28)	2.96 (0.92,10.48)	1.18 (0.43,3.41)	2.69 (0.53,13.96)	0.98 (0.24,4.20)	0.91 (0.33,2.60)	0.62 (0.07,5.40)		-	-	-	-	0.23 (0.13,0.42)	-	0.07 (0.04,0.13)	0.49 (0.44,0.54)
3HRPz	0.91 (0.26,2.97)	1.80 (0.47,8.01)	0.72 (0.19,3.07)	1.65 (0.28,9.89)	0.60 (0.13,3.10)	0.56 (0.17,1.92)	0.38 (0.04,3.79)	0.62 (0.14,2.61)		-	-	-	1.24 (0.80,1.90)	-	-	-
3RPz	0.89 (0.27,2.96)	1.78 (0.46,8.06)	0.71 (0.18,3.14)	1.62 (0.27,9.92)	0.59 (0.12,3.12)	0.55 (0.14,2.24)	0.38 (0.04,3.78)	0.61 (0.14,2.83)	0.98 (0.20,5.18)		-	-	0.82 (0.60,1.10)	-	-	-
4HR	1.04 (0.26,4.12)	2.07 (0.48,10.29)	0.83 (0.20,3.69)	1.89 (0.30,12.21)	0.69 (0.13,3.84)	0.64 (0.19,2.16)	0.44 (0.04,4.52)	0.70 (0.18,2.77)	1.15 (0.22,6.08)	1.16 (0.20,6.39)		-	-	-	-	0.51 (0.28,0.94)
4R	0.63 (0.18,2.08)	1.27 (0.34,5.16)	0.50 (0.14,1.85)	1.15 (0.21,6.39)	0.42 (0.09,2.00)	0.39 (0.12,1.28)	0.27 (0.03,2.48)	0.43 (0.13,1.38)	0.70 (0.15,3.24)	0.71 (0.14,3.40)	0.61 (0.15,2.33)		2.75 (1.56,4.86)	-	-	0.52 (0.32,0.84)
6H	0.86 (0.45,1.61)	1.72 (0.76,4.46)	0.69 (0.32,1.57)	1.58 (0.42,6.04)	0.58 (0.19,1.90)	0.54 (0.26,1.13)	0.36 (0.05,2.66)	0.58 (0.23,1.50)	0.95 (0.30,3.09)	0.97 (0.29,3.20)	0.83 (0.23,2.99)	1.37 (0.47,4.04)		-	0.29 (0.19,0.45)	-
6HE	0.99 (0.11,8.55)	2.00 (0.22,20.47)	0.79 (0.09,7.56)	1.81 (0.39,8.82)	0.66 (0.06,7.56)	0.62 (0.07,5.55)	0.42 (0.02,7.43)	0.68 (0.07,6.60)	1.11 (0.11,11.71)	1.12 (0.10,11.90)	0.96 (0.08,10.69)	1.58 (0.15,16.57)	1.16 (0.15,9.10)		-	-
6yH	0.15 (0.04,0.58)	0.30 (0.07,1.43)	0.12 (0.03,0.50)	0.28 (0.05,1.64)	0.10 (0.02,0.55)	0.10 (0.03,0.33)	0.07 (0.01,0.64)	0.10 (0.03,0.38)	0.17 (0.03,0.86)	0.17 (0.03,0.92)	0.15 (0.03,0.76)	0.24 (0.05,1.12)	0.18 (0.05,0.59)	0.15 (0.01,1.66)		-
9H	0.45 (0.13,1.49)	0.91 (0.25,3.70)	0.36 (0.11,1.27)	0.83 (0.15,4.63)	0.30 (0.07,1.45)	0.28 (0.09,0.87)	0.19 (0.02,1.79)	0.31 (0.11,0.86)	0.50 (0.11,2.31)	0.51 (0.10,2.48)	0.44 (0.13,1.41)	0.72 (0.31,1.71)	0.52 (0.18,1.50)	0.46 (0.04,4.68)	2.96 (0.68,12.95)	

Values given are odds ratios.
The segment below and to the left of the shaded cells is derived from the network meta-analysis, reflecting direct and indirect evidence of treatment effects (row versus column). The point estimate reflects the mean of the posterior distribution, and numbers in parentheses are 95% credible intervals. The segment above and to the right of the shaded cells gives pooled direct evidence (random-effects pairwise meta-analysis), where available (column versus row). Numbers in parentheses are 95% confidence intervals.



Values less than 1 favour placebo; values greater than 1 favour the comparator treatment. Solid error bars are 95% credible intervals; dashed error bars are 95% confidence interval.

Figure 5: Adherence (random effects) – relative effect of all options versus common comparator

Table 9: Adherence (random effects) – rankings for each comparator

	Probability best	Median rank (95%CrI)
3HRb	0.459	2 (1, 15)
6HE	0.128	8 (1, 16)
3H	0.125	4 (1, 13)
3HR	0.080	4 (1, 9)
3HRp	0.079	4 (1, 11)
4HR	0.043	7 (1, 14)
2RPz	0.028	6 (1, 12)
3RPz	0.028	9 (1, 15)
3HRPz	0.022	9 (2, 15)
Placebo / no treatment	0.003	8 (3, 13)
4R	0.003	12 (4, 15)
36H	0.003	13 (3, 16)
6H	0.000	9 (5, 13)
12H	0.000	13 (7, 16)
9H	0.000	14 (7, 16)
6yH	0.000	16 (13, 16)

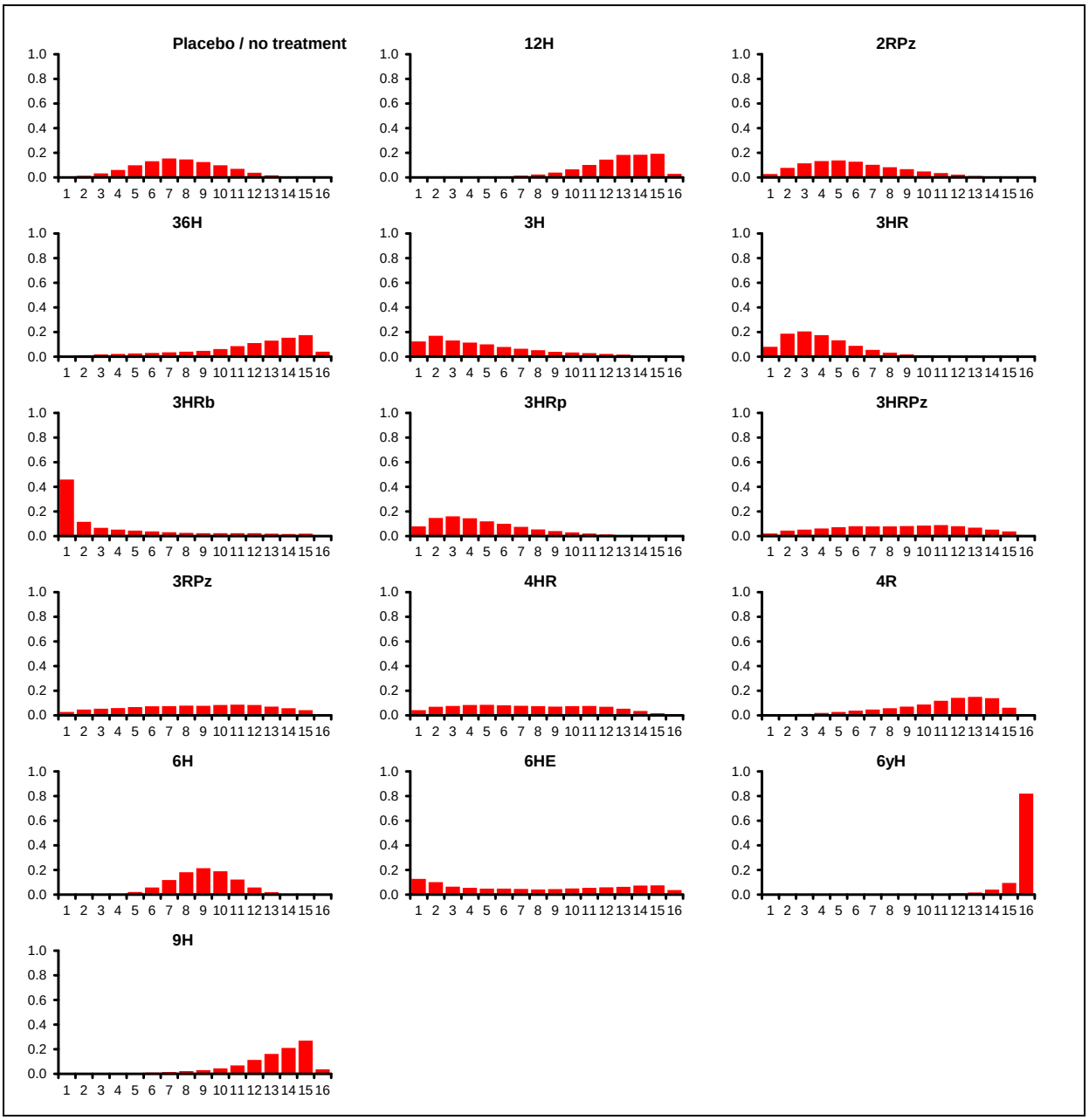


Figure 6: Adherence (random effects) – rank probability histograms

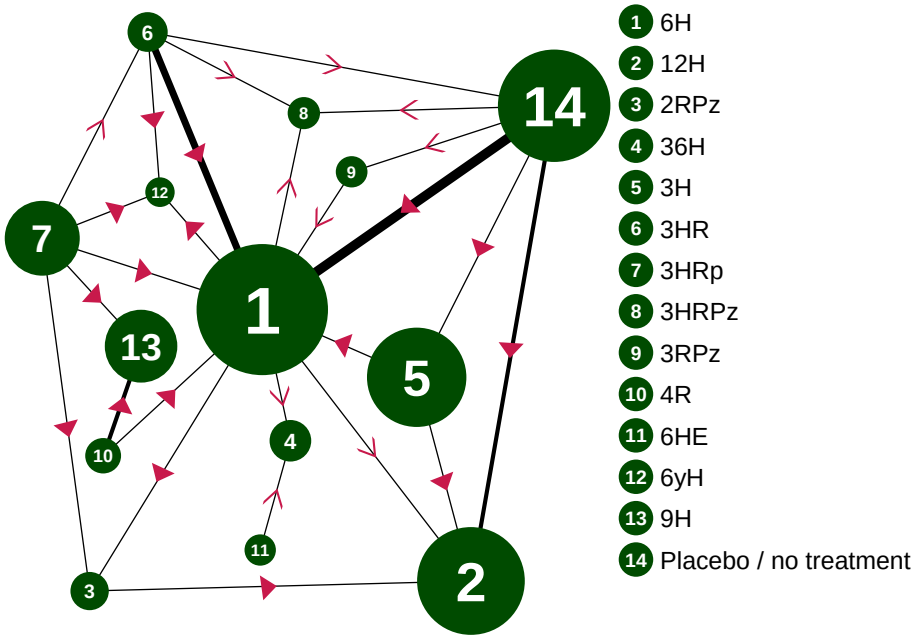
Table 10: Adherence (random effects) – model fit statistics

Residual deviance	Dbar	Dhat	pD	DIC	tau
49.18 (compared to 48 datapoints)	315.047	269.472	45.576	360.623	0.596 (95%CrI: 0.361, 1.078)

Table 11: Adherence (random effects) – notes

- Dichotomous synchronic (binomial; logit link); random effects
- Prior distribution for between-study heterogeneity: uniform (Min=0; Max=2)
- 50000 burn-ins; 10000 recorded iterations

L.1.3 Hepatotoxicity (≥1 event)



Size of nodes is proportional to total number of participants randomised to receive the treatment in question across the evidence-base. Width of connecting lines is proportional to number of trial-level comparisons available. Arrowheads indicate direction of effect in pairwise data (a > b denotes a is more effective than b) – filled arrowheads show comparisons where one option is significantly superior (p<0.05); outlined arrowheads show direction of trend where effect does not reach statistical significance.

