Appendix I: Imperial College – LTBI treatment report

Imperial College
London
Consultants

National Institute for Health and Care Excellence (NICE)

What is the cost-effectiveness of latent tuberculosis infection (LTBI) treatment with different regimens?

April 2015

The National Institute for Health and Care Excellence (NICE) has been asked to produce a guideline on treating latent tuberculosis infection. What follows is the cost effectiveness analysis developed to support the guideline development group (GDG) in coming to recommendations. This analysis has been conducted according to NICE methods outlined in the Guide to the methods of technology appraisals (2008) and the Methods for the development of NICE public health guidance (2009). Thus it follows the NICE reference case (the framework NICE requests all cost effectiveness analysis to follow) in the methodology utilised.

Disclaimer

Imperial College London has taken reasonable professional care in the preparing this report under the direction of NICE. Although reasonable efforts have been made in seeking evidence to inform this work, Imperial College London cannot guarantee completeness or accuracy or accept responsibility for exceptional errors or omissions.

Intellectual property and confidentiality

This report uses information which is the intellectual property of Imperial College London and information which is confidential to our relationship with the National Institute for Health and Care Excellence.

Authors

Dr Peter White, Imperial College London

Dr Mark Jit, London School of Hygiene and Tropical Medicine

Acknowledgments

We would like to thank the team at NICE, particularly Gabriel Rogers and Chris Gibbons, for their guidance in the conduct of the analysis and writing of this report, along with the GDG, who provided expert input, particularly Andrew Hayward, Ibrahim Abubakar, Marc Lipman, Michael Eisenhut, and Christine Bell. We thank Gabriel Rogers of NICE for provision of parameters and PSA samples relating to progression rates, regimens, efficacy and adverse-event frequencies.

Declaration of authors' other relevant interests

Peter White and Mark Jit have received funding from the Department of Health and the National Institute for Health Research (NIHR) to undertake TB modelling work. Peter White has received funding from Otsuka for retrospective analysis of treatment of MDR active TB in eastern Europe.

1. Description of decision problem

1.1 Population

The patient population considered was individuals who have been diagnosed with latent TB infection (LTBI). Four age-groups were considered (17-34 years, 35-50 years, 51-65 years, 66-86 years), because the incidence of adverse events due to treatment is age-dependent, and the lifetime risk of progressing from LTBI to active TB declines with age, due to shorter remaining life-expectancy. Age-groupings were determined by the availability of parameter estimates from the network meta-analysis of treatment regimens.

1.2 Intervention

The interventions considered are different treatment regimens for LTBI, when diagnosed in individuals in different age groups.

1.3 Comparator(s)

The comparator is not treating LTBI.

1.4 Outcome(s)

The beneficial health outcome of LTBI treatment is reduced incidence of active TB in the treated-patient cohort. This benefits the individual patient, including in averting the risk of mortality due to active TB, as well as averting the need for treatment. In addition, there are population-level benefits, as averting active TB averts transmission to others, averting the need to identify them, and treat them for LTBI or active TB. However, LTBI treatment can cause adverse events, so there are disutilities for some patients treated for LTBI. Treating LTBI and the adverse events arising from that treatment both incur costs, whilst averting active TB averts costs of treating the active

TB, and tracing, testing and, where applicable, treating the contacts of those cases of active TB.

In line with the NICE reference case a cost utility analysis was used to analyse cost effectiveness of LTBI treatment.

1.5 Main resource use to the NHS

Administering LTBI treatment, monitoring patients on treatment, treating adverse events arising from LTBI treatment, treating active TB, and investigating contacts of active TB cases are routine activities, whose costs have been considered in the analysis.

1.6 Limitations of analysis

The main limitations of the work are due to gaps in available evidence. Most trials of LTBI treatment have occurred in patient groups or settings that are different from those who would potentially be treated in England. In addition, limitations in our understanding of TB transmission patterns in the UK led us to follow previous NICE guidance (National Collaborating Centre for Chronic Conditions, CG117, 2011) in limiting the consideration of transmission of TB to secondary cases, and not to consider further 'rounds' of transmission, as this is a very complex calculation which is beyond the scope of this work. This means that some of the population-level benefit of LTBI treatment has not been captured, although it is likely to be small, as most TB in the UK is imported, indicating that there is relatively little sustained transmission in the general population. We assumed that the patients studied in the trials considered in the network meta-analysis were representative of patients considered for treatment as consideration of screening practices was beyond the scope of our analysis.

2. Modelling

2.1 Overview

A deterministic cohort model was used to evaluate the cost-effectiveness of LTBI treatment, taking account of costs of LTBI treatment and adverse events arising because of it, disutilities of those adverse events, costs and disutilities (including mortality) of active TB, transmission of infection from cases of active TB, as well as the costs of tracing, testing, and, where applicable, treatment, of contacts of active TB cases. The time-horizon was the lifetime of the patient cohort and the perspective taken was that of the NHS.

2.2 Population

The patient population considered was individuals who have been diagnosed with latent TB infection (LTBI). Four age-groups were considered (17-34 years, 35-50 years, 51-65 years, 66-86 years), because the incidence of adverse events due to treatment is age-dependent, and the lifetime risk of progressing from LTBI to active TB declines with age, due to shorter remaining life-expectancy. The age-groups used were determined by the parameter estimates supplied to us by NICE. At the start of the simulation, there is a uniform age-distribution within each age-group; age-related parameters take account of the changing age-composition over time of each age-group.

2.3 Model structure & assumptions

The model is a cohort model considering 10,000 individuals diagnosed with LTBI. Individuals are either treated for LTBI or not treated, in the first year. The regimens considered were specified by NICE are were 3H (3 months of treatment with isoniazid), 6H (6 months, isoniazid), 9H (9 months, isoniazid), 12H (12 months, isoniazid), 2RPz (2 months, rifampicin and pyrazinamide), 3HR (3 months, isoniazid and rifampicin).

The benefits of treating LTBI are a reduction in the rate of progression to active TB, leading to a reduction in morbidity, mortality and costs of treatment of both the patient cohort and their contacts who might otherwise become infected from the active-TB cases, and the costs contact tracing from active TB costs. However, in addition to the cost of LTBI treatment, for some patients LTBI treatment incurs adverse events, causing morbidity, and even potential mortality, as well as costs of treatment.

The model structure and its parameterisation was presented on several occasions to the GDG for approval.

The model proceeds in annual time-steps and is run for the lifetime of the patient cohort being considered. Discounting is applied (to costs and QALYs) at 3.5% per annum. In each model year, the following events can occur: individuals progress to active TB (and might die of it), die of non-TB causes, or survive. In the model no-one survives to reach 102 years. Individuals who have been treated for LTBI have their rate of progression to active TB reduced according to the efficacy of treatment (efficacy is expressed as the proportionate reduction in rate of progression).

When a case of active TB occurs, affected individuals incur morbidity, a proportion suffers mortality (specified by the case-fatality ratio) and the health service incurs a cost of treating the index case, and investigating contacts and treating them if appropriate. Secondary cases of TB arise from these (primary) cases, due to transmission; we assume that each primary case results in 0.2 (range 0.1 – 0.3) secondary cases as suggested by NICE. Following previous NICE guidance (National Collaborating Centre for Chronic Conditions, CG117, 2011), secondary cases are assumed to occur the year after the corresponding primary case.

We assume that treatment options remain unchanged, and that current practice with regard to management of cases of active TB, and their contacts where appropriate, remain unchanged through time.

The total QALYs accrued by the patient cohort, and costs incurred for LTBI treatment for each regimen (where given) and for management of active TB cases, are calculated, along with costs and QALY losses associated with secondary cases. Cost-effectiveness of different options is compared using incremental cost-effectiveness ratios (ICERs). Univariate analysis of the progression rate to active TB in the absence

of treatment was performed; here, Incremental Net Benefit (INB) valuing a QALY at £20,000 was calculated, as it is easier to display graphically.

The data sources are described below.

2.4 Model diagram

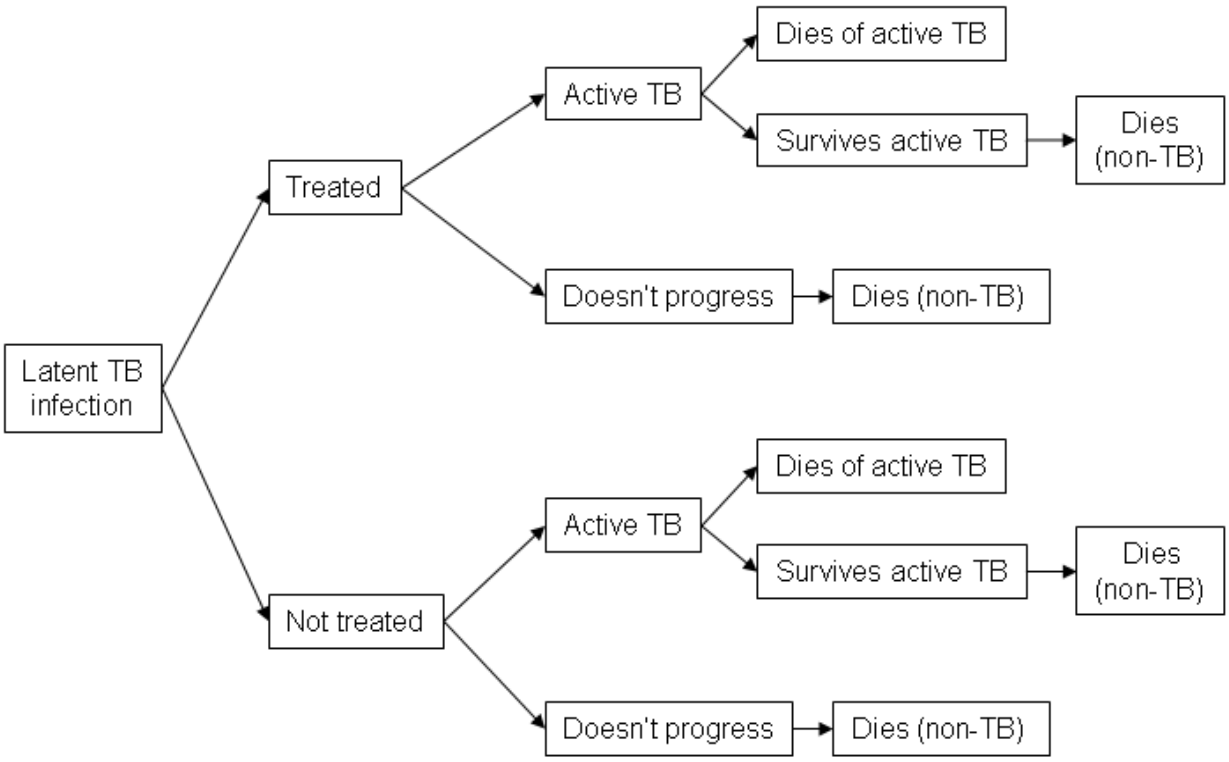

Figure 2.4 Model diagram

2.5 Data sources

Parameter estimates and data sources are summarised in Table 2.5. Estimates of the rate of progression to active TB, treatment efficacy, and frequencies of adverse events for each treatment regimen were derived from estimates supplied by NICE. As NICE supplied frequencies of events in placebo and treatment arms of trials, calculations were performed as follows. For efficacy, the frequency of occurrence of active TB in the treatment arm was subtracted from that of the placebo arm and this difference divided by the frequency of occurrence in the placebo arm, in order to calculate the proportionate reduction in progression to active TB in those who were treated. For adverse events, placebo-arm event frequencies were deducted from those in the treatment arms, to estimate excess events ascribable to treatment.

