

National Institute for Health and Care
Excellence (NICE)

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

Addendum to report of April 2015

August 2015

The National Institute for Health and Care Excellence (NICE) has been asked to produce a guideline on treating latent tuberculosis infection. What follows an addendum to cost effectiveness analysis report of April 2015. 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.

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Declaration of authors' other relevant interests

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1. Introduction

Here we present numbers of deaths due to LTBI treatment and due to active TB for different LTBI treatment regimens. The population, interventions (i.e. treatment regimens), comparator, parameter estimates, model structure, data sources, limitations, etc are identical to those in the main report of April 2015, with the exception that as the risk of death due to LTBI treatment is so small for most regimens the size of the patient cohort was increased to 1 million to for ease of interpreting the results. The outcomes considered are deaths due to LTBI treatment, arising due to hepatotoxicity, and deaths due to active TB.

2. Analysis

Probabilistic sensitivity analysis (PSA) was performed, for each combination of regimen and age group. In this analysis the values of the parameters used in the deterministic model were varied probabilistically. Samples of progression rates in treated and untreated patients, and frequencies of adverse events, were provided by NICE. Results presented are medians and inter-quartile ranges. Results are also presented as numbers needed to treat (NNT) to avert 1 death due to active TB, and numbers needed to harm (NNH): the number of patients whose treatment for LTBI is expected to cause 1 death due to that treatment. NNT and NNH are the reciprocals of the median numbers of active TB deaths averted by LTBI treatment, and median numbers of deaths due to LTBI treatment, respectively.

3. Results

The risk of death due to progression to active TB and the risk of death due to LTBI treatment, in terms of numbers of deaths occurring in a cohort of 1 million patients, are presented for each age-group of patients diagnosed with LTBI, for each LTBI treatment regimen and for the no-treatment option (**Table 3.1**). Also presented are the numbers of deaths due to active TB that are averted by LTBI treatment, and the net numbers of deaths averted by LTBI treatment (i.e. the numbers of deaths due to active TB that are averted by LTBI treatment minus the numbers of deaths caused by LTBI treatment).

We also present the results in terms of numbers needed to treat (NNT) to avert 1 death due to active TB and numbers needed to harm (NNH): the number of patients whose treatment for LTBI is expected to cause 1 death due to that treatment (**Table 3.2**).

If LTBI were not treated then the median numbers of deaths due to active TB occurring in the cohorts of 1 million patients diagnosed with LTBI are 9,891 (17-34 years), 9,769 (35-50 years), 8,633 (51-65 years), and 5,078 (66+ years), despite treatment for the active TB. Note that there is considerable uncertainty in these estimates (**Table 3.1**).

Treatment for LTBI incurs a very small risk of death due to LTBI treatment, with the median number of deaths ranging from 0 for 3H and 3HR in 17-34 year-olds to 112 for 2RPz in those aged 66+ years. For each regimen, the risk of death increases with age. The 2RPz regimen has the highest risk of death due to LTBI treatment, for all ages. Although there is considerable *relative* uncertainty in these estimates, the *absolute* uncertainty is typically small, with even the upper bound of the inter-quartile range being small, bearing in mind that the analysis considers treatment of 1 million patients.

The risk of death due to LTBI treatment is much smaller than the risk of death due to progression to active TB in the absence of LTBI treatment, despite treatment for active TB.

For all regimens in all age-groups, the median net number of deaths averted by LTBI treatment is positive, meaning that the risk of death is greatest for the no treatment option and that LTBI treatment reduces the patients' risk of death.

However, there is considerable uncertainty in the net numbers of deaths averted, and for 3H and 3HR in all age-groups, the inter-quartile range includes negative net numbers of deaths averted.

The NNT estimates are much smaller than the number needed to harm (NNH) estimates (**Table 3.2**), indicating that the probability of benefit from LTBI treatment (i.e. death from active TB being averted) is much greater than the probability of harm (i.e. death due to LTBI treatment).