Figure 7: Hepatotoxicity (random effects) – evidence network

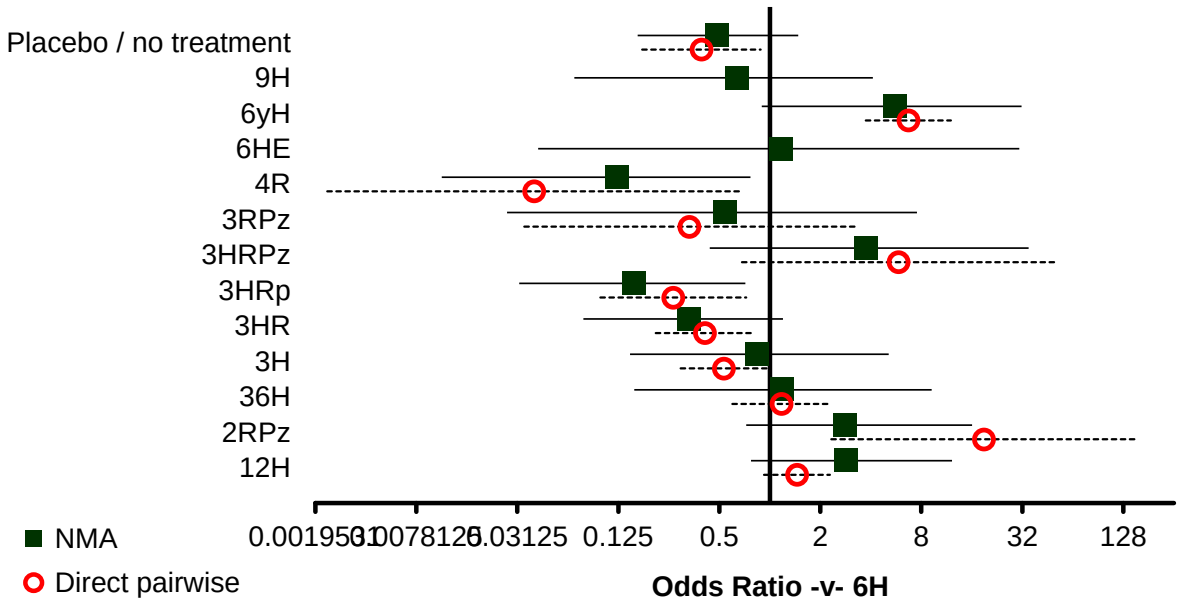
Table 12: Hepatotoxicity (random effects) – input data

	6H	12H	2RPz	36H	3H	3HR	3HRp	3HRPz	3RPz	4R	6HE	6yH	9H	Placebo / no treatment
Jimenez-Fuentes et al. (2013)	10/294					4/296								
Swaminathan et al. (2012)				3/339							3/344			
White et al. (2012)										8/180			21/184	
Chan et al. (2012)	11/183									0/190				
Sterling et al. (2011)							18/4040						103/3759	
Martinson et al. (2011)	18/327					8/329	5/328					46/164		
Samandari et al. (2011)	16/989			19/1006										
Menzies et al. (2008)										3/420			16/427	
Schechter et al. (2006)			20/193				2/206							
Leung et al. (2003)	1/36		14/40											
Quigley et al. (2001)	3/360								1/360					0/360
Gordin et al. (2000)		26/792	11/791											
Whalen et al. (1997)	1/536					0/556		5/462						1/464
Hawken et al. (1997)	18/342													12/342
Anon. (1982)	32/6965	46/6919			17/6956									7/6990
Byrd et al. (1977)		11/60												4/60

Table 13: Hepatotoxicity (random effects) – relative effectiveness of all pairwise combinations

	6H	12H	2RPz	36H	3H	3HR	3HRp	3HRPz	3RPz	4R	6HE	6yH	9H	Placebo / no treatment
6H		1.45 (0.92,2.28)	18.85 (2.33,152.56)	1.17 (0.60,2.29)	0.53 (0.29,0.96)	0.41 (0.21,0.80)	0.27 (0.10,0.72)	5.85 (0.68,50.28)	0.33 (0.03,3.20)	0.04 (0.00,0.67)	-	6.69 (3.73,12.01)	-	0.39 (0.17,0.88)
12H	2.88 (0.77,12.20)		0.42 (0.20,0.85)	-	0.37 (0.21,0.64)	-	-	-	-	-	-	-	-	0.19 (0.10,0.38)
2RPz	2.82 (0.72,16.09)	0.98 (0.23,5.34)		-	-	-	0.08 (0.02,0.37)	-	-	-	-	-	-	-
36H	1.18 (0.16,9.23)	0.41 (0.03,4.55)	0.42 (0.03,4.60)		-	-	-	-	-	-	0.99 (0.20,4.92)	-	-	-
3H	0.85 (0.15,5.10)	0.30 (0.04,1.72)	0.30 (0.03,2.21)	0.71 (0.05,11.63)		-	-	-	-	-	-	-	-	0.41 (0.17,0.99)
3HR	0.33 (0.08,1.20)	0.11 (0.01,0.65)	0.12 (0.01,0.69)	0.28 (0.02,3.03)	0.39 (0.04,3.32)		0.62 (0.20,1.92)	13.38 (0.74,242.62)	-	-	-	15.64 (7.17,34.12)	-	3.60 (0.15,88.63)
3HRp	0.16 (0.03,0.72)	0.05 (0.01,0.34)	0.05 (0.01,0.27)	0.13 (0.01,1.69)	0.18 (0.02,1.82)	0.48 (0.08,3.04)		-	-	-	-	25.18 (9.77,64.90)	6.30 (3.81,10.41)	-
3HRPz	3.76 (0.44,34.87)	1.30 (0.11,15.90)	1.31 (0.08,16.84)	3.19 (0.17,61.48)	4.49 (0.30,69.13)	11.38 (1.18,138.90)	24.07 (1.80,362.60)		-	-	-	-	-	0.20 (0.02,1.70)
3RPz	0.54 (0.03,7.54)	0.18 (0.01,3.34)	0.19 (0.01,3.54)	0.45 (0.01,12.96)	0.63 (0.02,14.57)	1.63 (0.07,34.38)	3.45 (0.12,74.02)	0.14 (0.00,4.13)		-	-	-	-	0.33 (0.01,8.19)
4R	0.12 (0.01,0.77)	0.04 (0.00,0.36)	0.04 (0.00,0.35)	0.10 (0.00,1.46)	0.15 (0.01,1.70)	0.37 (0.03,3.41)	0.78 (0.08,4.72)	0.03 (0.00,0.52)	0.22 (0.01,7.19)		-	-	3.42 (1.70,6.87)	-
6HE	1.17 (0.04,30.66)	0.41 (0.01,13.38)	0.41 (0.01,13.90)	0.99 (0.07,12.62)	1.39 (0.03,54.89)	3.58 (0.11,129.30)	7.60 (0.20,290.80)	0.31 (0.01,16.15)	2.27 (0.03,179.90)	9.73 (0.24,609.30)		-	-	-
6yH	5.60 (0.89,31.65)	1.97 (0.19,15.86)	1.99 (0.17,15.32)	4.75 (0.31,67.59)	6.59 (0.52,74.47)	16.98 (2.60,115.40)	35.66 (4.90,256.40)	1.47 (0.09,22.09)	10.39 (0.39,332.20)	45.54 (4.32,765.90)	4.80 (0.12,196.30)		-	-
9H	0.64 (0.07,4.12)	0.22 (0.02,1.90)	0.23 (0.02,1.69)	0.54 (0.02,8.25)	0.76 (0.04,9.20)	1.93 (0.18,17.07)	4.15 (0.61,20.12)	0.17 (0.01,2.74)	1.18 (0.04,38.64)	5.26 (1.38,24.02)	0.54 (0.01,22.97)	0.12 (0.01,1.17)		-
Placebo / no treatment	0.49 (0.16,1.48)	0.17 (0.04,0.61)	0.17 (0.02,0.86)	0.41 (0.04,4.18)	0.58 (0.10,3.38)	1.49 (0.29,8.74)	3.14 (0.51,20.44)	0.13 (0.01,1.20)	0.90 (0.06,18.71)	3.99 (0.49,57.15)	0.41 (0.01,14.12)	0.09 (0.01,0.73)	0.76 (0.09,9.36)	

Values given are odds ratios.
The segment below and to the left of the shaded cells is derived from the network meta-analysis, reflecting direct and indirect evidence of treatment effects (row versus column). The point estimate reflects the mean of the posterior distribution, and numbers in parentheses are 95% credible intervals. The segment above and to the right of the shaded cells gives pooled direct evidence (random-effects pairwise meta-analysis), where available (column versus row). Numbers in parentheses are 95% confidence intervals.



Values less than 1 favour the comparator treatment; values greater than 1 favour 6H. Solid error bars are 95% credible intervals; dashed error bars are 95% confidence interval.

Figure 8: Hepatotoxicity (random effects) – relative effect of all options versus common comparator

Table 14: Hepatotoxicity (random effects) – rankings for each comparator

	Probability best	Median rank (95%CrI)
4R	0.473	2 (1, 6)
3HRp	0.263	2 (1, 6)
3RPz	0.118	6 (1, 13)
6HE	0.058	9 (1, 14)
3HR	0.054	4 (1, 9)
3H	0.013	7 (2, 12)
Placebo / no treatment	0.012	5 (2, 9)
36H	0.006	9 (3, 13)
9H	0.002	6 (2, 12)
3HRPz	0.001	12 (5, 14)
6H	0.000	8 (5, 11)
2RPz	0.000	11 (7, 14)
12H	0.000	12 (7, 14)
6yH	0.000	13 (8, 14)