Table 2.5 Model parameters and data sources

Parameter	Value	Source / Reference
Discount rate per annum	3.5%	
Size of patient cohort	10,000	Arbitrary
Mortality due to non-TB causes	Age-dependent	Office for National Statistics
Annual rate of progression to active TB in patients diagnosed with LTBI in the absence of treatment	Varies	Supplied by NICE
Case-fatality ratio of active TB	17-44 years: 1.2% 45-64 years: 4.8% 65+ years: 17.6%	Adapted from Crofts et al. 2008
Cost of managing an active TB case, including treatment of index case, and investigation, and treatment where appropriate, of contacts	£5,329 PSA: gamma: α: 8.333; β: 639.435	NICE guidance (National Collaborating Centre for Chronic Conditions CG117, 2011) (adjusted for inflation: PSSRU, 2014)
Number of secondary TB cases per primary case	0.2 PSA: 0.1-0.3	Suggested by NICE

3. Resource identification, measurement and valuation

3.1 NHS costs

Drug costs were obtained from the NHS drug tariff (2014) (for H and R) and British National Formulary (2013) (for Pz); quantities of drugs used for each regimen were supplied by NICE.

Staff costs were calculated from the amounts of staff time required for administration of LTBI treatment, based on GDG advice, and the cost of that time according to NHS reference costs (Curtis 2013). GDG advice was the minimum amount of staff time required was the same for all regimens, whilst more-extensive use of staff time was regimen-dependent. Minimum staff costs corresponded to an initial consultation with a doctor (unit cost £126) and 1-month follow-up with a nurse (unit cost £64). The highest-staff-cost option comprises an initial consultation with a doctor and a nurse, one or more follow-up consultations with a doctor during treatment, and a final consultation with a doctor at the end of treatment. The number of follow-up consultations depends upon the regimen and is as follows: 3H: 2; 6H: 5; 9H: 8; 12H: 11; 2RPz: 1; 3HR: 3. In the base-case analysis the minimum staff cost was used, whilst in the PSA costs were varied across their ranges.

Table 3.1 Costs of each LTBI treatment regimen

Regimen	Drug costs (£)	Staff costs (£)
3H	173	190 – 567
6H	341	190 – 945
9H	681	190 – 1,322
12H	693	190 – 1,700
2RPz	171	190 – 441
3HR	206	190 – 693

Costs of treating adverse events due to LTBI treatment were based on literature and GDG advice regarding healthcare resources required, with costs calculated using NHS reference costs.

Table 3.2 Costs of adverse events due to LTBI treatment

Adverse event	Cost of treatment (£)	Source / Reference
Hepatotoxicity	587 PSA: gamma: α: 6.679; β: 87.889	Pareek et al. 2011
Nausea and vomiting	63 (consultation)	NHS Reference costs (Curtis 2013)

4. Quality of life

Health-related quality of life weights for individuals without active TB of different ages were those estimated by Kind et al. (1999).

For cases of active TB, QALY loss due to morbidity was taken from previous NICE guidance (National Collaborating Centre for Chronic Conditions, CG117, 2011). QALY loss due to active-TB mortality is captured through the consequent reduction in the size of the cohort. For secondary cases, QALY loss due to morbidity is calculated in the same way as for primary cases; QALY loss due to mortality (0.267) is calculated from the life-expectancy and case-fatality ratio of the average age of a TB case, which is 30-34 years (Public Health England, 2014).

For hepatotoxicity due to LTBI treatment, the utility weight was obtained from de Perio et al. (2009), and the duration was as advised by the GDG (i.e. 1 week).

For nausea and vomiting due to LTBI treatment, the utility weight was based on GDG advice to use the utility weight estimated for nausea and vomiting due to other chemotherapy (Nafees et al. 2008) and a duration of 2-3 days.

Table 4.1 Quality-of-life weights for individuals without active TB of different ages (adapted from Kind et al. 1999)

Age (years)	QoL weight
<25	0.94
25-34	0.93
35-44	0.91
45-54	0.85
55-64	0.8
65-74	0.78
75+	0.73

Table 4.2 QALY losses due to morbidity due to active TB and adverse events due to LTBI treatment

Event	QALY loss	Source / Reference
Active TB	0.0838 PSA: α: 5.427; β: 0.0154	National Collaborating Centre for Chronic Conditions, CG117, 2011
Hepatotoxicity	0.00033 PSA: α: 65.753; β: $7x10^{-5}$	GDG and de Perio et al. 2009
Nausea and vomiting	0.0046 PSA: α: 109.67; β: $3x10^{-6}$	GDG and Nafees et al. 2008

5 Analysis

5.1 Validation

The model is a standard method and has been discussed at several meetings with the GDG, who provided advice on parameterisation. It is not possible to formally validate the model against a suitable independent data-set because no such data exist.

5.2 Sensitivity analysis

5.2.1 Structural uncertainty

Structural uncertainty was not evaluated due to limitations of time and resources, and was not requested by the GDG. However, the model structure was presented on several occasions to the GDG.

5.2.2 Deterministic sensitivity analysis

Univariate sensitivity analysis was performed, for each combination of regimen and age group, by varying the rate of progression to active TB in untreated patients.

Time and resource constraints meant that not all possible sensitivity analyses could be performed. The GDG's view was that it was most important to examine the effect of the untreated progression rate.

Additional univariate sensitivity analysis subsequently requested by NICE compared different rates of secondary cases arising per primary case, and compared higher staff costs for LTBI treatment with the base case.

5.2.3 Probabilistic sensitivity analysis

Probabilistic sensitivity analysis (PSA) was performed, for each combination of regimen and age group. Samples of progression rates in treated and untreated

patients, and frequencies of adverse events, were provided by NICE. In addition, costs per active TB case, per hepatotoxicity event, and for treatment of LTBI, and QALY losses due to active TB, nausea and vomiting, and heptatoxicity, were varied; gamma distributions were used, except for staff costs, which were uniformly-distributed.

6. Results

6.1 Base case analysis

For each age group, each regimen is compared with no treatment (**Table 6.1.1**). In all cases there was an increase in QALYs – i.e. QALYs lost due to adverse events caused by LTBI treatment were outweighed by QALYs gained by reducing rates of occurrence of active TB. In all cases there was a net increase in costs – i.e. the additional costs of treating LTBI exceeded the cost-savings from reduced rates of active TB. The majority of QALY gains from treating LTBI arise from averting progression to active disease in those who are treated, rather than from averting transmission and thus preventing secondary cases.

Incremental cost-effectiveness ratios (ICERs) varied markedly, across regimens within an age-group. Comparing age-groups, cost-effectiveness was similar across the 17-34, 35-50, and 51-65 years groups: although the older cohorts have shorter remaining lifetimes, meaning that their lifetime risk of progression to active TB is lower, the case-fatality ratio of active TB is higher in older ages. However, in the oldest age-group, 66+ years, the lifetime risk of progression to active TB is reduced by the shorter remaining lifetime, making treatment of LTBI in this age-group less cost-effective.

For all age-groups, the most cost-effective regimen appears to be 2RPz, which dominates all other options, having the lowest incremental costs and the greatest incremental QALYs. Aside from this regimen, the most cost-effective regimens are 6H and 3HR.

Table 6.1.1 (a) Base-case analysis of treatment for latent TB infection in 10,000 patients aged 17-34 years

QALYs: Quality Adjusted Life Years; ICER: Incremental Cost-Effectiveness Ratio. Costs and QALY losses of secondary cases are included in the overall cost and QALY calculations.

17-34			Compared with no treatment incremental...			Numbers of events		Secondary cases		
Option	Cost (£M)	Total QALYs	Cost (£M)	QALYs	ICER (£/QALY)	Adverse events	Active TB	Number (Undisc.)	Costs (£k) (Discounted)	QALY loss (Discounted)
No treatment	3.00	217,746	-	-	-	-	1175	235	486	32
3H	5.97	217,823	2.96	77	38,269	5	918	184	378	25
6H	6.39	217,971	3.38	225	15,033	145	423	85	172	11
9H	10.00	217,949	6.99	203	34,461	360	497	99	203	13
12H	9.57	218,012	6.57	266	24,668	360	284	57	115	8
2RPz	3.76	218,082	0.75	336	2,242	52	47	9	19	1
3HR	5.48	217,918	2.48	173	14,348	112	599	120	245	16

(b) Base-case analysis of treatment for latent TB infection in 10,000 patients aged 35-50 years

35-50			Compared with no treatment incremental...			Numbers of events		Secondary cases		
Option	Cost (£M)	Total QALYs	Cost (£M)	QALYs	ICER (£/QALY)	Adverse events	Active TB	Number (Undisc.)	Costs (£k) (Discounted)	QALY loss (Discounted)
No treatment	2.72	182,901	-	-	-	-	882	176	439	29
3H	5.74	183,005	3.03	104	29,227	13	686	137	341	22
6H	6.30	183,200	3.58	299	11,969	167	314	63	155	10
9H	9.89	183,171	7.18	270	26,594	394	370	74	183	12
12H	9.52	183,254	6.81	353	19,275	394	210	42	104	7
2RPz	3.80	183,345	1.08	444	2,435	138	35	7	17	1
3HR	5.33	183,131	2.62	230	11,382	116	446	89	221	15

(c) Base-case analysis of treatment for latent TB infection in 10,000 patients aged 51-65 years

51-65			Compared with no treatment incremental...			Numbers of events		Secondary cases		
Option	Cost (£M)	Total QALYs	Cost (£M)	QALYs	ICER (£/QALY)	Adverse events	Active TB	Number (Undisc.)	Costs (£k) (Discounted)	QALY loss (Discounted)
No treatment	2.23	139,845	-	-	-	-	593	119	360	24
3H	5.37	139,956	3.14	111	28,377	27	460	92	279	18
6H	6.14	140,163	3.92	318	12,330	206	209	42	126	8
9H	9.72	140,132	7.49	287	26,135	453	246	49	149	10
12H	9.44	140,219	7.21	374	19,272	453	140	28	84	6
2RPz	3.86	140,314	1.64	469	3,494	286	23	5	14	1
3HR	5.09	140,090	2.86	245	11,682	122	298	60	180	12

(d) Base-case analysis of treatment for latent TB infection in 10,000 patients aged 66+ years

66+			Compared with no treatment incremental...			Numbers of events		Secondary cases		
Option	Cost (£M)	Total QALYs	Cost (£M)	QALYs	ICER (£/QALY)	Adverse events	Active TB	Number (Undisc.)	Costs (£k) (Discounted)	QALY loss (Discounted)
No treatment	1.36	79,786	-	-	-	-	292	58	221	15
3H	4.78	79,846	3.41	60	57,082	156	226	45	171	11
6H	6.04	79,958	4.68	171	27,299	551	102	20	77	5
9H	9.66	79,940	8.30	154	54,042	967	120	24	91	6
12H	9.54	79,987	8.17	201	40,662	967	68	14	51	3
2RPz	4.52	80,035	3.16	249	12,717	1469	11	2	8	1
3HR	4.69	79,920	3.32	133	24,900	176	145	29	110	7

6.2 Deterministic sensitivity analysis

We consider progression rates in untreated individuals ranging from 1/15x to 15x the base case progression rate of 0.001955. The upper end of this range exceeds the progression rates estimated for HIV-positive individuals by Horsburgh et al. (2010). For ease of interpretation of the graphs, we present the incremental net benefit (INB), valuing a QALY at £20,000, of each regimen compared with no treatment. Where INB is greater than zero then treatment would be considered cost-effective if a QALY were valued at £20,000; where INB is less than zero then treatment would not be considered cost-effective by this criterion.