Table 3.1 (a) Numbers of deaths due to active TB and LTBI treatment, numbers of deaths due to active TB averted by LTBI treatment in comparison with no treatment, and net numbers of deaths averted by LTBI treatment, for different treatment options in 1,000,000 patients diagnosed with LTBI aged 17-34 years. No discounting has been applied in calculation of deaths due to active TB. Net numbers of deaths averted by LTBI treatment are the numbers of deaths due to active TB that are averted by LTBI treatment minus the numbers of deaths caused by LTBI treatment.

Treatment option	Deaths due to active TB: Median (IQR)	Deaths due to LTBI treatment: Median (IQR)	Active TB deaths averted by LTBI treatment: Median (IQR)	Net deaths averted by LTBI treatment: Median (IQR)
No treatment	9891 (5634, 17334)			
3H	7399 (3322, 14841)	0 (0, 1)	1962 (-1915, 5308)	1962 (-1914, 5308)
6H	3392 (1711, 7953)	1 (1, 1)	4762 (2249, 9457)	4760 (2248, 9456)
9H	3983 (1757, 9146)	2 (1, 2)	3928 (1412, 8728)	3927 (1410, 8727)
12H	2403 (1117, 5455)	2 (1, 2)	6440 (3576, 11769)	6438 (3574, 11767)
2RPz	352 (70, 2294)	4 (2, 9)	7503 (3730, 14107)	7487 (3728, 14097)
3HR	5412 (1208, 18021)	0 (0, 0)	2611 (-4786, 8193)	2611 (-4786, 8193)

(b) Numbers of deaths due to active TB and LTBI treatment, numbers of deaths due to active TB averted by LTBI treatment in comparison with no treatment, and net numbers of deaths averted by LTBI treatment, for different treatment options in 1,000,000 patients diagnosed with LTBI aged 35-50 years.

Treatment option	Deaths due to active TB: Median (IQR)	Deaths due to LTBI treatment: Median (IQR)	Active TB deaths averted by LTBI treatment: Median (IQR)	Net deaths averted by LTBI treatment: Median (IQR)
No treatment	9769 (5490, 17586)			
3H	7261 (3219, 14997)	1 (0, 2)	1978 (-2075, 5450)	1977 (-2076, 5449)
6H	3287 (1650, 7819)	3 (1, 5)	4818 (2210, 9773)	4807 (2207, 9771)
9H	3867 (1695, 9028)	4 (2, 8)	3995 (1420, 9025)	3992 (1409, 9020)
12H	2322 (1075, 5320)	4 (2, 8)	6415 (3530, 12193)	6409 (3527, 12183)
2RPz	338 (67, 2215)	11 (4, 26)	7395 (3640, 14521)	7385 (3633, 14513)
3HR	5278 (1164, 20865)	0 (0, 1)	2338 (-6498, 7741)	2335 (-6502, 7733)

(c) Numbers of deaths due to active TB and LTBI treatment, numbers of deaths due to active TB averted by LTBI treatment in comparison with no treatment, and net numbers of deaths averted by LTBI treatment, for different treatment options in 1,000,000 patients diagnosed with LTBI aged 51-65 years.

Treatment option	Deaths due to active TB: Median (IQR)	Deaths due to LTBI treatment: Median (IQR)	Active TB deaths averted by LTBI treatment: Median (IQR)	Net deaths averted by LTBI treatment: Median (IQR)
No treatment	8633 (4797, 15895)			
3H	6390 (2802, 13494)	2 (1, 4)	1704 (-1957, 4975)	1703 (-1961, 4965)
6H	2863 (1430, 6891)	6 (3, 10)	4278 (1929, 8925)	4265 (1925, 8910)
9H	3373 (1470, 7984)	9 (5, 16)	3618 (1259, 8280)	3607 (1251, 8254)
12H	2017 (931, 4658)	9 (5, 16)	5757 (3112, 11219)	5745 (3102, 11196)
2RPz	292 (58, 1924)	21 (10, 49)	6503 (3163, 13290)	6468 (3122, 13269)
3HR	4620 (1008, 19128)	1 (0, 3)	2004 (-6834, 6922)	2004 (-6834, 6923)

(d) Numbers of deaths due to active TB and LTBI treatment, numbers of deaths due to active TB averted by LTBI treatment in comparison with no treatment, and net numbers of deaths averted by LTBI treatment, for different treatment options in 1,000,000 patients diagnosed with LTBI aged 66+ years.