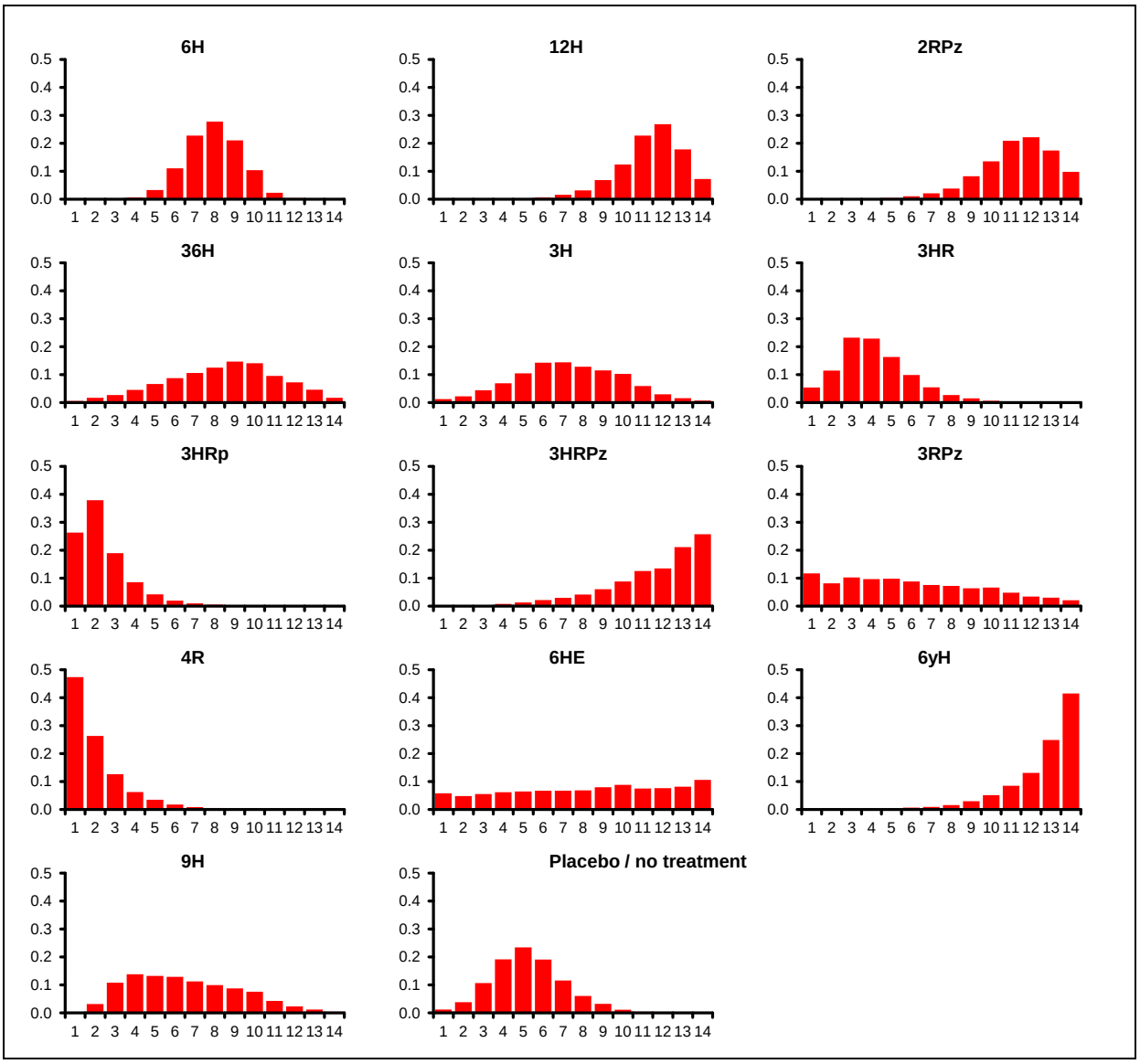


Figure 9: Hepatotoxicity (random effects) – rank probability histograms

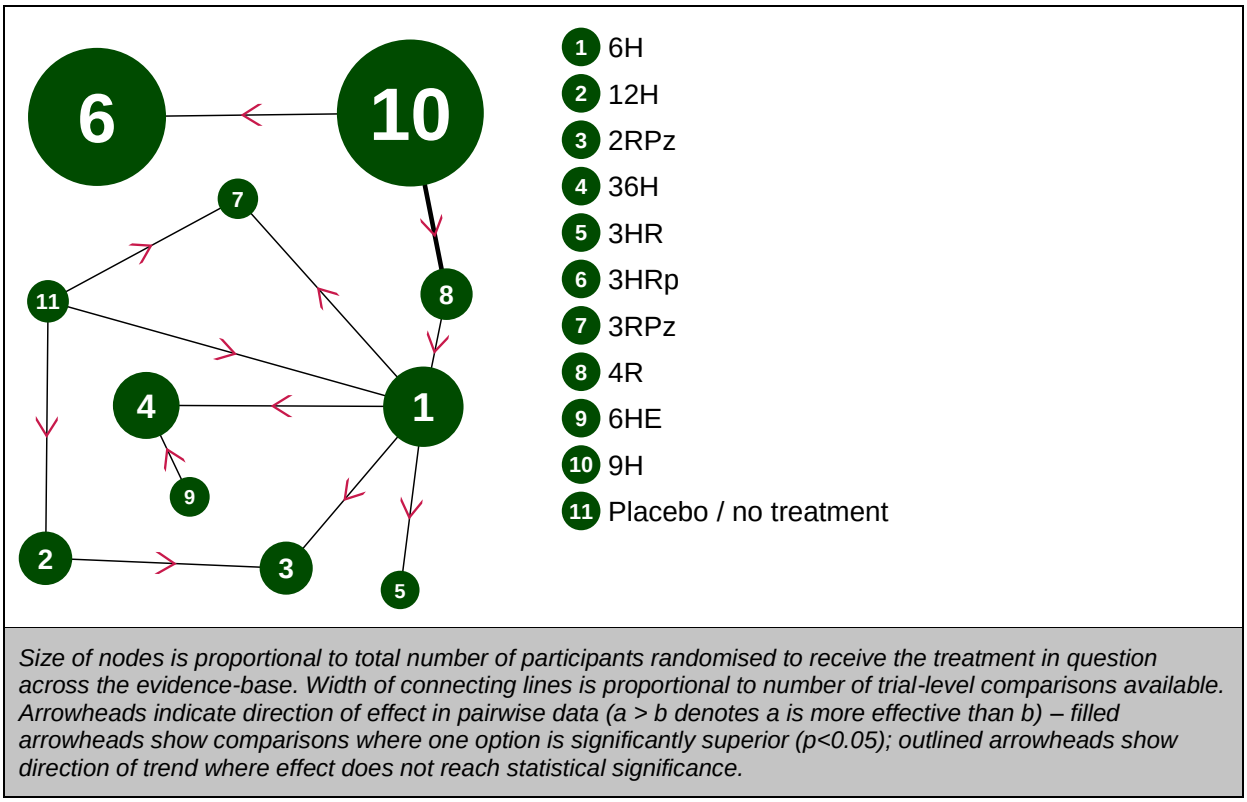
Table 15: Hepatotoxicity (random effects) – model fit statistics

Residual deviance	Dbar	Dhat	pD	DIC	tau
38.95 (compared to 39 datapoints)	187.155	152.485	34.67	221.826	0.822 (95%CrI: 0.282, 1.673)

Table 16: Hepatotoxicity (random effects) – notes

- Dichotomous synchronic (binomial; logit link); random effects
- Prior distribution for between-study heterogeneity: uniform (Min=0; Max=2)
- 50000 burn-ins; 10000 recorded iterations

L.1.4 Rash (≥1 event)



Size of nodes is proportional to total number of participants randomised to receive the treatment in question across the evidence-base. Width of connecting lines is proportional to number of trial-level comparisons available. Arrowheads indicate direction of effect in pairwise data (a > b denotes a is more effective than b) – filled arrowheads show comparisons where one option is significantly superior (p<0.05); outlined arrowheads show direction of trend where effect does not reach statistical significance.

Figure 10: Rash (fixed effects) – evidence network

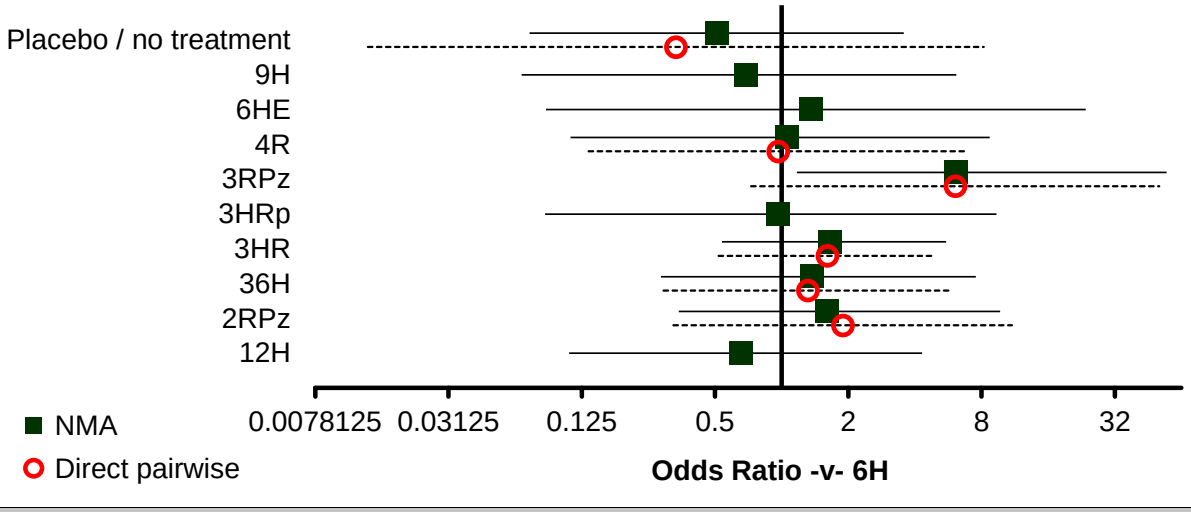
Table 17: Rash (fixed effects) – input data

	6H	12H	2RPz	36H	3HR	3HRp	3RPz	4R	6HE	9H	Placebo / no treatment
Jimenez-Fuentes et al. (2013)	5/294				8/296						
Swaminathan et al. (2012)				2/339					2/344		
White et al. (2012)								16/180		12/184	
Chan et al. (2012)	2/183							2/190			
Sterling et al. (2011)						31/4040				21/3759	
Samandari et al. (2011)	3/989			4/1006							
Menzies et al. (2008)								9/420		5/427	
Leung et al. (2003)	2/36		4/40								
Quigley et al. (2001)	1/360						6/360				0/360
Gordin et al. (2000)		5/792	11/791								
Byrd et al. (1977)		7/60									6/60

Table 18: Rash (fixed effects) – relative effectiveness of all pairwise combinations

	6H	12H	2RPz	36H	3HR	3HRp	3RPz	4R	6HE	9H	Placebo / no treatment
6H		-	1.89 (0.32, 10.99)	1.31 (0.29, 5.88)	1.61 (0.52, 4.97)	-	6.08 (0.73, 50.80)	0.96 (0.13, 6.91)	-	-	0.33 (0.01, 8.19)
12H	0.65 (0.11, 4.32)		2.22 (0.77, 6.42)	-	-	-	-	-	-	-	0.84 (0.27, 2.67)
2RPz	1.61 (0.34, 9.70)	2.49 (0.91, 7.89)		-	-	-	-	-	-	-	-
36H	1.38 (0.28, 7.55)	2.14 (0.17, 23.99)	0.85 (0.08, 8.18)		-	-	-	-	0.99 (0.14, 7.04)	-	-
3HR	1.65 (0.54, 5.54)	2.55 (0.28, 22.34)	1.00 (0.12, 7.44)	1.20 (0.16, 8.70)		-	-	-	-	-	-
3HRp	0.96 (0.09, 9.34)	1.45 (0.06, 28.18)	0.58 (0.03, 10.00)	0.71 (0.04, 10.84)	0.59 (0.04, 7.10)		-	-	-	0.73 (0.42, 1.27)	-
3RPz	6.12 (1.17, 54.81)	9.44 (1.22, 113.10)	3.77 (0.47, 40.84)	4.56 (0.41, 65.23)	3.76 (0.48, 44.05)	6.69 (0.36, 159.30)		-	-	-	0.08 (0.00, 1.35)
4R	1.06 (0.11, 8.71)	1.61 (0.08, 27.72)	0.64 (0.03, 9.62)	0.78 (0.05, 10.70)	0.65 (0.05, 6.96)	1.10 (0.47, 2.60)	0.16 (0.01, 2.66)		-	0.65 (0.34, 1.23)	-
6HE	1.36 (0.09, 23.66)	2.07 (0.07, 58.78)	0.82 (0.03, 21.72)	0.99 (0.10, 9.67)	0.82 (0.04, 18.00)	1.40 (0.04, 61.69)	0.21 (0.01, 6.04)	1.28 (0.04, 50.26)		-	-
9H	0.70 (0.07, 6.15)	1.05 (0.05, 19.27)	0.42 (0.02, 6.83)	0.51 (0.03, 7.47)	0.42 (0.03, 4.86)	0.72 (0.41, 1.25)	0.11 (0.00, 1.90)	0.66 (0.34, 1.23)	0.51 (0.01, 16.43)		-
Placebo / no treatment	0.51 (0.07, 3.57)	0.77 (0.24, 2.34)	0.31 (0.06, 1.31)	0.36 (0.03, 4.77)	0.30 (0.03, 3.00)	0.53 (0.03, 12.49)	0.08 (0.01, 0.55)	0.48 (0.03, 9.71)	0.37 (0.01, 11.06)	0.73 (0.04, 16.15)	

Values given are odds ratios.
The segment below and to the left of the shaded cells is derived from the network meta-analysis, reflecting direct and indirect evidence of treatment effects (row versus column). The point estimate reflects the mean of the posterior distribution, and numbers in parentheses are 95% credible intervals. The segment above and to the right of the shaded cells gives pooled direct evidence (random-effects pairwise meta-analysis), where available (column versus row). Numbers in parentheses are 95% confidence intervals.



Values less than 1 favour the comparator treatment; values greater than 1 favour 6H. Solid error bars are 95% credible intervals; dashed error bars are 95% confidence interval.