The results for each regimen are shown for each age-group (**Figure 6.2.1**). For comparability, the same scales are used for each graph.

As the progression rate increases, INB increases. This is because the amount of active TB disease that occurs in the absence of treatment – and therefore the amount of disease averted by treatment – increases.

Additionally, for each age-group a narrower range of values is shown (**Figure 6.2.2**), so that the progression rate corresponding to an INB of zero for each regimen and age-group can be seen. These graphs have different scales.

Consistent with the base-case analysis, the regimen that crosses the threshold INB=£0 at the lowest progression rate is 2RPz, with 6H and 3HR crossing the threshold at higher progression rates, which are approximately the same for 6H and 3HR. Other regimens reach the INB=£0 threshold at higher progression rates.

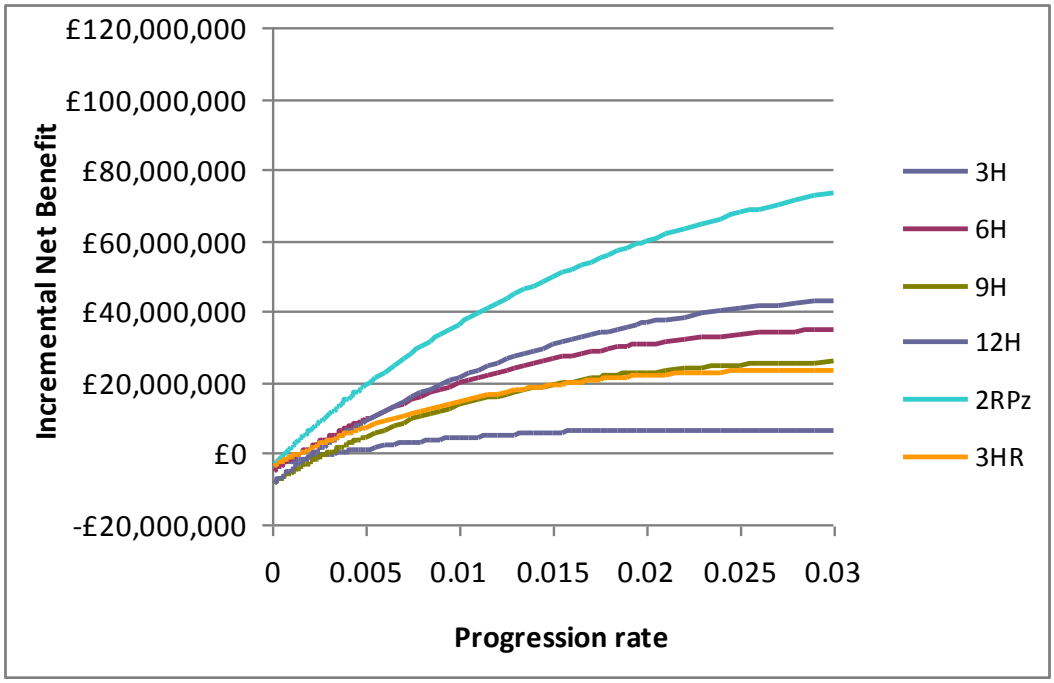

Figure 6.2.1(a) Univariate analysis of the relationship between progression rate and Incremental Net Benefit (INB) in 10,000 patients with LTBI, aged 17-34 years

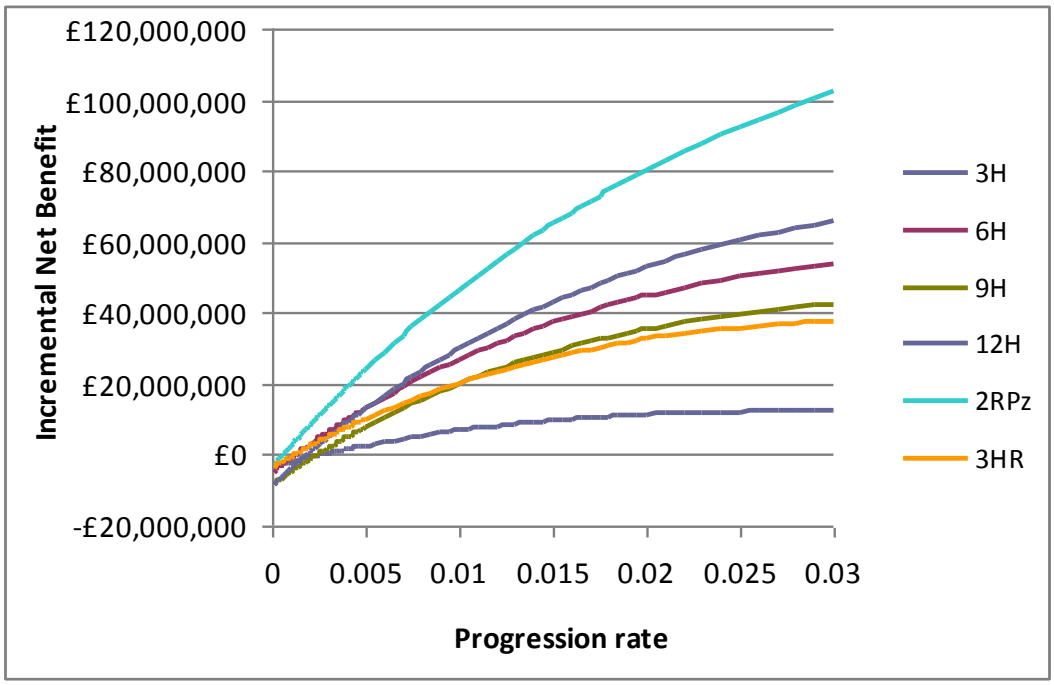

Figure 6.2.1(b) Univariate analysis of the relationship between progression rate and Incremental Net Benefit (INB) in 10,000 patients with LTBI, aged 35-50 years

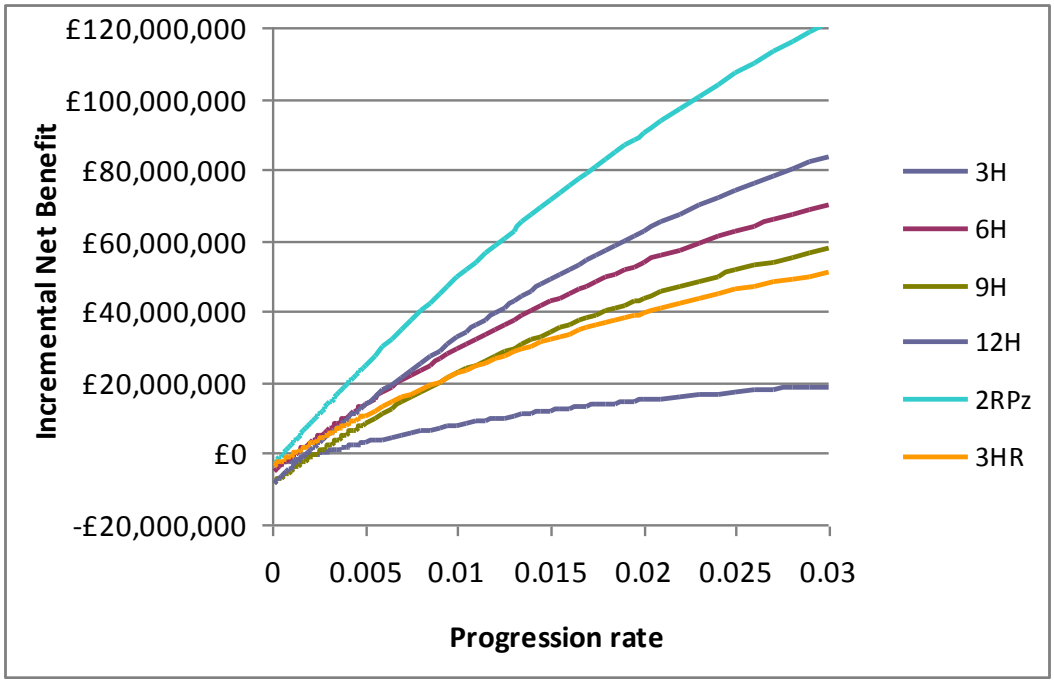

Figure 6.2.1(c) Univariate analysis of the relationship between progression rate and Incremental Net Benefit (INB) in 10,000 patients with LTBI, aged 51-65 years