Treatment option	Deaths due to active TB: Median (IQR)	Deaths due to LTBI treatment: Median (IQR)	Active TB deaths averted by LTBI treatment: Median (IQR)	Net deaths averted by LTBI treatment: Median (IQR)
No treatment	5078 (2797, 9510)			
3H	3837 (1669, 8245)	12 (6, 20)	927 (-1284, 2897)	903 (-1296, 2889)
6H	1705 (849, 4143)	34 (24, 45)	2485 (1100, 5269)	2450 (1063, 5244)
9H	2011 (872, 4812)	52 (37, 71)	2075 (660, 4926)	2017 (604, 4879)
12H	1199 (552, 2785)	52 (37, 71)	3366 (1787, 6712)	3319 (1742, 6657)
2RPz	173 (34, 1143)	112 (57, 206)	3812 (1833, 7959)	3662 (1683, 7845)
3HR	2762 (598, 11860)	5 (-1, 13)	1108 (-4580, 4064)	1108 (-4588, 4059)

Table 3.2 (a) Numbers needed to treat to avert 1 death due to active TB, and numbers of patients needed to be treated to cause 1 death due to LTBI treatment in patients diagnosed with LTBI, aged 17-34 years. NNT: “Number needed to treat”: Number needed to treat to avert 1 death due to active TB; NNH: “Number needed to harm”: number of patients whose treatment for LTBI is expected to cause 1 death due to that treatment. No discounting has been applied in calculation of deaths due to active TB.

Regimen	NNT	NNH
3H	510	3,103,942
6H	210	1,024,013
9H	255	658,406
12H	155	658,406
2RPz	133	253,024
3HR	383	7,595,988

(b) Numbers needed to treat to avert 1 death due to active TB, and numbers of patients needed to be treated to cause 1 death due to LTBI treatment in patients diagnosed with LTBI, aged 35-50 years.

Regimen	NNT	NNH
3H	506	1,116,910
6H	208	347,511
9H	250	225,260
12H	156	225,260
2RPz	135	92,885
3HR	428	2,820,686

(c) Numbers needed to treat to avert 1 death due to active TB, and numbers of patients needed to be treated to cause 1 death due to LTBI treatment in patients diagnosed with LTBI, aged 51-65 years.

Regimen	NNT	NNH
3H	587	555,904
6H	234	164,747
9H	276	109,788
12H	174	109,788
2RPz	154	46,797
3HR	499	1,433,462

(d) Numbers needed to treat to avert 1 death due to active TB, and numbers of patients needed to be treated to cause 1 death due to LTBI treatment in patients diagnosed with LTBI, aged 66+ years.

Regimen	NNT	NNH
3H	1,079	81,783
6H	402	29,288
9H	482	19,284
12H	297	19,284
2RPz	262	8,890
3HR	903	200,213

4. Interpretation of evidence

As previously reported, there is a large range of uncertainty in key parameter values estimated in the meta-analysis, which causes a wide range of uncertainty in net numbers of deaths averted by LTBI treatment. There is also considerable *relative* uncertainty in the numbers of deaths due to LTBI treatment but in *absolute* terms this uncertainty is very small.

On average, LTBI treatment reduces the patients' risk of death. However, for 3H and 3HR regimens in all age-groups, the inter-quartile range of PSA results includes negative net numbers of deaths averted.

Estimates of numbers needed to treat (NNT) to avert 1 death due to active TB are much smaller than the numbers needed to harm (NNH) estimates, indicating that the probability of benefit from LTBI treatment (i.e. death from active TB being averted) is much greater than the probability of harm (i.e. death due to LTBI treatment).