Figure 11: Rash (fixed effects) – relative effect of all options versus common comparator

Table 19: Rash (fixed effects) – rankings for each comparator

	Probability best	Median rank (95%CrI)
Placebo / no treatment	0.331	2 (1, 9)
9H	0.239	3 (1, 9)
6HE	0.156	7 (1, 11)
12H	0.133	4 (1, 9)
3HRp	0.040	5 (1, 11)
36H	0.038	7 (1, 11)
6H	0.025	5 (1, 9)
3HR	0.018	8 (2, 11)
4R	0.017	6 (2, 11)
2RPz	0.002	8 (3, 11)
3RPz	0.000	11 (6, 11)

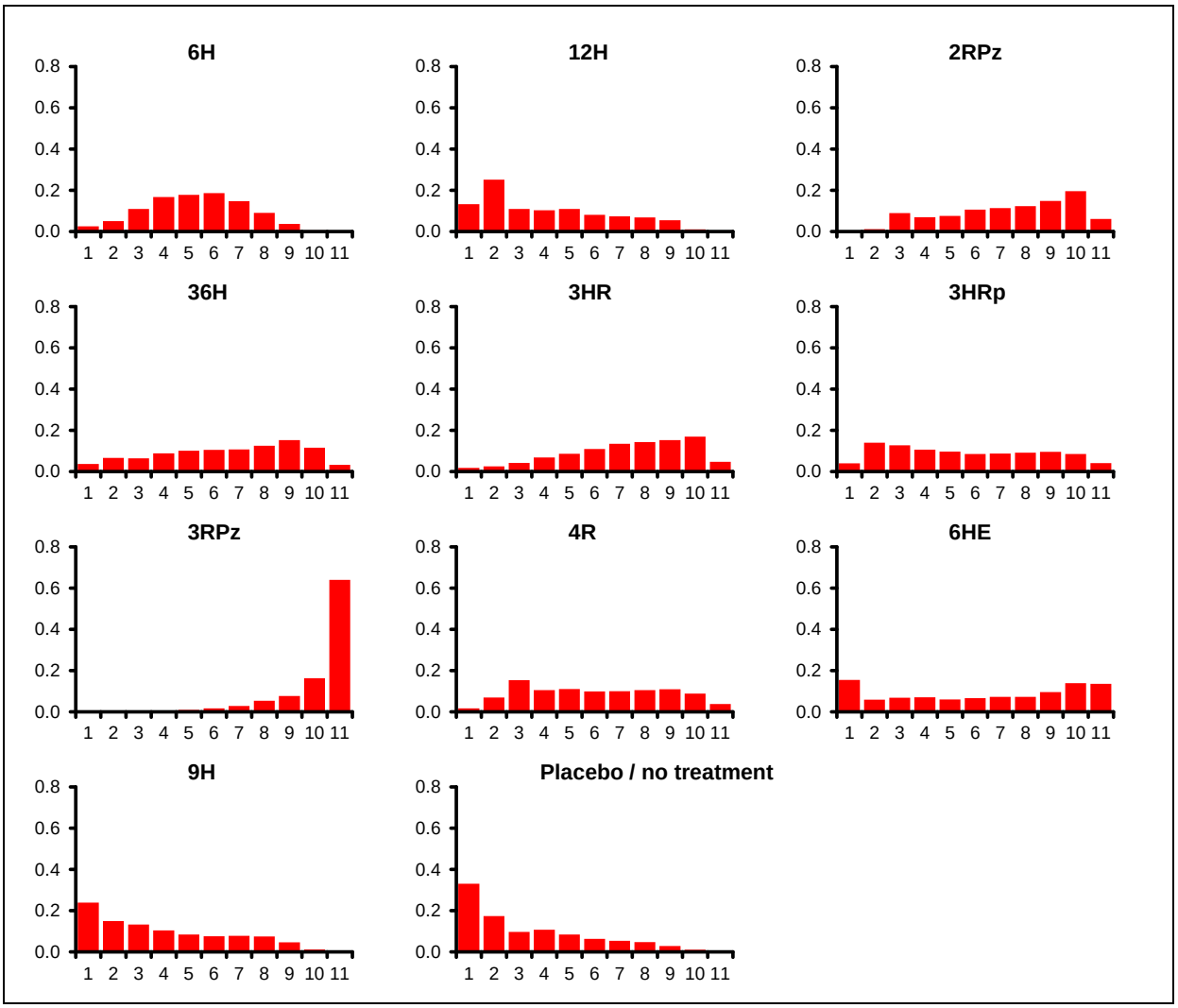


Figure 12: Rash (fixed effects) – rank probability histograms

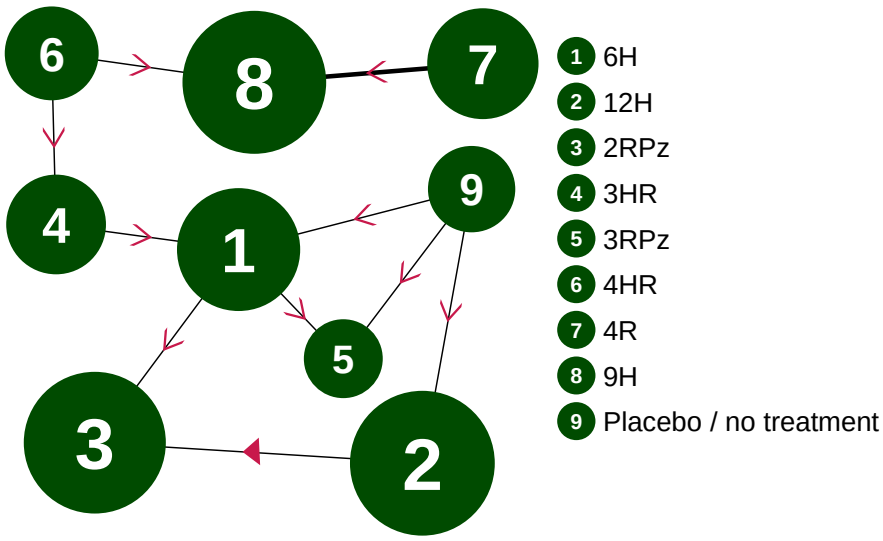
Table 20: Rash (fixed effects) – model fit statistics

Residual deviance	Dbar	Dhat	pD	DIC
22.14 (compared to 23 datapoints)	100.825	80.358	20.467	121.292

Table 21: Rash (fixed effects) – notes

- Dichotomous synchronic (binomial; logit link); fixed effects
- 50000 burn-ins; 10000 recorded iterations

L.1.5 Nausea / vomiting (≥1 event)



Size of nodes is proportional to total number of participants randomised to receive the treatment in question across the evidence-base. Width of connecting lines is proportional to number of trial-level comparisons available. Arrowheads indicate direction of effect in pairwise data (a > b denotes a is more effective than b) – filled arrowheads show comparisons where one option is significantly superior (p<0.05); outlined arrowheads show direction of trend where effect does not reach statistical significance.

Figure 13: Nausea/vomiting (fixed effects) – evidence network

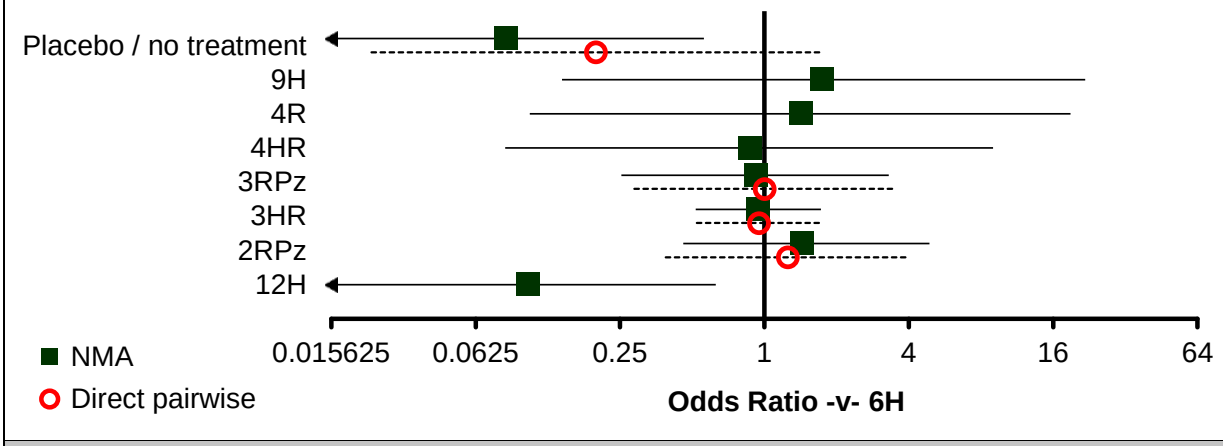
Table 22: Nausea/vomiting (fixed effects) – input data

	6H	12H	2RPz	3HR	3RPz	4HR	4R	9H	Placebo / no treatment
Jimenez-Fuentes et al. (2013)	24/294			23/296					
White et al. (2012)							16/180	19/184	
Menzies et al. (2008)							1/420	2/427	
Spyridis et al. (2007)						7/238		13/232	
Spyridis et al. (2007)				2/220		2/236			
Leung et al. (2003)	6/36		8/40						
Quigley et al. (2001)	5/360				5/360				1/360
Gordin et al. (2000)		1/792	15/791						
Byrd et al. (1977)		2/60							1/60

Table 23: Nausea/vomiting (fixed effects) – relative effectiveness of all pairwise combinations

	6H	12H	2RPz	3HR	3RPz	4HR	4R	9H	Placebo / no treatment
6H		-	1.25 (0.39, 4.03)	0.95 (0.52, 1.72)	1.00 (0.29, 3.48)	-	-	-	0.20 (0.02, 1.70)
12H	0.10 (0.01, 0.63)		15.29 (2.01, 116.03)	-	-	-	-	-	0.49 (0.04, 5.57)
2RPz	1.43 (0.46, 4.88)	13.47 (3.19, 114.80)		-	-	-	-	-	-
3HR	0.95 (0.52, 1.72)	9.13 (1.38, 91.80)	0.66 (0.17, 2.40)		-	0.93 (0.13, 6.67)	-	-	-
3RPz	0.92 (0.25, 3.30)	8.96 (1.06, 109.10)	0.64 (0.11, 3.43)	0.97 (0.23, 4.04)		-	-	-	0.20 (0.02, 1.70)
4HR	0.87 (0.08, 8.98)	8.74 (0.47, 194.50)	0.61 (0.04, 7.93)	0.93 (0.10, 8.74)	0.96 (0.07, 12.84)		-	1.96 (0.77, 5.00)	-
4R	1.42 (0.11, 18.92)	14.22 (0.61, 393.50)	0.99 (0.06, 16.63)	1.50 (0.12, 18.80)	1.55 (0.08, 26.76)	1.62 (0.51, 5.41)		1.23 (0.63, 2.41)	-
9H	1.75 (0.14, 21.75)	17.73 (0.83, 460.40)	1.23 (0.08, 19.00)	1.86 (0.16, 21.37)	1.93 (0.12, 31.44)	2.00 (0.79, 5.48)	1.23 (0.64, 2.45)		-
Placebo / no treatment	0.08 (0.01, 0.56)	0.80 (0.08, 6.19)	0.06 (0.00, 0.42)	0.09 (0.01, 0.65)	0.09 (0.01, 0.72)	0.09 (0.00, 1.86)	0.06 (0.00, 1.48)	0.04 (0.00, 1.09)	

Values given are odds ratios.
The segment below and to the left of the shaded cells is derived from the network meta-analysis, reflecting direct and indirect evidence of treatment effects (row versus column). The point estimate reflects the mean of the posterior distribution, and numbers in parentheses are 95% credible intervals. The segment above and to the right of the shaded cells gives pooled direct evidence (random-effects pairwise meta-analysis), where available (column versus row). Numbers in parentheses are 95% confidence intervals.



Values less than 1 favour the comparator treatment; values greater than 1 favour 6H. Solid error bars are 95% credible intervals; dashed error bars are 95% confidence interval.