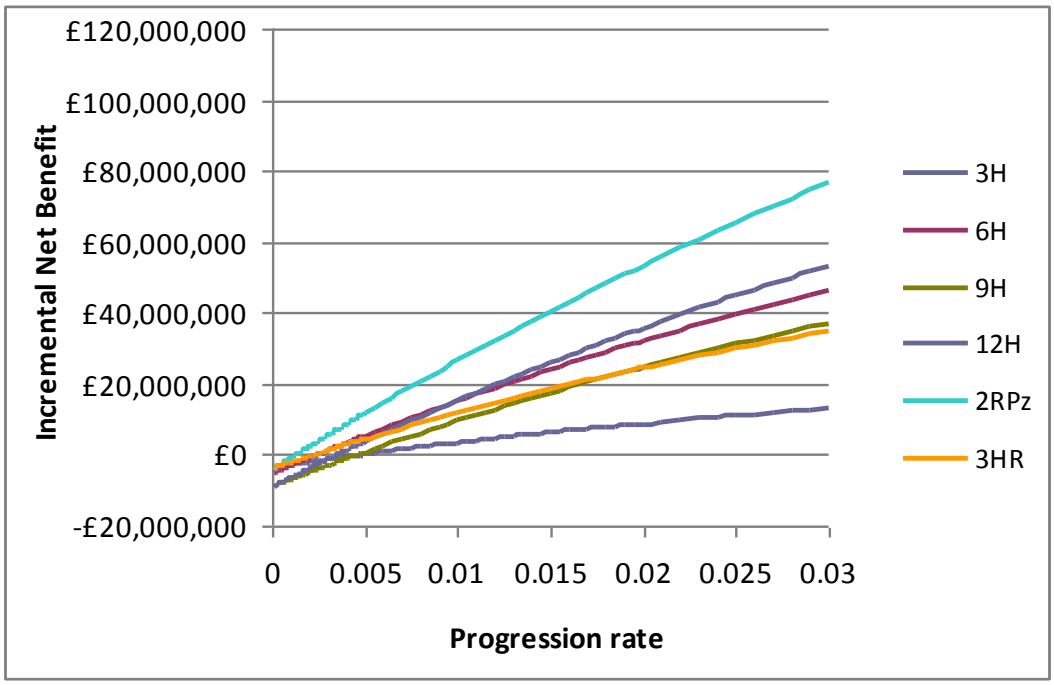

Figure 6.2.1(d) Univariate analysis of the relationship between progression rate and Incremental Net Benefit (INB) in 10,000 patients with LTBI, aged 66+ years

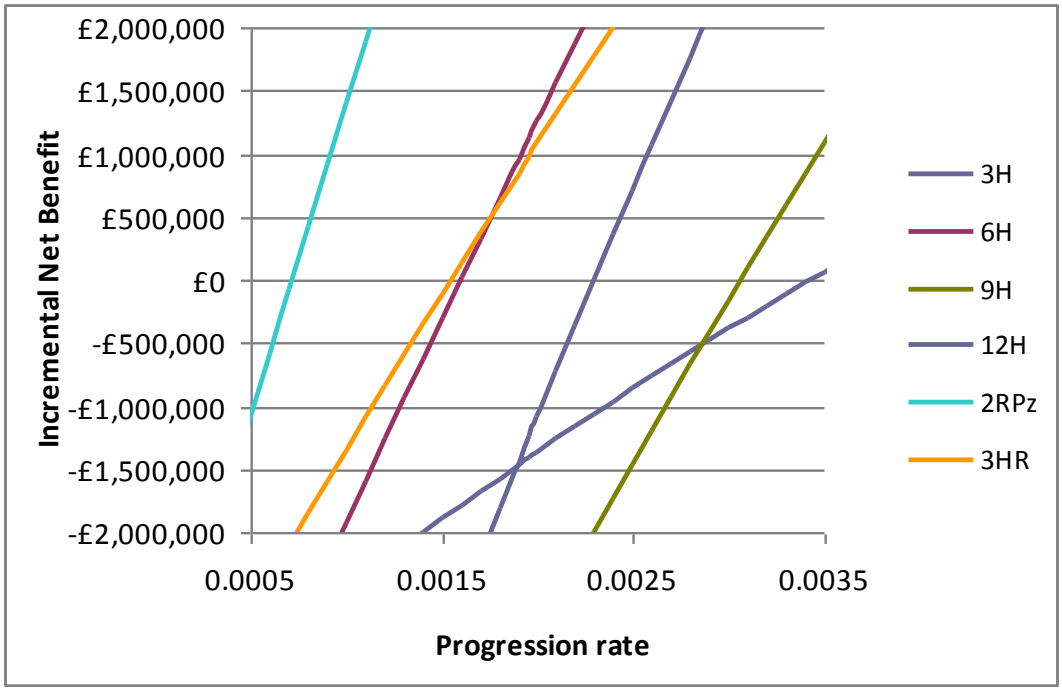

Figure 6.2.2(a) Univariate analysis of the relationship between progression rate and Incremental Net Benefit (INB) in 10,000 patients with LTBI, aged 17-34 years

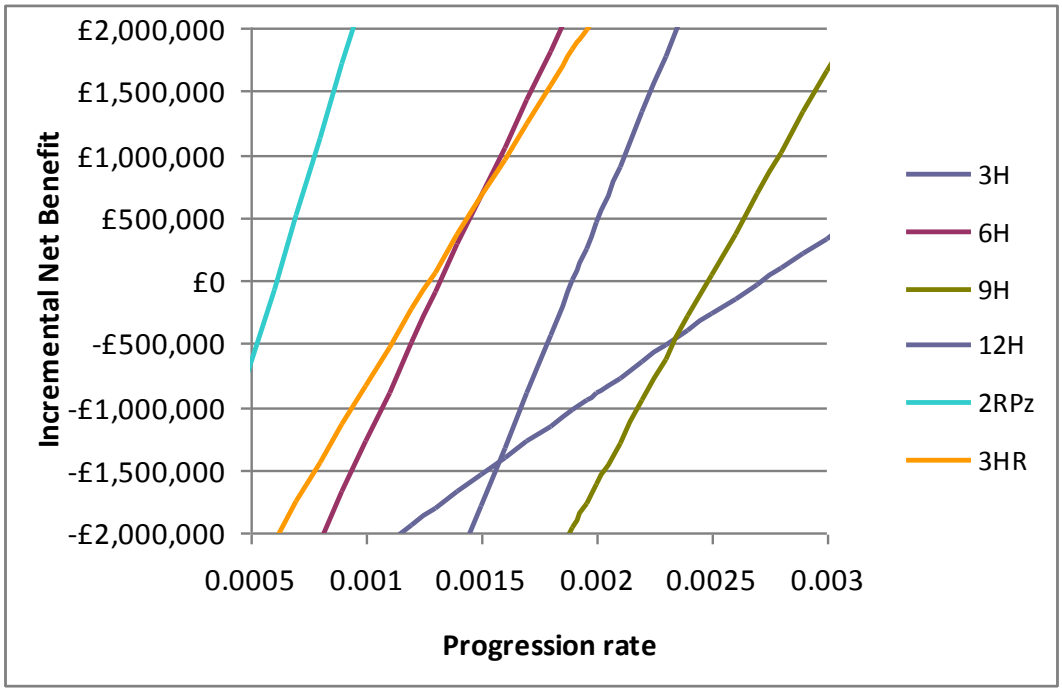

Figure 6.2.2(b) Univariate analysis of the relationship between progression rate and Incremental Net Benefit (INB) in 10,000 patients with LTBI, aged 35-50 years

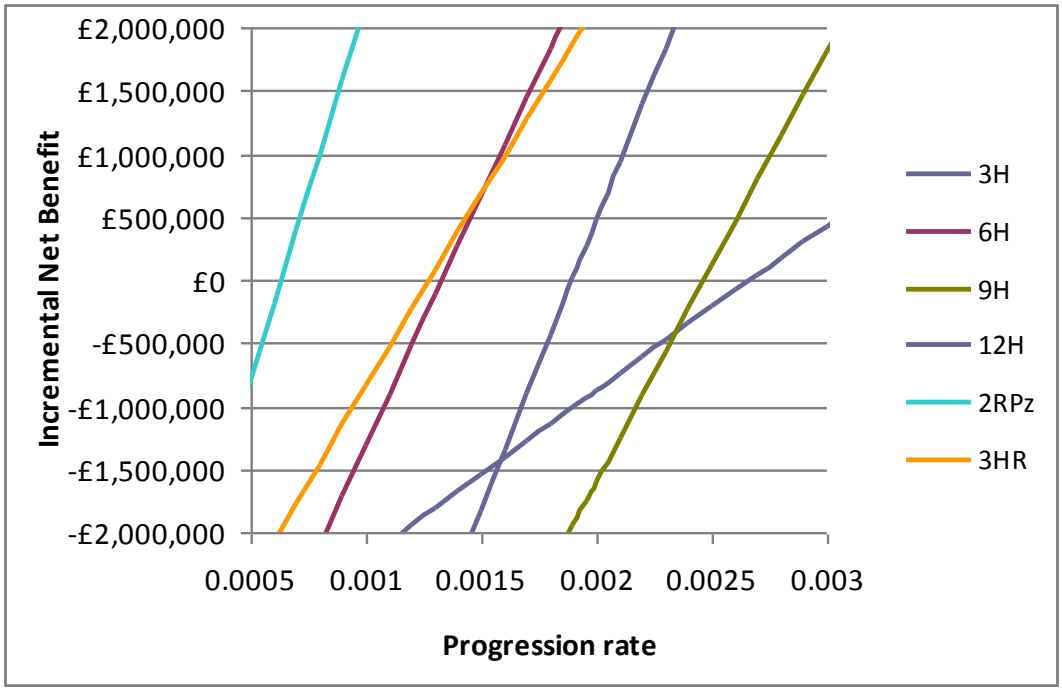

Figure 6.2.2(c) Univariate analysis of the relationship between progression rate and Incremental Net Benefit (INB) in 10,000 patients with LTBI, aged 51-65 years

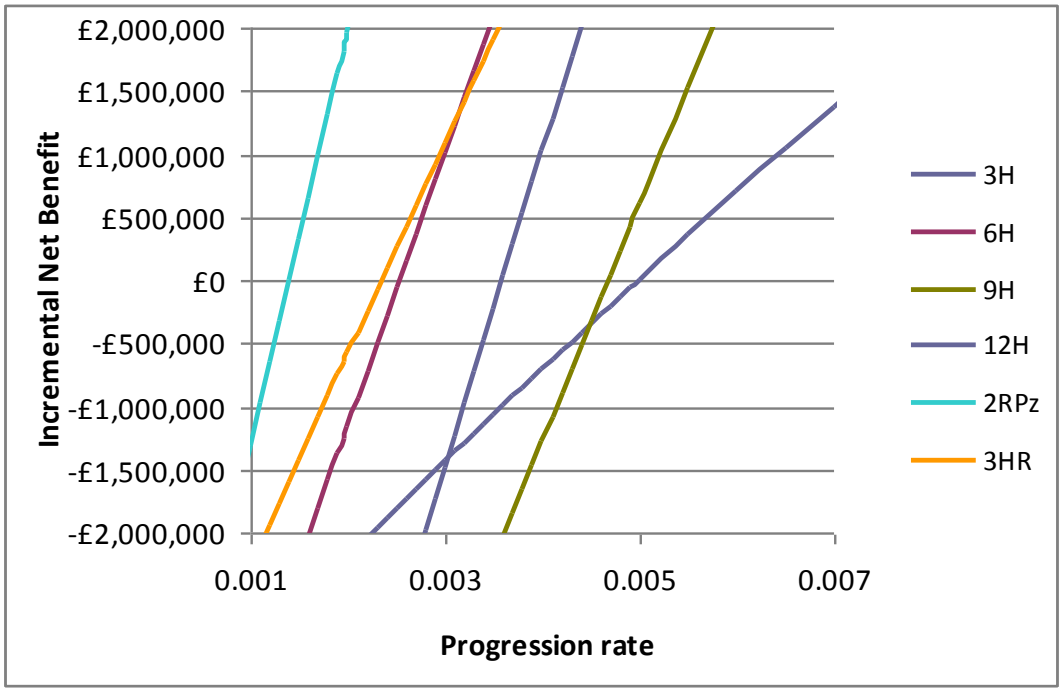

Figure 6.2.2(d) Univariate analysis of the relationship between progression rate and Incremental Net Benefit (INB) in 10,000 patients with LTBI, aged 66+ years

Tables 6.2.1 and **6.2.2** present the results of scenarios in which the number of secondary cases arising per primary case are reduced to 0.1 and increased to 0.3, respectively. All other parameter values are as in the base case. Higher rates of transmission make treatment for LTBI more cost-effective, but the difference is very small: there are no cases of the ICER for any regimen in any age-group crossing a threshold of £20,000/QALY or even £30,000/QALY as a result of increasing the transmission rate.

Table 6.2.3 presents the results of a scenario in which the staff costs for treating LTBI are increased to the maximum estimates. All other parameter values are as in the base case. Higher costs of treating LTBI make its treatment less cost-effective.

Table 6.2.1 (a) Analysis of treatment for latent TB infection in 10,000 patients aged 17-34 years, with number of secondary cases per primary case set to the minimum estimate

17-34			Compared with no treatment incremental...			Numbers of events		Secondary cases		
Option	Cost (£M)	Total QALYs	Cost (£M)	QALYs	ICER (£/QALY)	Adverse events	Active TB	Number (Undisc.)	Costs (£k) (Discounted)	QALY loss (Discounted)
No treatment	2.76	217,762	-	-	-	-	1175	117	243	16
3H	5.78	217,836	3.02	74	40,853	5	918	92	189	12
6H	6.30	217,977	3.54	215	16,487	145	423	42	86	6
9H	9.89	217,955	7.13	194	36,854	360	497	50	101	7
12H	9.52	218,016	6.76	254	26,583	360	284	28	58	4
2RPz	3.75	218,083	0.99	321	3,077	52	47	5	10	1
3HR	5.36	217,926	2.60	165	15,772	112	599	60	122	8

(b) Analysis of treatment for latent TB infection in 10,000 patients aged 35-50 years, with number of secondary cases per primary case set to the minimum estimate

35-50			Compared with no treatment incremental...			Numbers of events		Secondary cases		
Option	Cost (£M)	Total QALYs	Cost (£M)	QALYs	ICER (£/QALY)	Adverse events	Active TB	Number (Undisc.)	Costs (£k) (Discounted)	QALY loss (Discounted)
No treatment	2.50	182,916	-	-	-	-	882	88	220	14
3H	5.57	183,016	3.08	100	30,661	13	686	69	170	11
6H	6.22	183,205	3.72	290	12,847	167	314	31	77	5
9H	9.80	183,177	7.30	261	27,945	394	370	37	91	6
12H	9.47	183,258	6.98	342	20,389	394	210	21	52	3
2RPz	3.79	183,346	1.29	430	3,004	138	35	4	9	1
3HR	5.22	183,138	2.73	223	12,241	116	446	45	110	7

(c) Analysis of treatment for latent TB infection in 10,000 patients aged 51-65 years, with number of secondary cases per primary case set to the minimum estimate

51-65			Compared with no treatment incremental...			Numbers of events		Secondary cases		
Option	Cost (£M)	Total QALYs	Cost (£M)	QALYs	ICER (£/QALY)	Adverse events	Active TB	Number (Undisc.)	Costs (£k) (Discounted)	QALY loss (Discounted)
No treatment	2.05	139,857	-	-	-	-	593	59	180	12
3H	5.23	139,965	3.18	108	29,454	27	460	46	139	9
6H	6.08	140,167	4.03	310	13,013	206	209	21	63	4
9H	9.64	140,137	7.60	280	27,162	453	246	25	74	5
12H	9.40	140,222	7.35	365	20,128	453	140	14	42	3
2RPz	3.86	140,315	1.81	458	3,959	286	23	2	7	0
3HR	5.00	140,096	2.95	239	12,348	122	298	30	90	6

(d) Analysis of treatment for latent TB infection in 10,000 patients aged 66+ years, with number of secondary cases per primary case set to the minimum estimate

66+			Compared with no treatment incremental...			Numbers of events		Secondary cases		
Option	Cost (£M)	Total QALYs	Cost (£M)	QALYs	ICER (£/QALY)	Adverse events	Active TB	Number (Undisc.)	Costs (£k) (Discounted)	QALY loss (Discounted)
No treatment	1.25	79,794	-	-	-	-	292	29	110	7
3H	4.69	79,852	3.44	58	59,134	156	226	23	85	6
6H	6.00	79,960	4.75	167	28,507	551	102	10	38	3
9H	9.62	79,943	8.36	149	56,026	967	120	12	45	3
12H	9.51	79,989	8.26	195	42,256	967	68	7	26	2
2RPz	4.52	80,035	3.27	242	13,524	1469	11	1	4	0
3HR	4.63	79,923	3.38	130	26,028	176	145	15	55	4

Table 6.2.2 (a) Analysis of treatment for latent TB infection in 10,000 patients aged 17-34 years, with number of secondary cases per primary case set to the maximum estimate

17-34			Compared with no treatment incremental...			Numbers of events		Secondary cases		
Option	Cost (£M)	Total QALYs	Cost (£M)	QALYs	ICER (£/QALY)	Adverse events	Active TB	Number (Undisc.)	Costs (£k) (Discounted)	QALY loss (Discounted)
No treatment	3.25	217,730	-	-	-	-	1175	352	729	48
3H	6.16	217,811	2.91	81	35,913	5	918	275	566	37
6H	6.48	217,965	3.23	236	13,706	145	423	127	258	17
9H	10.10	217,942	6.85	212	32,278	360	497	149	304	20
12H	9.63	218,008	6.39	279	22,921	360	284	85	173	11
2RPz	3.77	218,081	0.52	352	1,480	52	47	14	29	2
3HR	5.60	217,910	2.36	181	13,049	112	599	180	367	24

(b) Analysis of treatment for latent TB infection in 10,000 patients aged 35-50 years, with number of secondary cases per primary case set to the maximum estimate

35-50			Compared with no treatment incremental...			Numbers of events		Secondary cases		
Option	Cost (£M)	Total QALYs	Cost (£M)	QALYs	ICER (£/QALY)	Adverse events	Active TB	Number (Undisc.)	Costs (£k) (Discounted)	QALY loss (Discounted)
No treatment	2.93	182,887	-	-	-	-	882	264	659	43
3H	5.91	182,994	2.98	107	27,881	13	686	206	511	34
6H	6.37	183,195	3.44	309	11,145	167	314	94	232	15
9H	9.98	183,165	7.05	278	25,325	394	370	111	274	18
12H	9.58	183,251	6.64	364	18,230	394	210	63	155	10
2RPz	3.81	183,345	0.87	458	1,901	138	35	11	26	2
3HR	5.44	183,124	2.51	237	10,576	116	446	134	331	22

(c) Analysis of treatment for latent TB infection in 10,000 patients aged 51-65 years, with number of secondary cases per primary case set to the maximum estimate

51-65			Compared with no treatment incremental...			Numbers of events		Secondary cases		
Option	Cost (£M)	Total QALYs	Cost (£M)	QALYs	ICER (£/QALY)	Adverse events	Active TB	Number (Undisc.)	Costs (£k) (Discounted)	QALY loss (Discounted)
No treatment	2.41	139,833	-	-	-	-	593	178	540	36
3H	5.51	139,947	3.10	113	27,351	27	460	138	418	28
6H	6.21	140,159	3.80	325	11,679	206	209	63	189	12
9H	9.79	140,127	7.39	294	25,157	453	246	74	223	15
12H	9.48	140,217	7.08	383	18,457	453	140	42	127	8
2RPz	3.87	140,314	1.47	481	3,051	286	23	7	21	1
3HR	5.18	140,084	2.77	251	11,048	122	298	89	270	18

(d) Analysis of treatment for latent TB infection in 10,000 patients aged 66+ years, with number of secondary cases per primary case set to the maximum estimate

66+			Compared with no treatment incremental...			Numbers of events		Secondary cases		
Option	Cost (£M)	Total QALYs	Cost (£M)	QALYs	ICER (£/QALY)	Adverse events	Active TB	Number (Undisc.)	Costs (£k) (Discounted)	QALY loss (Discounted)
No treatment	1.47	79,779	-	-	-	-	292	87	331	22
3H	4.86	79,841	3.39	61	55,140	156	226	68	256	17
6H	6.08	79,955	4.60	176	26,157	551	102	31	115	8
9H	9.71	79,937	8.23	158	52,165	967	120	36	136	9
12H	9.56	79,986	8.09	207	39,155	967	68	20	77	5
2RPz	4.53	80,035	3.05	256	11,954	1469	11	3	13	1
3HR	4.74	79,916	3.27	137	23,833	176	145	44	165	11

Table 6.2.3 (a) Analysis of treatment for latent TB infection in 10,000 patients aged 17-34 years, with staff costs for treatment of latent infection set to the maximum estimate

17-34			Compared with no treatment incremental...			Numbers of events		Secondary cases		
Option	Cost (£M)	Total QALYs	Cost (£M)	QALYs	ICER (£/QALY)	Adverse events	Active TB	Number (Undisc.)	Costs (£k) (Discounted)	QALY loss (Discounted)
No treatment	3.00	217,746	-	-	-	-	1175	235	486	32
3H	9.74	217,823	6.73	77	86,968	5	918	184	378	25
6H	13.94	217,971	10.93	225	48,563	145	423	85	172	11
9H	21.32	217,949	18.31	203	90,255	360	497	99	203	13
12H	24.67	218,012	21.67	266	81,360	360	284	57	115	8
2RPz	5.97	218,082	2.96	336	8,813	52	47	9	19	1
3HR	10.51	217,918	7.51	173	43,483	112	599	120	245	16

(b) Analysis of treatment for latent TB infection in 10,000 patients aged 35-50 years, with staff costs for treatment of latent infection set to the maximum estimate

35-50			Compared with no treatment incremental...			Numbers of events		Secondary cases		
Option	Cost (£M)	Total QALYs	Cost (£M)	QALYs	ICER (£/QALY)	Adverse events	Active TB	Number (Undisc.)	Costs (£k) (Discounted)	QALY loss (Discounted)
No treatment	2.72	182,901	-	-	-	-	882	176	439	29
3H	9.51	183,005	6.80	104	65,605	13	686	137	341	22
6H	13.85	183,200	11.13	299	37,204	167	314	63	155	10
9H	21.21	183,171	18.50	270	68,545	394	370	74	183	12
12H	24.62	183,254	21.91	353	62,027	394	210	42	104	7
2RPz	6.01	183,345	3.29	444	7,409	138	35	7	17	1
3HR	10.36	183,131	7.65	230	33,248	116	446	89	221	15