Figure 14: Nausea/vomiting (fixed effects) – relative effect of all options versus common comparator

Table 24: Nausea/vomiting (fixed effects) – rankings for each comparator

	Probability best	Median rank (95%CrI)
Placebo / no treatment	0.566	1 (1, 4)
12H	0.392	2 (1, 5)
4HR	0.027	5 (1, 8)
4R	0.011	7 (2, 9)
3RPz	0.002	5 (3, 9)
9H	0.001	8 (3, 9)
6H	0.000	5 (3, 9)
3HR	0.000	5 (3, 9)
2RPz	0.000	7 (3, 9)

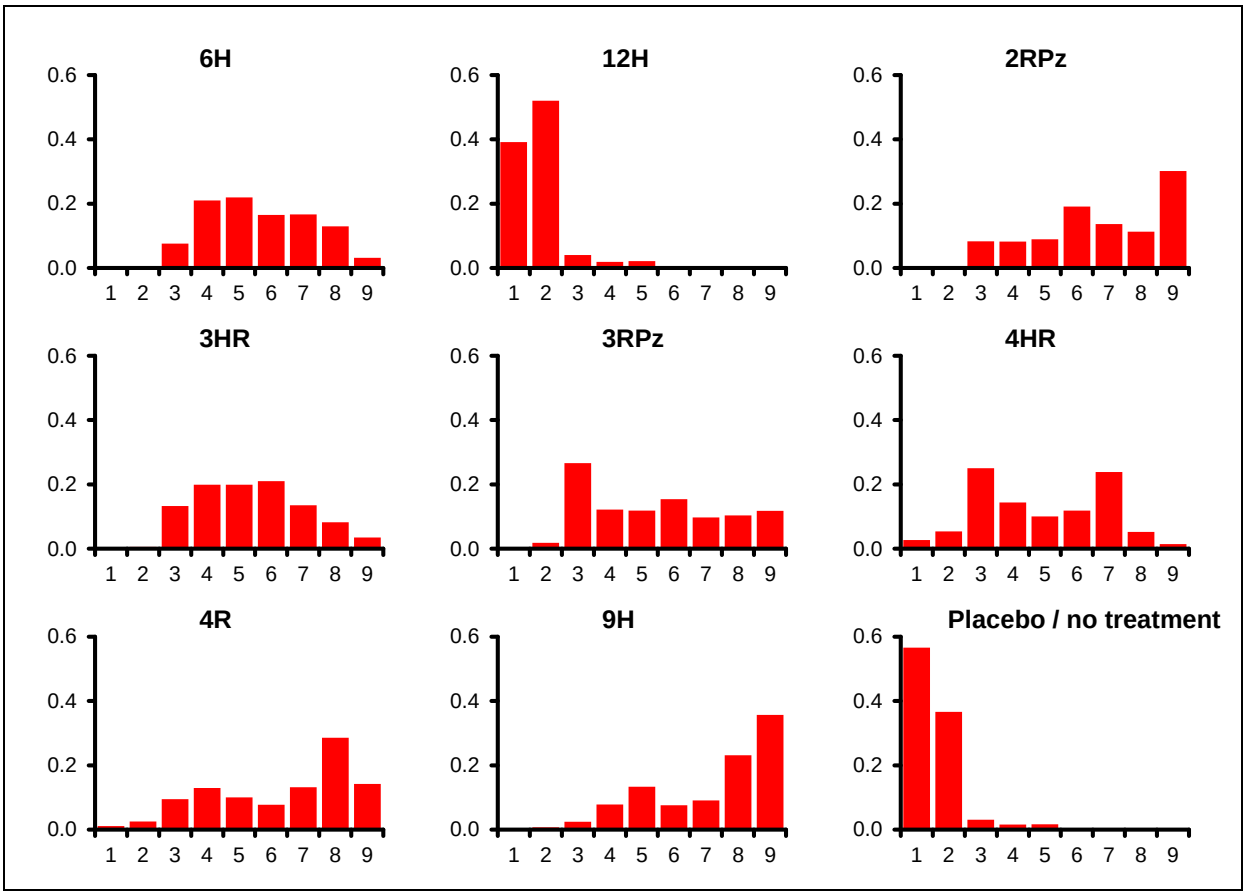


Figure 15: Nausea/vomiting (fixed effects) – rank probability histograms

Table 25: Nausea/vomiting (fixed effects) – model fit statistics

Residual deviance	Dbar	Dhat	pD	DIC
18.41 (compared to 19 datapoints)	82.635	66.111	16.524	99.159

Table 26: Nausea/vomiting (fixed effects) – notes

- Dichotomous synchronic (binomial; logit link); fixed effects
- 50000 burn-ins; 10000 recorded iterations (thinned from 200000)

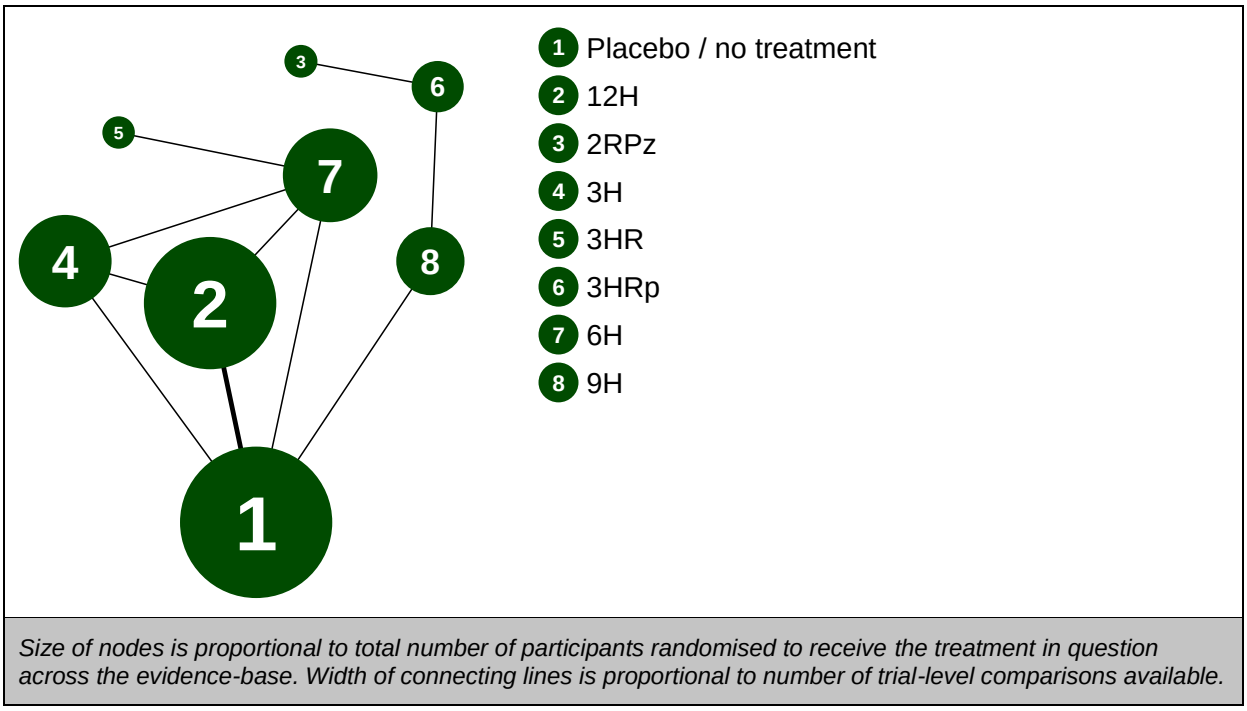
L.2 Restricted subgroup

Excludes studies that were conducted in countries with TB incidence of greater than 50 per 100,000 and those that were conducted only in people with HIV.

Table 27: Model selection for NMAs – restricted subgroup

Outcome	Model	DIC	Total residual deviance		SD	Preferred model
Active TB	FE	84.507	13.83	(14 datapoints)	–	FE
	RE	85.016	13.94		0.549 (95%CI: 0.022, 1.875)	
Adherence	FE	164.307	28.7	(20 datapoints)	–	RE
	RE	158.414	20.62		1.069 (95%CI: 0.176, 1.941)	
Hepatotoxicity	FE	98.809	16.08	(16 datapoints)	–	FE
	RE	99.997	16.03		0.622 (95%CI: 0.043, 1.853)	
Rash	no analysis possible due to disconnected networks					
Nausea / vomiting	FE	63.927	11.69	(12 datapoints)	–	FE
	RE	64.672	12.04		0.818 (95%CI: 0.035, 1.920)	

L.2.1 Development of active TB



Size of nodes is proportional to total number of participants randomised to receive the treatment in question across the evidence-base. Width of connecting lines is proportional to number of trial-level comparisons available.

Figure 16: Development of active TB (fixed effects) – evidence network

Table 28: Development of active TB (fixed effects) – input data

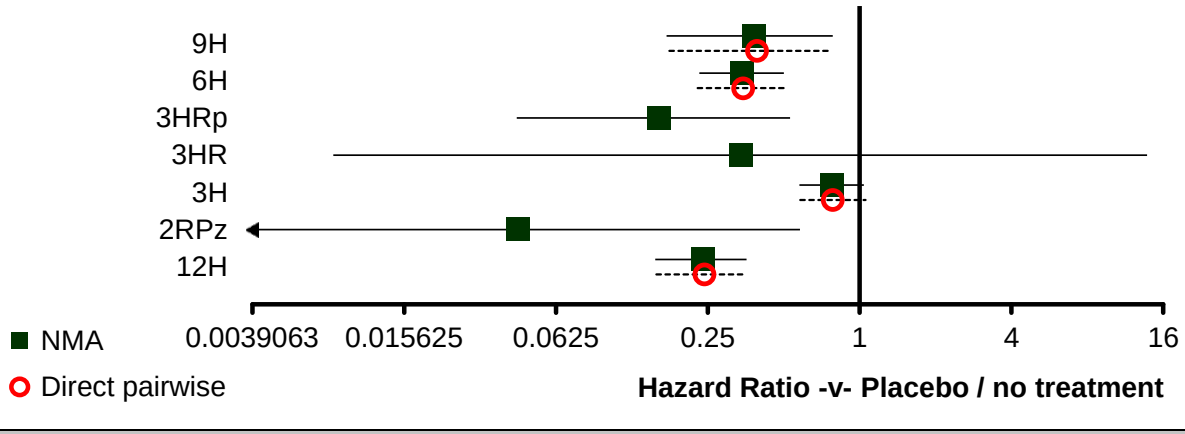
	Placebo / no treatment	12H	2RPz	3H	3HR	3HRp	6H	9H
Jimenez-Fuentes et al. (2013) - 5.00yr[a]					1/296		1/294	
Sterling et al. (2011) - 2.75yr[b]						7/10327		15/9619
Schechter et al. (2006) - 2.72yr[b]			1/522			3/564		
Anon. (1982) - 5.00yr[b]	97/33916	24/33333		76/33628			34/34000	
Debre et al. (1973) - 10.00yr[b]	24/9820							10/10372
Ferebee et al. (1963) - 3.45yr[b]	24/22523	5/22242						

(a) dichotomous data – proportion of participants developing active TB over duration of follow-up
(b) rate data – number of cases of active TB per patient-year

Table 29: Development of active TB (fixed effects) – relative effectiveness of all pairwise combinations

	Placebo / no treatment	12H	2RPz	3H	3HR	3HRp	6H	9H
Placebo / no treatment		N/A	N/A	N/A	N/A	N/A	N/A	N/A
12H	0.24 (0.15, 0.36)		N/A	N/A	N/A	N/A	N/A	N/A
2RPz	0.04 (0.00, 0.58)	0.19 (0.01, 2.57)		N/A	N/A	N/A	N/A	N/A
3H	0.78 (0.58, 1.04)	3.25 (2.11, 5.12)	17.64 (1.29, 642.40)		N/A	N/A	N/A	N/A
3HR	0.34 (0.01, 13.78)	1.43 (0.03, 57.79)	8.15 (0.09, 1274.00)	0.43 (0.01, 17.65)		N/A	N/A	N/A
3HRp	0.16 (0.04, 0.53)	0.66 (0.17, 2.37)	3.44 (0.39, 107.40)	0.20 (0.05, 0.69)	0.46 (0.01, 22.22)		N/A	N/A
6H	0.34 (0.23, 0.50)	1.43 (0.87, 2.38)	7.73 (0.57, 285.60)	0.44 (0.29, 0.66)	1.01 (0.03, 42.11)	2.16 (0.62, 8.31)		N/A
9H	0.38 (0.17, 0.78)	1.60 (0.66, 3.70)	8.37 (0.76, 292.70)	0.49 (0.21, 1.07)	1.12 (0.03, 47.56)	2.39 (0.97, 6.64)	1.11 (0.45, 2.47)	

Values given are hazard ratios.
The segment below and to the left of the shaded diagonal is derived from the network meta-analysis, reflecting direct and indirect evidence of treatment effects (row versus column). The point estimate reflects the mean of the posterior distribution, and numbers in parentheses are 95% credible intervals. Because it is not easily possible to pool dichotomous and rate data and derive analogous estimates of hazard ratios from a single frequentist analysis of direct data only, the segment above and to the right of the shaded diagonal is left blank



Values less than 1 favour the comparator treatment; values greater than 1 favour placebo. Error bars are 95% credible intervals. Direct pairwise estimates are drawn from inconsistency model.

Figure 17: Development of active TB (fixed effects) – relative effect of all options versus common comparator

Table 30: Development of active TB (fixed effects) – rankings for each comparator

	Probability best	Median rank (95%CrI)
2RPz	0.730	1 (1, 6)
3HR	0.153	5 (1, 8)
3HRp	0.077	2 (1, 5)
12H	0.038	3 (1, 5)
6H	0.002	5 (3, 6)
9H	0.000	5 (3, 6)
3H	0.000	7 (6, 8)
Placebo / no treatment	0.000	8 (7, 8)

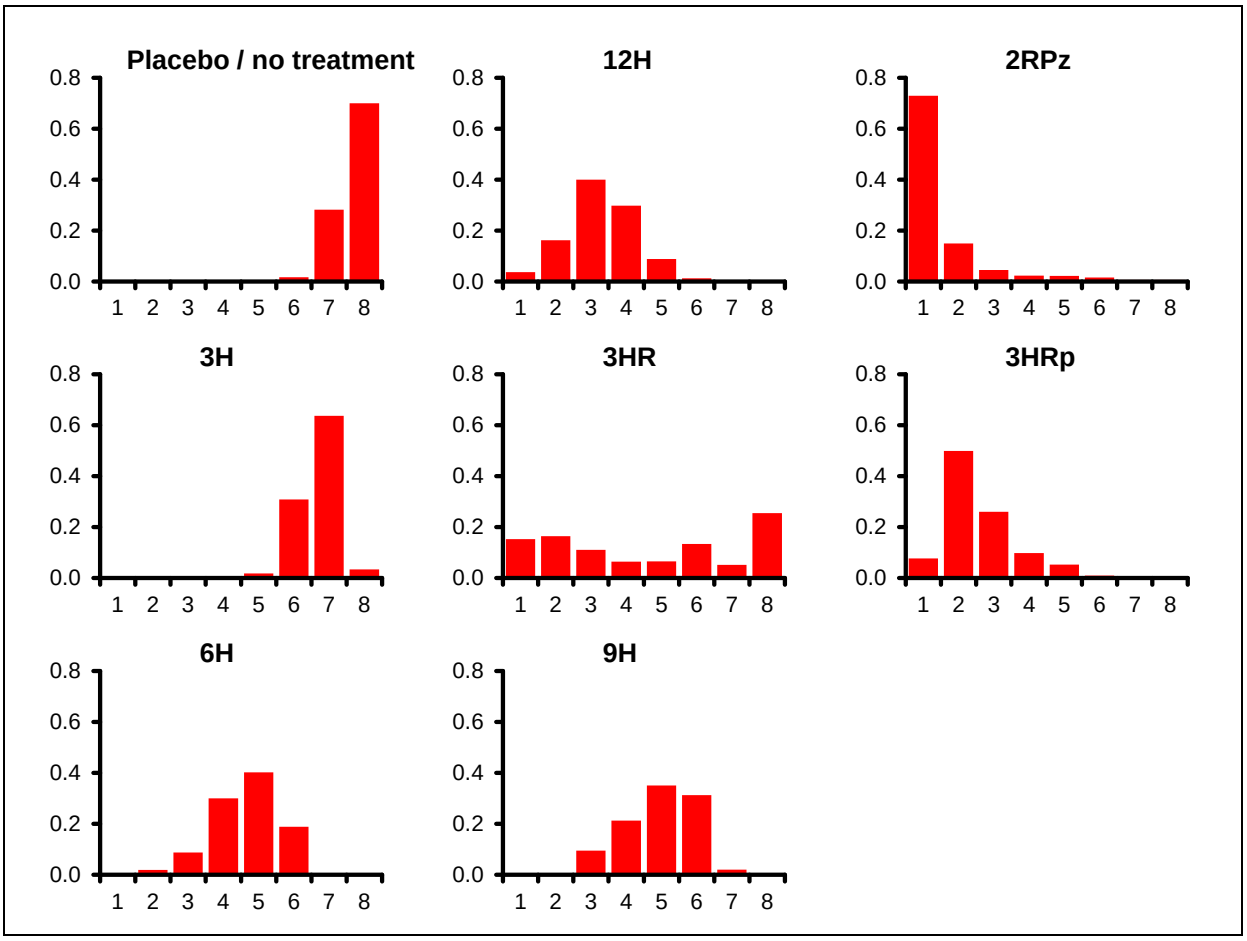


Figure 18: Development of active TB (fixed effects) – rank probability histograms

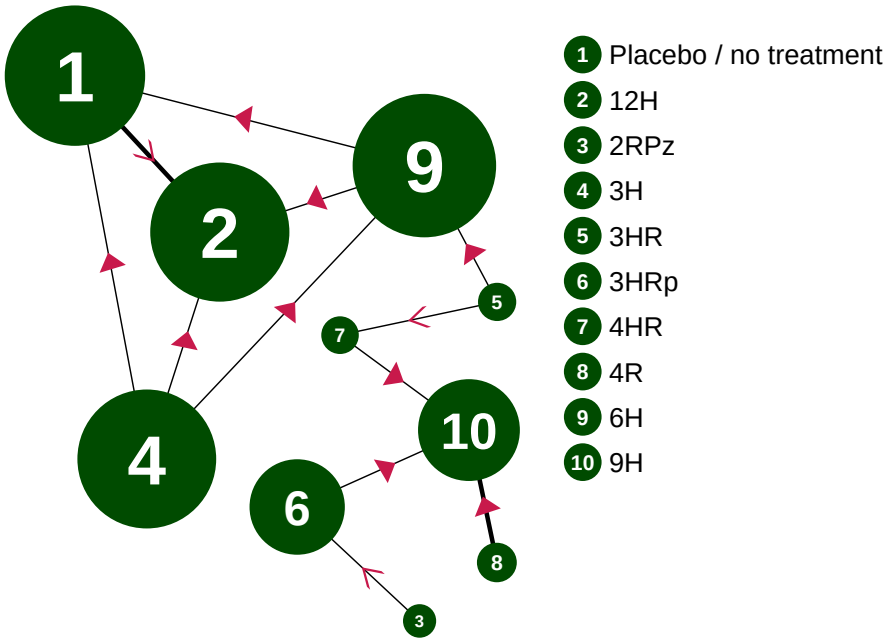
Table 31: Development of active TB (fixed effects) – model fit statistics

Residual deviance	Dbar	Dhat	pD	DIC
13.83 (compared to 14 datapoints)	6.337	4.562	1.775	8.112

Table 32: Development of active TB (fixed effects) – notes

- Count (Poisson; log link); fixed effects
- 50000 burn-ins; 10000 recorded iterations

L.2.2 Adherence



Size of nodes is proportional to total number of participants randomised to receive the treatment in question across the evidence-base. Width of connecting lines is proportional to number of trial-level comparisons available. Arrowheads indicate direction of effect in pairwise data (a > b denotes a is more effective than b) – filled arrowheads show comparisons where one option is significantly superior (p<0.05); outlined arrowheads show direction of trend where effect does not reach statistical significance.

Figure 19: Adherence (random effects) – evidence network

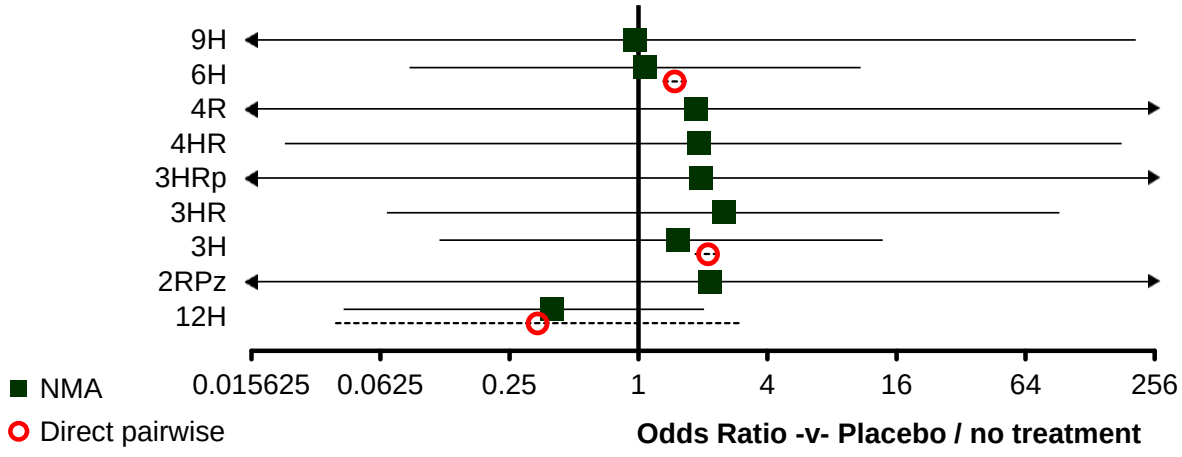
Table 33: Adherence (random effects) – input data

	Placebo / no treatment	12H	2RPz	3H	3HR	3HRp	4HR	4R	6H	9H
Jimenez-Fuentes et al. (2013)					213/296				154/294	
White et al. (2012)								60/180		47/184
Sterling et al. (2011)						3273/3986				2585/3745
Menzies et al. (2008)								328/420		255/427
Spyridis et al. (2007)							220/238			200/232
Spyridis et al. (2007)					209/220		221/236			
Schechter et al. (2006)			181/193			192/206				
Anon. (1982)	6291/6990	6089/6919		6608/6956					6477/6965	
Byrd et al. (1977)	59/60	50/60								

Table 34: Adherence (random effects) – relative effectiveness of all pairwise combinations

	Placebo / no treatment	12H	2RPz	3H	3HR	3HRp	4HR	4R	6H	9H
Placebo / no treatment		0.34 (0.04, 2.94)	-	2.11 (1.85, 2.41)	-	-	-	-	1.47 (1.31, 1.66)	-
12H	0.40 (0.04, 2.02)		-	2.59 (2.27, 2.95)	-	-	-	-	1.81 (1.61, 2.03)	-
2RPz	2.16 (0.00, 1610.00)	5.17 (0.01, 4929.00)		-	-	0.91 (0.41, 2.02)	-	-	-	-
3H	1.53 (0.12, 13.79)	3.60 (0.40, 47.39)	0.70 (0.00, 315.50)		-	-	-	-	0.70 (0.61, 0.81)	-
3HR	2.52 (0.07, 92.18)	5.85 (0.23, 295.30)	1.13 (0.01, 170.80)	1.65 (0.05, 73.87)		-	0.78 (0.35, 1.73)	-	0.43 (0.30, 0.60)	-
3HRp	1.97 (0.01, 798.90)	4.70 (0.02, 2368.00)	0.90 (0.07, 12.05)	1.31 (0.01, 631.60)	0.80 (0.01, 78.72)		-	-	-	0.49 (0.44, 0.54)
4HR	1.92 (0.02, 179.70)	4.52 (0.08, 567.10)	0.86 (0.01, 64.06)	1.25 (0.02, 137.20)	0.78 (0.06, 11.29)	0.95 (0.02, 29.76)		-	-	0.51 (0.28, 0.94)
4R	1.87 (0.01, 533.50)	4.46 (0.03, 1726.00)	0.83 (0.01, 44.32)	1.20 (0.01, 401.20)	0.75 (0.01, 48.52)	0.91 (0.04, 20.12)	0.97 (0.04, 22.95)		-	0.52 (0.32, 0.84)
6H	1.08 (0.09, 10.89)	2.54 (0.29, 36.62)	0.49 (0.00, 134.50)	0.70 (0.06, 9.63)	0.43 (0.03, 5.25)	0.54 (0.00, 80.56)	0.55 (0.01, 19.69)	0.58 (0.00, 63.62)		-
9H	0.97 (0.01, 209.00)	2.34 (0.02, 639.00)	0.43 (0.01, 15.13)	0.64 (0.00, 151.80)	0.39 (0.01, 16.98)	0.48 (0.04, 5.58)	0.51 (0.04, 6.92)	0.52 (0.09, 3.30)	0.91 (0.01, 107.80)	

Values given are odds ratios.
The segment below and to the left of the shaded cells is derived from the network meta-analysis, reflecting direct and indirect evidence of treatment effects (row versus column). The point estimate reflects the mean of the posterior distribution, and numbers in parentheses are 95% credible intervals. The segment above and to the right of the shaded cells gives pooled direct evidence (random-effects pairwise meta-analysis), where available (column versus row). Numbers in parentheses are 95% confidence intervals.



Values less than 1 favour placebo; values greater than 1 favour the comparator treatment. Solid error bars are 95% credible intervals; dashed error bars are 95% confidence interval.