(c) Analysis of treatment for latent TB infection in 10,000 patients aged 51-65 years, with staff costs for treatment of latent infection set to the maximum estimate

51-65			Compared with no treatment incremental...			Numbers of events		Secondary cases		
Option	Cost (£M)	Total QALYs	Cost (£M)	QALYs	ICER (£/QALY)	Adverse events	Active TB	Number (Undisc.)	Costs (£k) (Discounted)	QALY loss (Discounted)
No treatment	2.23	139,845	-	-	-	-	593	119	360	24
3H	9.14	139,956	6.91	111	62,403	27	460	92	279	18
6H	13.69	140,163	11.47	318	36,094	206	209	42	126	8
9H	21.04	140,132	18.81	287	65,618	453	246	49	149	10
12H	24.54	140,219	22.31	374	59,611	453	140	28	84	6
2RPz	6.07	140,314	3.85	469	8,204	286	23	5	14	1
3HR	10.12	140,090	7.89	245	32,217	122	298	60	180	12

(d) Analysis of treatment for latent TB infection in 10,000 patients aged 66+ years, with staff costs for treatment of latent infection set to the maximum estimate

66+			Compared with no treatment incremental...			Numbers of events		Secondary cases		
Option	Cost (£M)	Total QALYs	Cost (£M)	QALYs	ICER (£/QALY)	Adverse events	Active TB	Number (Undisc.)	Costs (£k) (Discounted)	QALY loss (Discounted)
No treatment	1.36	79,786	-	-	-	-	292	58	221	15
3H	8.55	79,846	7.18	60	120,162	156	226	45	171	11
6H	13.59	79,958	12.23	171	71,377	551	102	20	77	5
9H	20.98	79,940	19.62	154	127,778	967	120	24	91	6
12H	24.64	79,987	23.27	201	115,789	967	68	14	51	3
2RPz	6.73	80,035	5.37	249	21,610	1469	11	2	8	1
3HR	9.72	79,920	8.35	133	62,617	176	145	29	110	7

6.3 Probabilistic sensitivity analysis

Probabilistic sensitivity analysis was performed for each combination of age-group and regimen. In this analysis the values of the parameters used in of the deterministic model were varied probabilistically. The results are presented on cost-effectiveness planes (**Figure 6.3.1**). In summary, there is a wide range of uncertainty in incremental costs and QALYs, both of which may be negative or positive. Whilst the range of incremental costs and QALYs is wide, the results are clustered diagonally, with relatively little variation in the relationship between costs and QALYs, indicating that the overall uncertainty is strongly affected by uncertainty in estimates of efficacy and progression rate (based on their joint parameter distributions provided by NICE).

Results of the PSA are summarised in **Tables 6.3.1** and **6.3.2**. **Table 6.3.1** shows that there is a very large range of uncertainty in both incremental costs and QALYs, with the latter typically varying from strongly negative to strongly positive. **Table 6.3.2** reports the proportion of PSA samples that are below the cost-effectiveness threshold of £20,000 / QALY. This analysis suggests that if a QALY is valued at £20,000 then 2RPz only is likely to be considered more cost-effective than no treatment for age groups 17-34, 35-50, and 51-65 years, although there is considerable uncertainty, with the maximum probability of being cost-effective not exceeding 72%. For the 66+ years age-group no option is likely to be considered cost-effective if a QALY is valued at £20,000.

Cost-effectiveness acceptability curves are presented in **Figure 6.3.2**. If a QALY is valued at £30,000 then the only regimen that is likely to be cost-effective is 2RPz, in all age groups. If a QALY is valued at £40,000 then 2RPz is likely to be cost-effective in all age groups, and 6H is likely to be cost-effective in age-groups 35-50 years and 51-65 years (but with probabilities of only 57%-58%). If a QALY is valued at £50,000 then 2RPz is likely to be cost-effective in all age groups, 6H is likely to be cost-effective in age-groups 35-50 years and 51-65 years (but with probabilities of only 60%-63%), and 12H is likely to be cost-effective in age-groups 35-50 years and 51-65 years (but with probabilities of only 54%-57%).

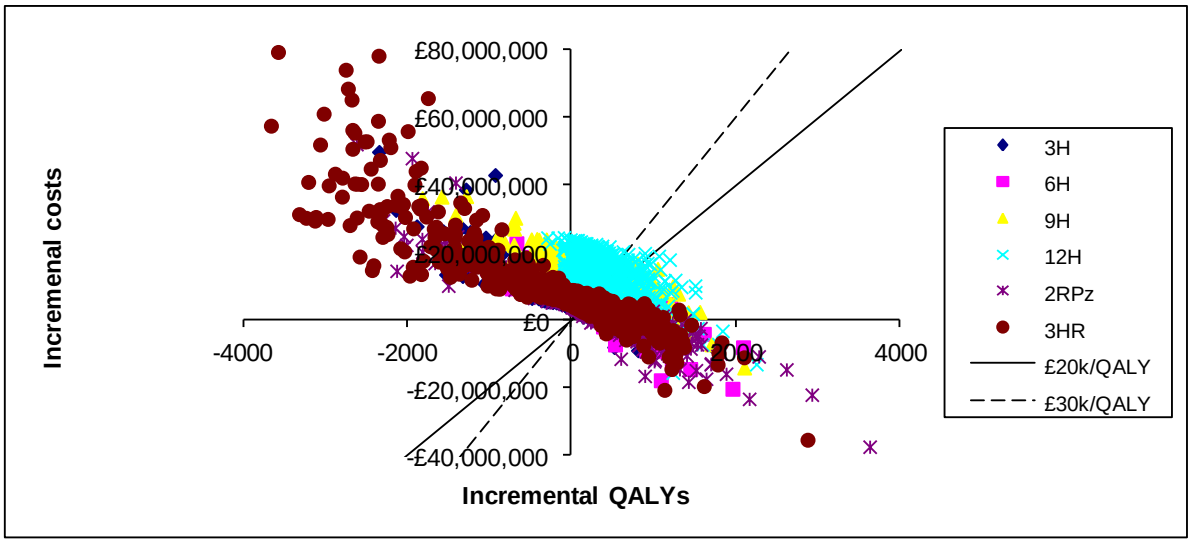

Figure 6.3.1(a) Probabilistic sensitivity analysis of the incremental costs and QALYs of each treatment regimen compared with no treatment in 10,000 patients with LTBI, aged 17-34 years. The solid line shows the cost-effectiveness threshold of £20,000 / QALY; the dashed line shows the cost-effectiveness threshold of £30,000 / QALY.

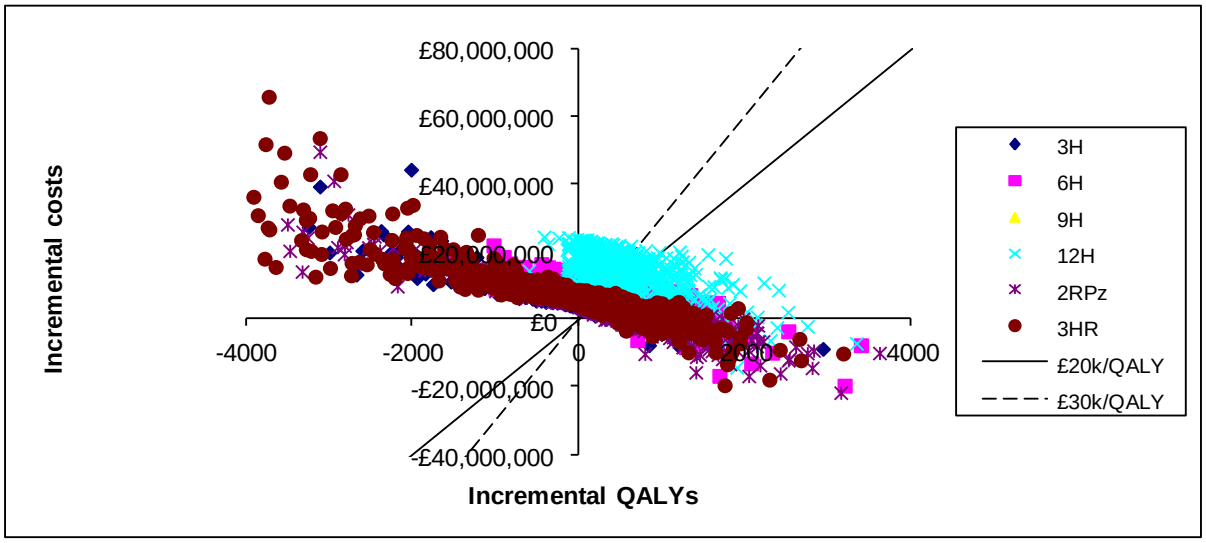

Figure 6.3.1(b) Probabilistic sensitivity analysis of the incremental costs and QALYs of each treatment regimen compared with no treatment in 10,000 patients with LTBI, aged 35-50 years. The solid line shows the cost-effectiveness threshold of £20,000 / QALY; the dashed line shows the cost-effectiveness threshold of £30,000 / QALY.

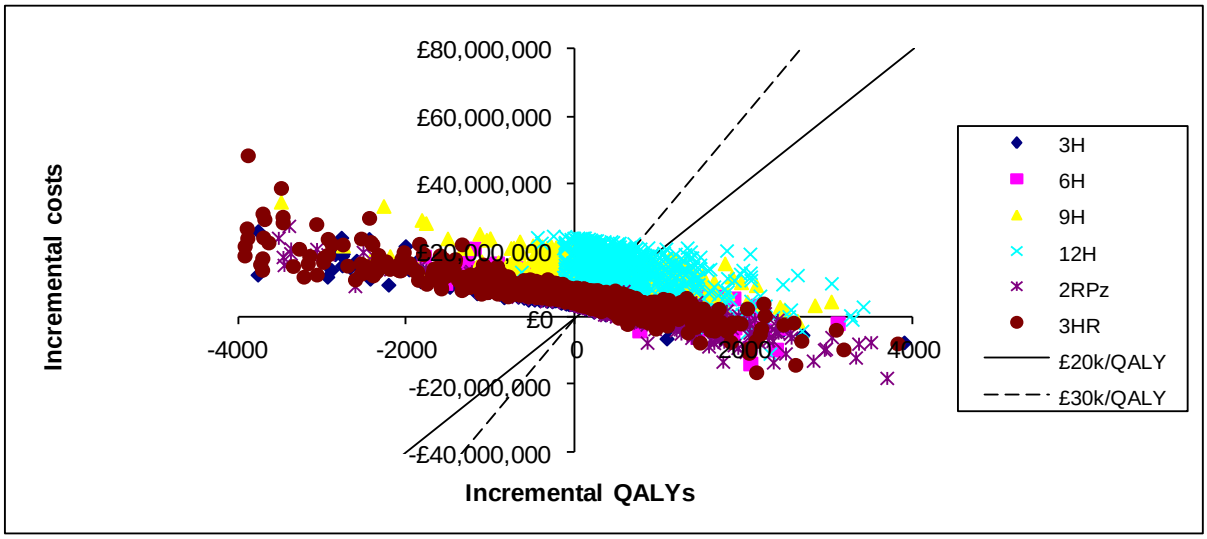

Figure 6.3.1(c) Probabilistic sensitivity analysis of the incremental costs and QALYs of each treatment regimen compared with no treatment in 10,000 patients with LTBI, aged 51-65 years. The solid line shows the cost-effectiveness threshold of £20,000 / QALY; the dashed line shows the cost-effectiveness threshold of £30,000 / QALY.