Figure 20: Adherence (random effects) – relative effect of all options versus common comparator

Table 35: Adherence (random effects) – rankings for each comparator

	Probability best	Median rank (95%CrI)
2RPz	0.250	4 (1, 10)
3HR	0.200	4 (1, 9)
3H	0.138	5 (1, 10)
4R	0.123	4 (1, 10)
3HRp	0.109	4 (1, 10)
4HR	0.079	5 (1, 10)
Placebo / no treatment	0.067	7 (1, 10)
6H	0.025	7 (2, 10)
9H	0.006	7 (2, 10)
12H	0.004	10 (3, 10)

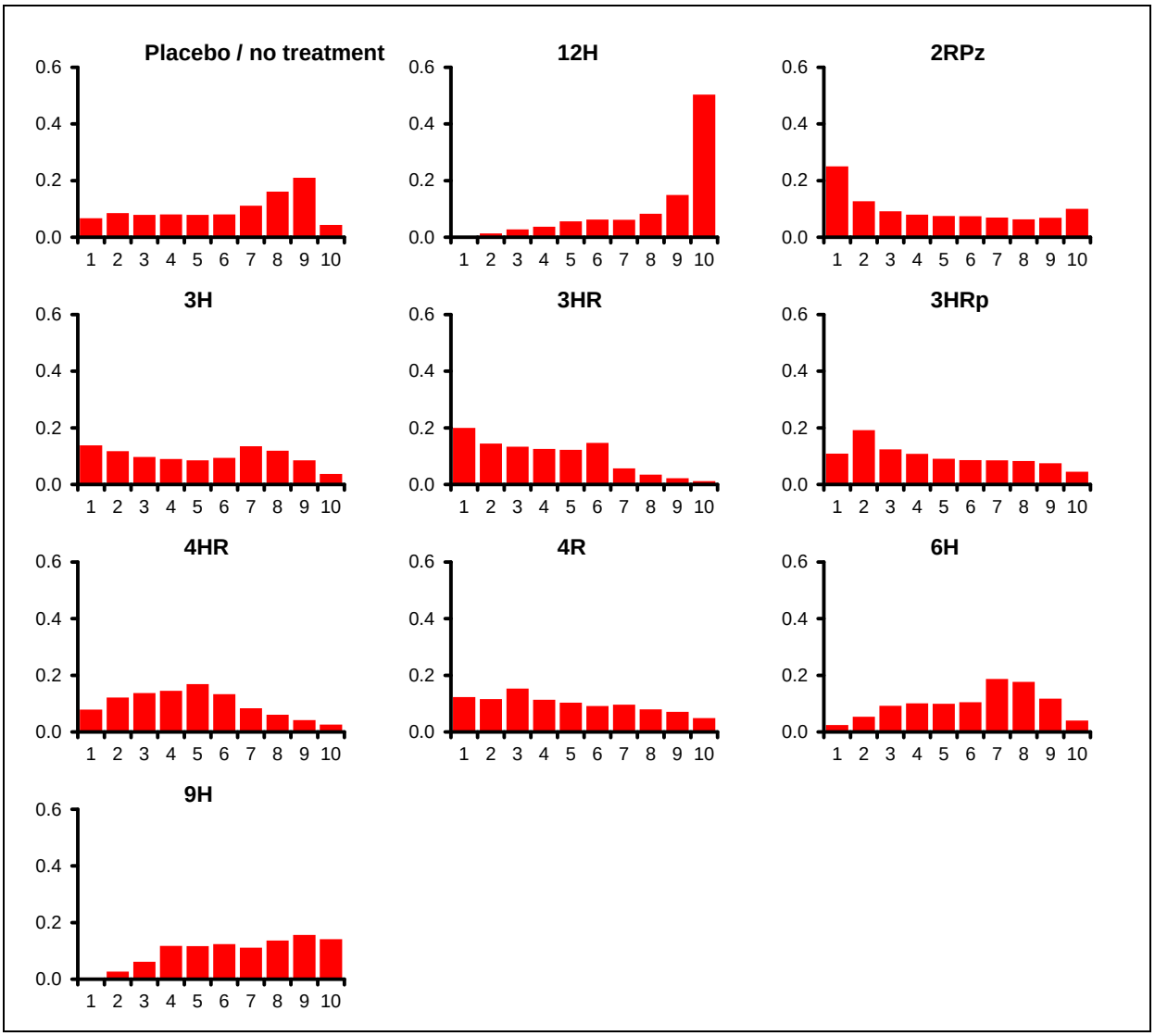


Figure 21: Adherence (random effects) – rank probability histograms

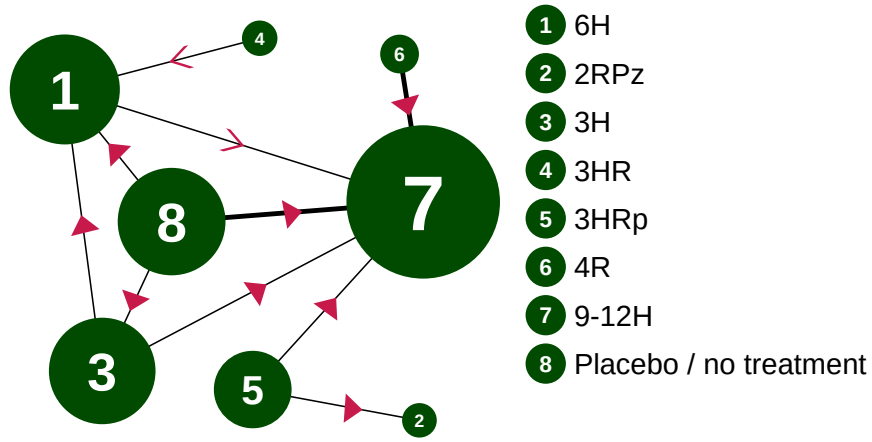
Table 36: Adherence (random effects) – model fit statistics

Residual deviance	Dbar	Dhat	pD	DIC	tau
20.62 (compared to 20 datapoints)	138.402	118.39	20.012	158.414	1.069 (95%CrI: 0.176, 1.941)

Table 37: Adherence (random effects) – notes

- Dichotomous synchronic (binomial; logit link); random effects
- Prior distribution for between-study heterogeneity: uniform (Min=0; Max=2)
- 50000 burn-ins; 10000 recorded iterations

L.2.3 Hepatotoxicity (≥1 event)



Size of nodes is proportional to total number of participants randomised to receive the treatment in question across the evidence-base. Width of connecting lines is proportional to number of trial-level comparisons available. Arrowheads indicate direction of effect in pairwise data (a > b denotes a is more effective than b) – filled arrowheads show comparisons where one option is significantly superior (p<0.05); outlined arrowheads show direction of trend where effect does not reach statistical significance.

Figure 22: Hepatotoxicity (fixed effects) – evidence network

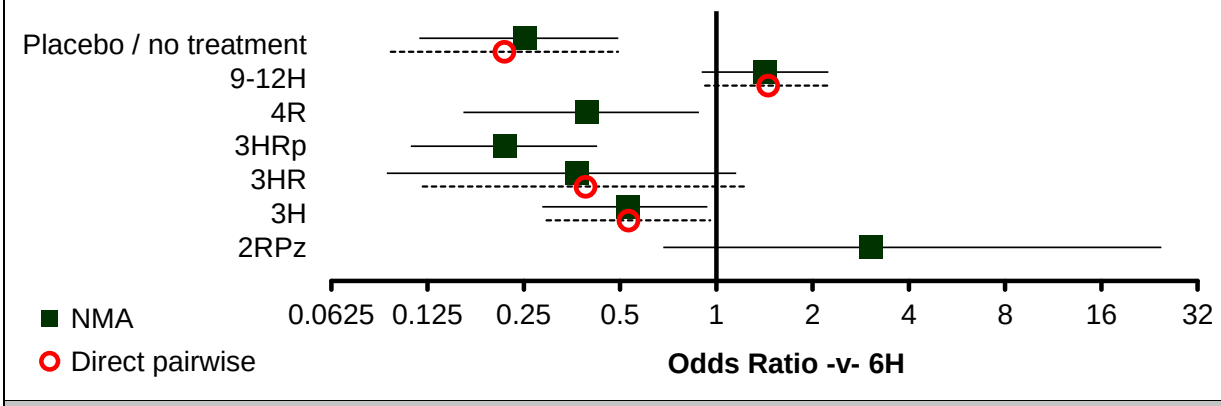
Table 38: Hepatotoxicity (fixed effects) – input data

	6H	2RPz	3H	3HR	3HRp	4R	9-12H	Placebo / no treatment
Jimenez-Fuentes et al. (2013)	10/294			4/296				
White et al. (2012)						8/180	21/184	
Sterling et al. (2011)					18/4040		103/3759	
Menzies et al. (2008)						3/420	16/427	
Schechter et al. (2006)		20/193			2/206			
Anon. (1982)	32/6965		17/6956				46/6919	7/6990
Byrd et al. (1977)							11/60	4/60

Table 39: Hepatotoxicity (fixed effects) – relative effectiveness of all pairwise combinations

	6H	2RPz	3H	3HR	3HRp	4R	9-12H	Placebo / no treatment
6H		-	0.53 (0.29, 0.96)	0.39 (0.12, 1.25)	-	-	1.45 (0.92, 2.28)	0.22 (0.10, 0.49)
2RPz	3.06 (0.68, 24.64)		-	-	0.08 (0.02, 0.37)	-	-	-
3H	0.53 (0.29, 0.94)	0.17 (0.02, 0.79)		-	-	-	2.73 (1.56, 4.77)	0.41 (0.17, 0.99)
3HR	0.37 (0.09, 1.15)	0.12 (0.01, 0.79)	0.69 (0.16, 2.53)		-	-	-	-
3HRp	0.22 (0.11, 0.42)	0.07 (0.01, 0.27)	0.42 (0.19, 0.89)	0.60 (0.16, 2.68)		-	6.30 (3.81, 10.41)	-
4R	0.39 (0.16, 0.88)	0.13 (0.01, 0.64)	0.75 (0.30, 1.83)	1.08 (0.25, 5.12)	1.79 (0.75, 4.21)		3.53 (1.77, 7.05)	-
9-12H	1.42 (0.90, 2.24)	0.47 (0.06, 1.95)	2.68 (1.57, 4.86)	3.88 (1.13, 15.99)	6.43 (4.00, 11.07)	3.59 (1.85, 7.61)		0.18 (0.09, 0.35)
Placebo / no treatment	0.25 (0.12, 0.49)	0.08 (0.01, 0.40)	0.48 (0.21, 1.03)	0.68 (0.17, 3.08)	1.15 (0.48, 2.62)	0.64 (0.24, 1.71)	0.18 (0.09, 0.33)	

Values given are odds ratios.
The segment below and to the left of the shaded cells is derived from the network meta-analysis, reflecting direct and indirect evidence of treatment effects (row versus column). The point estimate reflects the mean of the posterior distribution, and numbers in parentheses are 95% credible intervals. The segment above and to the right of the shaded cells gives pooled direct evidence (random-effects pairwise meta-analysis), where available (column versus row). Numbers in parentheses are 95% confidence intervals.



Values less than 1 favour the comparator treatment; values greater than 1 favour 6H. Solid error bars are 95% credible intervals; dashed error bars are 95% confidence interval.