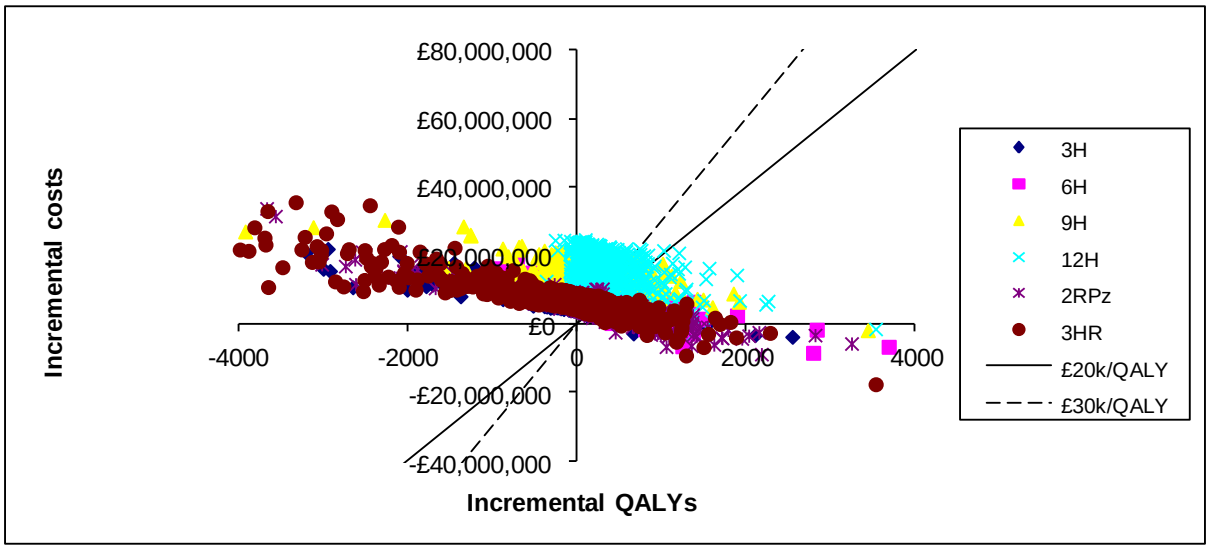

Figure 6.3.1(d) Probabilistic sensitivity analysis of the incremental costs and QALYs of each treatment regimen compared with no treatment in 10,000 patients with LTBI, aged 66+ years. The solid line shows the cost-effectiveness threshold of £20,000 / QALY; the dashed line shows the cost-effectiveness threshold of £30,000 / QALY.

Table 6.3.1 (a) Mean results of the probabilistic sensitivity analysis of the incremental costs and QALYs of each treatment regimen compared with no treatment in 10,000 patients with LTBI, aged 17-34 years. The results presented are the mean incremental costs, mean incremental QALYs gained and mean incremental net benefit (NB) of LTBI treatment if a QALY is valued at £20,000. Figures in brackets are the 95% ranges.

17-34	Mean incremental…		
	Cost (£M)	QALYs	NB (£M)
3H	5.5 (-1.2,16.5)	15.8 (-1126.6, 698.2)	-5.2 (-41.3,14.9)
6H	6.9 (-2.5,13)	239.3 (-277.3, 1015.9)	-2.1 (-18.8,20.7)
9H	12.7 (4.2,20.7)	187.9 (-435.6, 970.5)	-8.9 (-28,14.6)
12H	13.4 (1.8,22.5)	324.4 (-50.1, 1136.1)	-6.9 (-21.8,19.6)
2RPz	2.2 (-9.7,15.1)	317.9 (-1077.2, 1393)	4.1 (-37.7,34.9)
3HR	8.6 (-4.4,42.2)	-136.6 (-2619.2, 1103.2)	-11.3 (-95,25.7)

(b) Mean results of the probabilistic sensitivity analysis of the incremental costs and QALYs of each treatment regimen compared with no treatment in 10,000 patients with LTBI, aged 35-50 years

35-50	Mean incremental…		
	Cost (£M)	QALYs	NB (£M)
3H	5.5 (-0.8,15.8)	6.2 (-1873.7, 974.1)	-5.4 (-55.2,20.3)
6H	7.1 (-1.6,12.9)	328.0 (-395.1, 1440)	-0.5 (-20.7,28.8)
9H	12.9 (4.7,20.6)	253.7 (-628.8, 1370.9)	-7.8 (-30.8,21.6)
12H	13.7 (2.3,22.5)	446.7 (-68.2, 1705.4)	-4.7 (-21.6,28.9)
2RPz	2.6 (-8.5,14.9)	423.3 (-1517.6, 1983.6)	5.9 (-45.8,45.9)
3HR	8.6 (-3.5,41.1)	-267.2 (-4668.1, 1535)	-14.0 (-136.2,34.8)

(c) Mean results of the probabilistic sensitivity analysis of the incremental costs and QALYs of each treatment regimen compared with no treatment in 10,000 patients with LTBI, aged 51-65 years

51-65	Mean incremental…		
	Cost (£M)	QALYs	NB (£M)
3H	5.6 (0,14.5)	-15.5 (-2332.9, 1082.7)	-5.9 (-60.6,21.8)
6H	7.4 (-0.4,12.7)	360.5 (-464.7, 1694)	-0.2 (-21.2,31.8)
9H	13.2 (5.6,20.4)	274.0 (-710.6, 1543.3)	-7.7 (-32,23.8)
12H	14.2 (3.5,22.7)	493.0 (-72.7, 1978.1)	-4.3 (-21.6,31.3)
2RPz	3.2 (-6.7,13.5)	446.9 (-1771.6, 2247.2)	5.8 (-49.4,49.2)
3HR	8.6 (-2,39.9)	-440.2 (-7392.2, 1711.1)	-17.4 (-187.6,36.8)

(d) Mean results of the probabilistic sensitivity analysis of the incremental costs and QALYs of each treatment regimen compared with no treatment in 10,000 patients with LTBI, aged 66+ years

66+	Mean incremental…		
	Cost (£M)	QALYs	NB (£M)
3H	5.7 (1.9,11.5)	-25.6 (-1384.6, 642.1)	-6.2 (-39.4,10.8)
6H	8.2 (2.4,12.8)	201.5 (-268.4, 963.4)	-4.2 (-16.8,14.2)
9H	13.9 (7.6,20.2)	149.0 (-409.6, 874.1)	-10.9 (-26,7)
12H	15.3 (6.9,23.2)	276.1 (-40.7, 1134.6)	-9.7 (-22.5,12.5)
2RPz	4.6 (-1.7,11.6)	226.3 (-1070.9, 1287.7)	-0.1 (-33.4,25.7)
3HR	8.3 (0.6,33.6)	-408.4 (-6625, 967.5)	-16.5 (-159.2,19.1)

Table 6.3.2 Summary of probabilistic sensitivity analysis of the incremental costs and QALYs of each treatment regimen compared with no treatment in 10,000 patients with LTBI, in different age groups. Numbers in the table report the percentage of PSA samples that correspond to cost-effectiveness within the threshold of £20,000 / QALY. Percentages exceeding 50% – i.e. where the intervention is probably cost-effective if QALY is valued at £20,000 – are highlighted in blue.

Age	Regimen					
	3H	6H	9H	12H	2RPz	3HR
17-34	25.0	30.3	14.1	18.6	66.0	30.7
35-50	29.6	36.4	18.5	24.6	71.3	34.3
51-65	29.8	36.9	18.9	25.1	71.0	34.4
66+	16.6	19.2	6.7	9.4	44.2	21.7

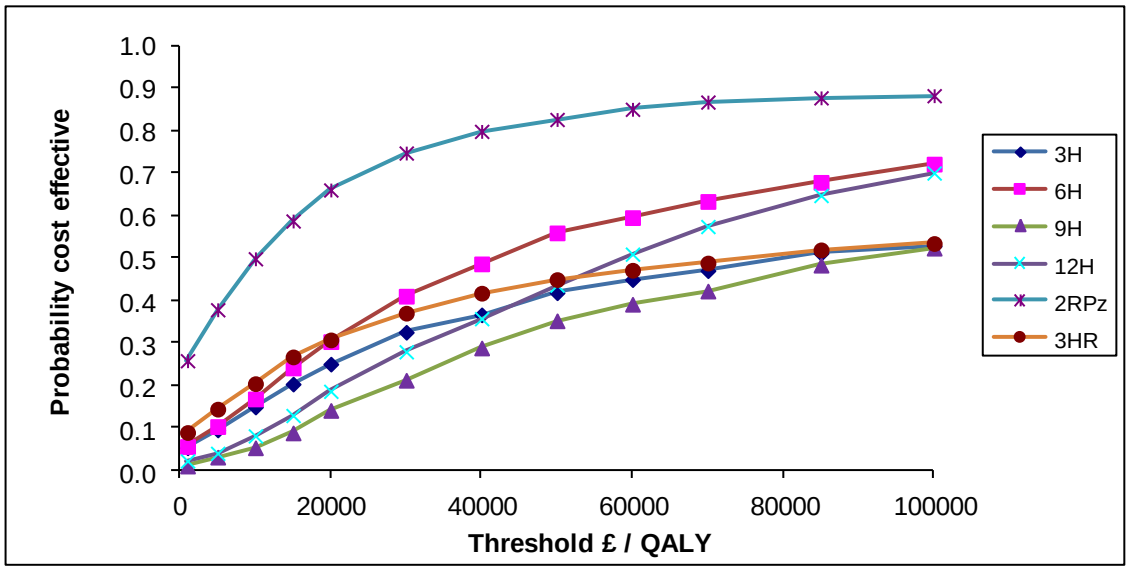

Figure 6.3.2 (a) Cost-effectiveness acceptability curves for each regimen compared with no treatment in 10,000 patients with LTBI, aged 17-34 years