Figure 23: Hepatotoxicity (fixed effects) – relative effect of all options versus common comparator

Table 40: Hepatotoxicity (fixed effects) – rankings for each comparator

	Probability best	Median rank (95%CrI)
3HRp	0.477	2 (1, 4)
Placebo / no treatment	0.290	2 (1, 4)
3HR	0.187	3 (1, 6)
4R	0.045	4 (1, 5)
3H	0.002	5 (3, 5)
6H	0.000	6 (5, 7)
9-12H	0.000	7 (6, 8)
2RPz	0.000	8 (6, 8)

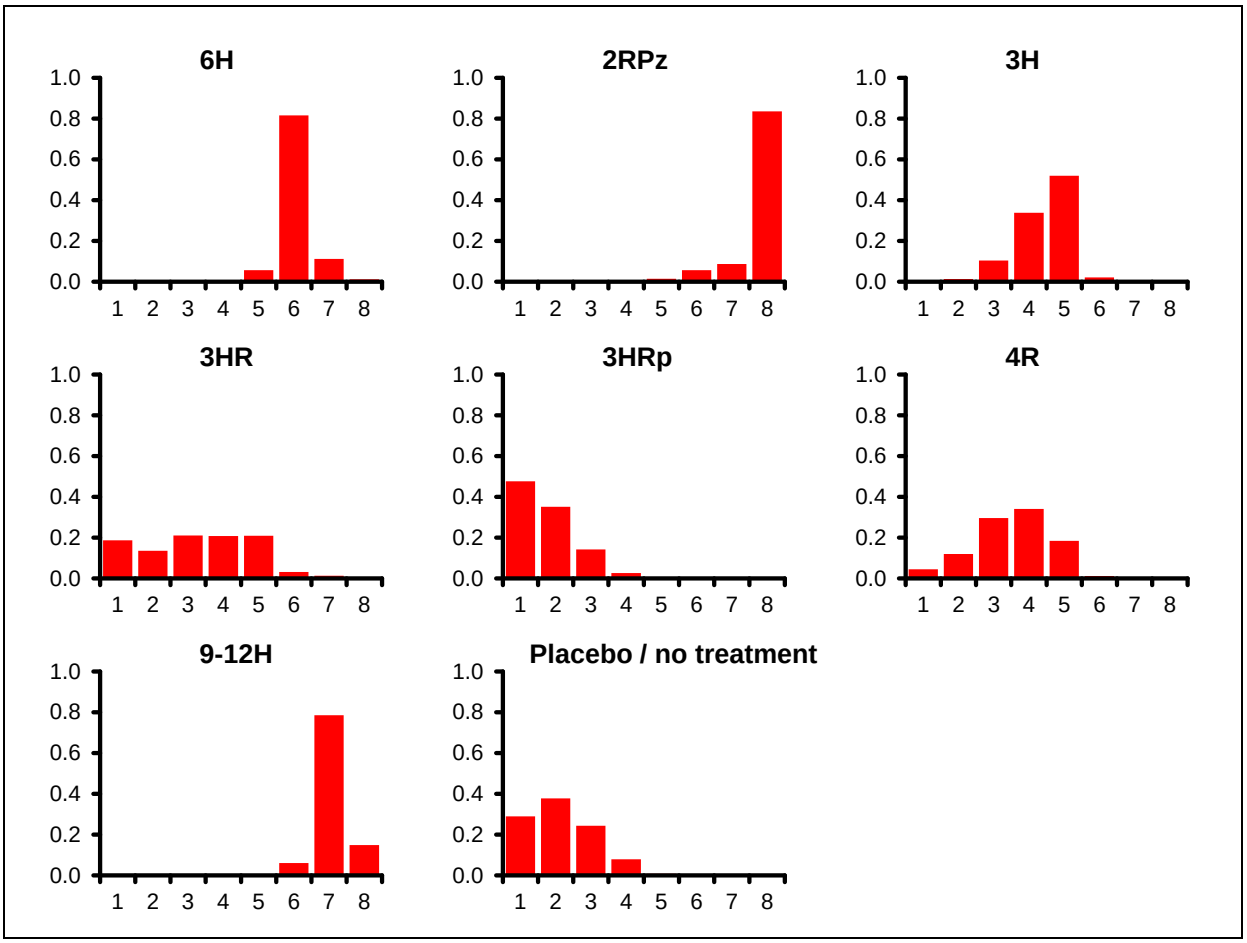


Figure 24: Hepatotoxicity (fixed effects) – rank probability histograms

Table 41: Hepatotoxicity (fixed effects) – model fit statistics

Residual deviance	Dbar	Dhat	pD	DIC
16.08 (compared to 16 datapoints)	84.903	70.998	13.906	98.809

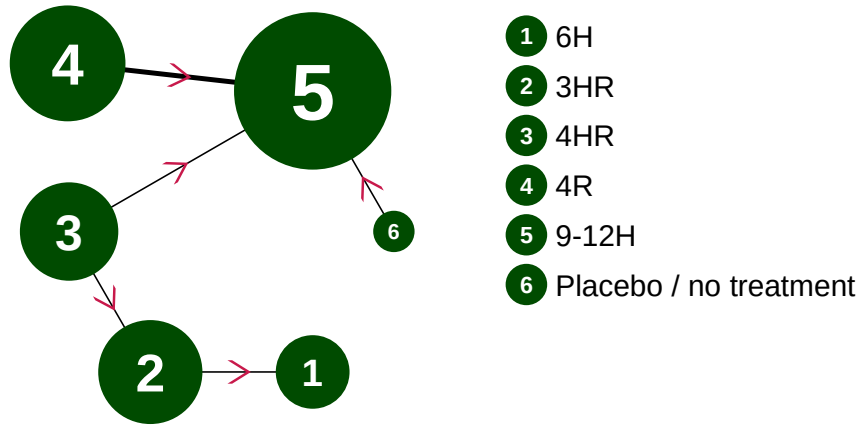
Table 42: Hepatotoxicity (fixed effects) – notes

- Dichotomous synchronic (binomial; logit link); fixed effects
- 50000 burn-ins; 10000 recorded iterations

L.2.4 Rash (≥1 event)

No network possible

L.2.5 Nausea/vomiting (≥1 event)



Size of nodes is proportional to total number of participants randomised to receive the treatment in question across the evidence-base. Width of connecting lines is proportional to number of trial-level comparisons available. Arrowheads indicate direction of effect in pairwise data (a > b denotes a is more effective than b) – filled arrowheads show comparisons where one option is significantly superior (p<0.05); outlined arrowheads show direction of trend where effect does not reach statistical significance.

Figure 25: Nausea/vomiting (fixed effects) – evidence network

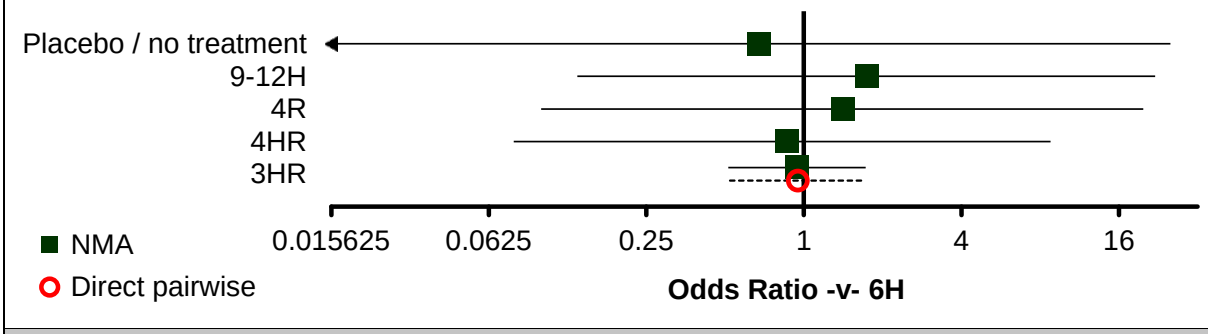
Table 43: Nausea/vomiting (fixed effects) – input data

	6H	3HR	4HR	4R	9-12H	Placebo / no treatment
Jimenez-Fuentes et al. (2013)	24/294	23/296				
White et al. (2012)				16/180	19/184	
Menzies et al. (2008)				1/420	2/427	
Spyridis et al. (2007)			7/238		13/232	
Spyridis et al. (2007)		2/220	2/236			
Byrd et al. (1977)					2/60	1/60

Table 44: Nausea/vomiting (fixed effects) – relative effectiveness of all pairwise combinations

	6H	3HR	4HR	4R	9-12H	Placebo / no treatment
6H		0.95 (0.52, 1.72)	-	-	-	-
3HR	0.94 (0.51, 1.72)		0.93 (0.13, 6.67)	-	-	-
4HR	0.86 (0.08, 8.78)	0.91 (0.09, 8.42)		-	1.96 (0.77, 5.00)	-
4R	1.41 (0.10, 19.85)	1.50 (0.11, 19.24)	1.66 (0.52, 5.45)		1.23 (0.63, 2.41)	-
9-12H	1.75 (0.14, 21.99)	1.86 (0.15, 21.67)	2.03 (0.80, 5.54)	1.23 (0.62, 2.43)		0.49 (0.04, 5.57)
Placebo / no treatment	0.68 (0.01, 25.19)	0.72 (0.01, 25.88)	0.81 (0.02, 13.28)	0.50 (0.01, 7.22)	0.41 (0.01, 5.39)	

Values given are odds ratios.
The segment below and to the left of the shaded cells is derived from the network meta-analysis, reflecting direct and indirect evidence of treatment effects (row versus column). The point estimate reflects the mean of the posterior distribution, and numbers in parentheses are 95% credible intervals. The segment above and to the right of the shaded cells gives pooled direct evidence (random-effects pairwise meta-analysis), where available (column versus row). Numbers in parentheses are 95% confidence intervals.



Values less than 1 favour the comparator treatment; values greater than 1 favour 6H. Solid error bars are 95% credible intervals; dashed error bars are 95% confidence interval.

Figure 26: Nausea/vomiting (fixed effects) – relative effect of all options versus common comparator

Table 45: Nausea/vomiting (fixed effects) – rankings for each comparator

	Probability best	Median rank (95%CrI)
6H	0.152	3 (1, 6)
3HR	0.170	3 (1, 6)
4HR	0.189	3 (1, 5)
4R	0.048	4 (1, 6)
9-12H	0.002	5 (2, 6)
Placebo / no treatment	0.439	2 (1, 6)

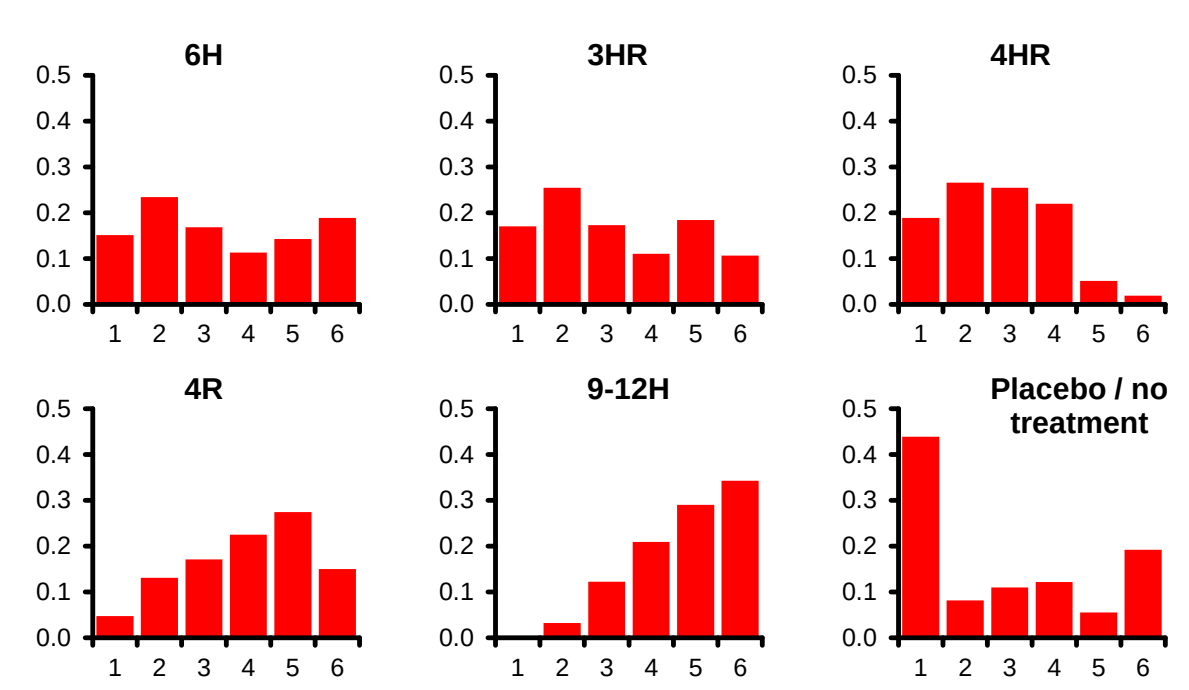


Figure 27: Nausea/vomiting (fixed effects) – rank probability histograms

Table 46: Nausea/vomiting (fixed effects) – model fit statistics

Residual deviance	Dbar	Dhat	pD	DIC
11.69 (compared to 12 datapoints)	53.25	42.573	10.677	63.927

Table 47: Nausea/vomiting (fixed effects) – notes

- Dichotomous synchronic (binomial; logit link); fixed effects
- 50000 burn-ins; 10000 recorded iterations