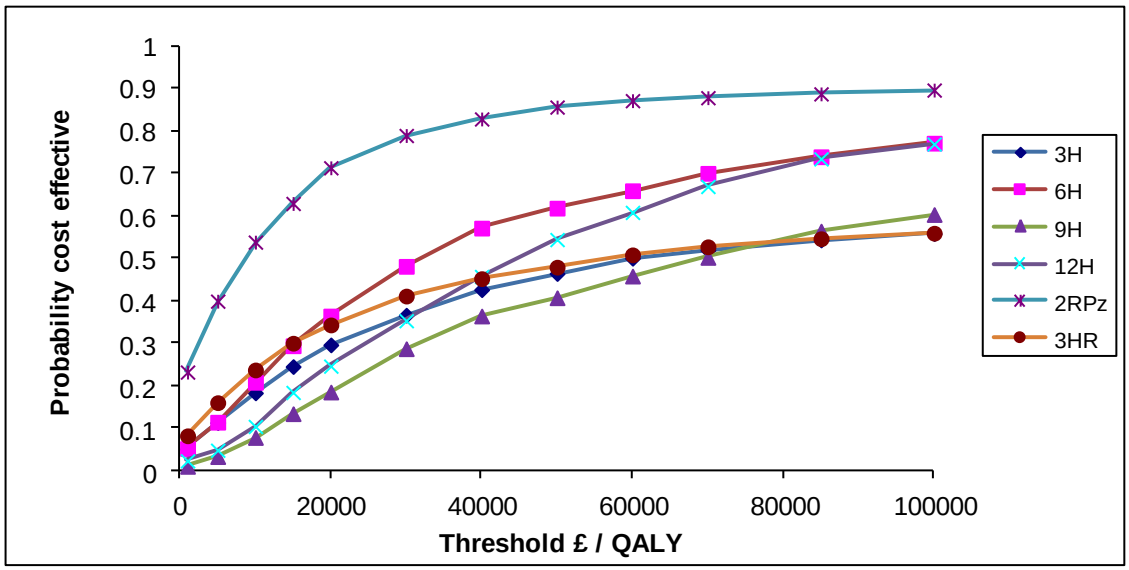

Figure 6.3.2 (b) Cost-effectiveness acceptability curves for each regimen compared with no treatment in 10,000 patients with LTBI, aged 35-50 years

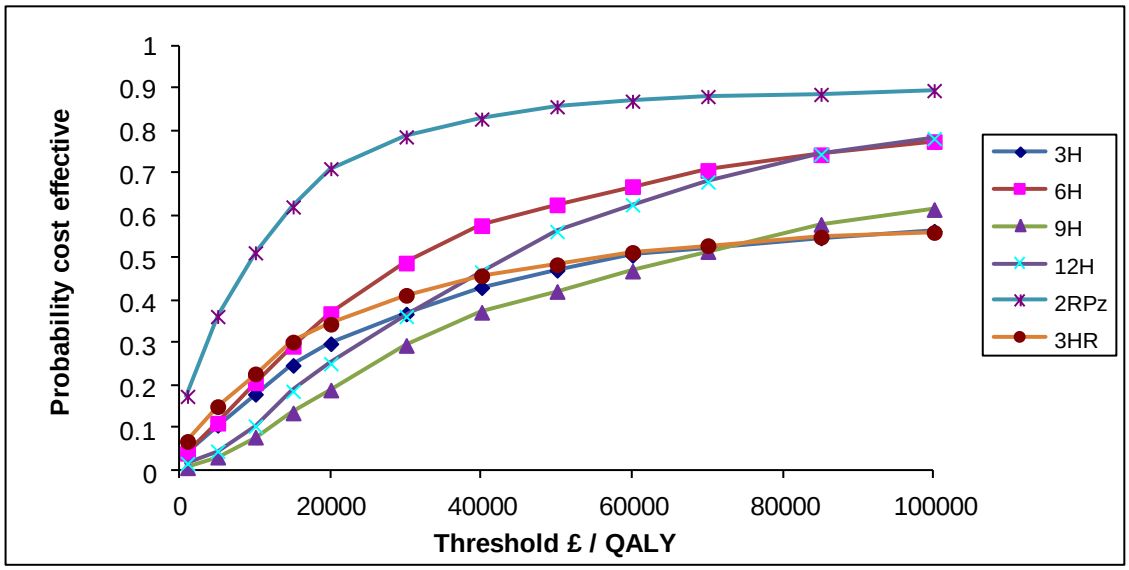

Figure 6.3.2 (c) Cost-effectiveness acceptability curves for each regimen compared with no treatment in 10,000 patients with LTBI, aged 51-65 years

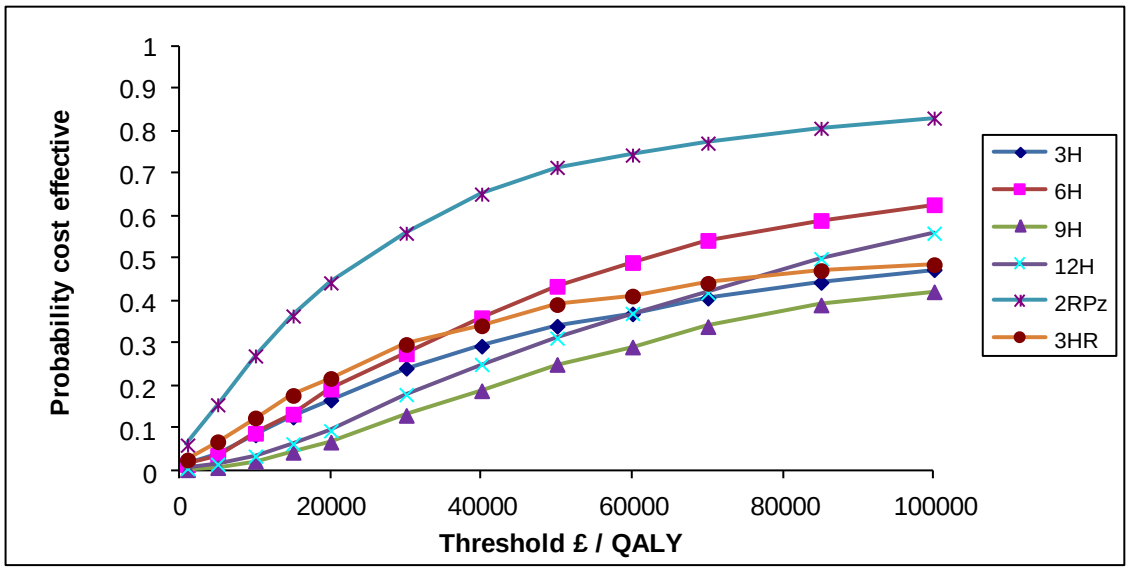

Figure 6.3.2 (d) Cost-effectiveness acceptability curves for each regimen compared with no treatment in 10,000 patients with LTBI, aged 66+ years

7.7 Interpretation of economic evidence

7.7.1 Summary of findings

Based on the parameter values estimated from the meta-analysis and considering uncertainty in staff costs, LTBI treatment is only likely to be cost-effective in age-groups 17-34, 35-50, and 51-65 years, using 2RPz. In the 66+ years age-group no treatment option is likely to be considered cost-effective.

Univariate analysis highlights the importance of the progression rate in affecting cost-effectiveness of LTBI treatment. The higher the staff costs of treating LTBI the less likely it is to be cost-effective. Varying the rate of transmission over the range considered makes very little difference to cost-effectiveness, and does not result in any regimen in any age-group crossing threshold values of £20,000/QALY or £30,000/QALY.

The PSA highlights the large range of uncertainty in parameter values and the consequent uncertainty in cost-effectiveness of LTBI treatment. Note that in the PSA staff costs of LTBI treatment are varied, whilst in the base case and deterministic sensitivity analysis the staff costs are fixed at the minimum value. Therefore, the mean cost of treatment in the PSA will be higher than the corresponding cost in the other analyses.

7.7.2 Relevance to different patient groups

In patient groups with higher rates of progression from LTBI to active TB disease, treatment for LTBI would be more likely to be cost-effective. In addition, if there are patient groups in which rates of transmission from active TB cases are particularly high then the population-level benefits of averting active TB would make LTBI treatment more cost-effective.

7.7.3 Main strengths and weaknesses of the evaluation

We have used a well-established modelling method and have presented the model to the GDG several times. Multiple treatment regimens and multiple age-groups have been considered. A large number of model runs have been performed to explore a wide range of parameter space, encompassing the range of values for the effectiveness of treatment and frequency of adverse events due to treatment. The model considers transmission of infection from cases of active TB that arise in the patient cohort, as well as the costs of tracing, testing, and, where applicable, treatment, of contacts of active TB cases.

The main limitations of the work are due to gaps in available evidence. Most trials of LTBI treatment have occurred in patient groups or settings that are different from those who would potentially be treated in England. In addition, limitations in our understanding of TB transmission patterns in the UK led us to follow previous NICE guidance (National Collaborating Centre for Chronic Conditions, CG117, 2011) to limit the consideration of transmission of TB to secondary cases, and not to consider further 'rounds' of transmission, as this is a very complex calculation which is beyond the scope of this work. This means that some of the population-level benefit of LTBI treatment has not been captured, although it is likely to be small, as most TB in the UK is imported, indicating that there is relatively little sustained transmission in the general population. We assumed that the patients studied in the trials considered in the network meta-analysis were representative of patients considered for treatment as consideration of screening practices was beyond the scope of our analysis.

References

British National Formulary 65 (2013). British Medical Association and the Royal Pharmaceutical Society of Great Britain.

Crofts JP, Pebody R, Grant A, Watson JM, Abubakar, I. Estimating tuberculosis case mortality in England and Wales, 2001-2002. *Int J Tuberc Lung Dis* 2008; 12, 308–313.

Curtis L. Unit costs of health and social care. Personal Social Services Research Unit, 2013.

de Perio et al. Cost-effectiveness of Interferon Gamma Release Assays vs Tuberculin Skin Tests in Health Care Workers. Arch Int Med 2009; 169:179.

Horsburgh CR, O'Donnell M, Chamblee S, Moreland JL, Johnson J, Marsh BJ, Narita M, Johnson LS, von Reyn CF. Revisiting Rates of Reactivation Tuberculosis: A Population-based Approach. Am J Respir Crit Care Med 2010; 182: 420–425.

Kind P, Hardman G, Macran S. UK population norms for EQ-5D. Discussion Paper 172. UK: Centre for Health Economics, University of York, 1999.

Nafees et al. Health state utilities for non small cell lung cancer. Health and Quality of Life Outcomes 2008; 6:84 (http://www.hqlo.com/content/6/1/84)

National Collaborating Centre for Chronic Conditions. CG117: Clinical diagnosis and management of tuberculosis, and measures for its prevention and control. NICE; 2011.

NHS drug tariff (http://www.ppa.org.uk/ppa/edt_intro.htm)

Office for National Statistics: http://www.ons.gov.uk/ons/publications/index.html

Pareek M, Watson JP, Ormerod LP, Kon OM, Woltmann G, White PJ, Abubakar I, Lalvani A. Screening of immigrants in the UK for imported latent tuberculosis: a multicentre cohort study and cost-effectiveness analysis Lancet Infect Dis 2011; 11: 435–44.

Personal Social Services Research Unit (PSSRU) 2014: www.pssru.ac.uk/project-pages/unit-costs/2014

Public Health England, 2014. Tuberculosis in the UK: 2014 report. PHE publications gateway number: 2014353. Published September 2014.