

Title: SIRCLE – a randomised controlled cost comparison of self-administered Short-course Isoniazid and Rifapentine for Cost-effective Latent tuberculosis Eradication

Authors: Justin T Denholm¹⁻³, Emma S McBryde, Damon Eisen, Alan Street², Elizabeth Matchett², Caroline Chen⁶, Thomas Shultz², Beverly Biggs², Karin Leder^{2,7}

1. Victorian Tuberculosis Program, Melbourne Health, Melbourne, Victoria, Australia
2. Victorian Infectious Diseases Service, Royal Melbourne Hospital, Parkville, Victoria, Australia.
3. Department of Microbiology and Immunology, University of Melbourne, Parkville, Victoria, Australia
4. James Cook University, Townsville, Queensland, Australia
5. Townsville Hospital, Townsville, Queensland, Australia
6. Pharmacy Department, Royal Melbourne Hospital, Parkville, Victoria, Australia.
7. School of Public Health and Preventive Medicine, Monash University, Victoria Australia

Corresponding author: Justin Denholm, Victorian Tuberculosis Program, Doherty Institute, 792 Elizabeth Street, Melbourne, 3000. (p) +61 3 9342 9428, (e) justin.denholm@mh.org.au

Authors contributions: JD, EM, DE, AS and BB developed the initial study protocol. All authors were involved in study conduct and oversight. JTD prepared the initial draft of study report, and all authors contributed to preparation of the final manuscript.

Acknowledgements: Funding for this study was provided through a grant by the John Burge Trust, administered by the State Trustees of Victoria. Rifapentine was provided by Sanofi. Neither organisation played a role in study design, conduct, analysis or manuscript preparation. The authors retain responsibility for this data and manuscript submission.

Manuscript word count: 1,482

This is the author manuscript accepted for publication and has undergone full peer review but has not been through the copyediting, typesetting, pagination and proofreading process, which may lead to differences between this version and the Version of Record. Please cite this article as doi: [10.1111/imj.13601](https://doi.org/10.1111/imj.13601)

Abstract

This randomised controlled trial compared costs of 9 months of daily isoniazid (9H) with 12 weeks of weekly isoniazid and rifapentine (3HP). Primary outcome measure was total healthcare system costs (AUD) per completed course of LTBI therapy. Overall, 34 of 40 participants in the 9H group (85%) and 36/40 in the 3HP group (90%) completed therapy. The cost per completed course of 9H was 601 AUD, while that of 3HP was significantly lower at 511 AUD ($p<0.01$). This study provides cost analysis evidence to support the use of 3HP for the treatment of LTBI in Australia.

Key words: latent tuberculosis; tuberculosis; antitubercular agents; preventative medicine; controlled clinical trial

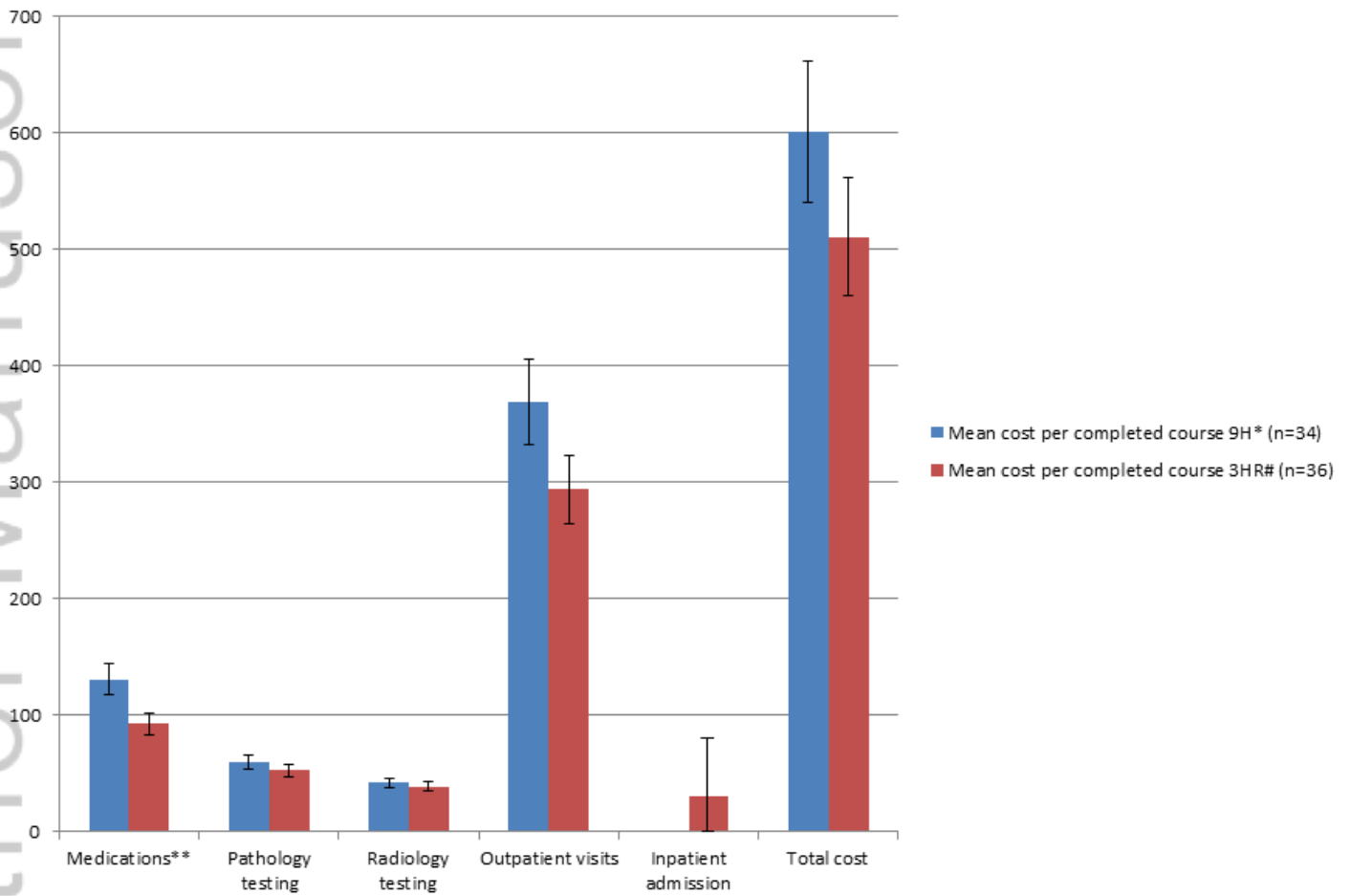


Figure 1a.tif

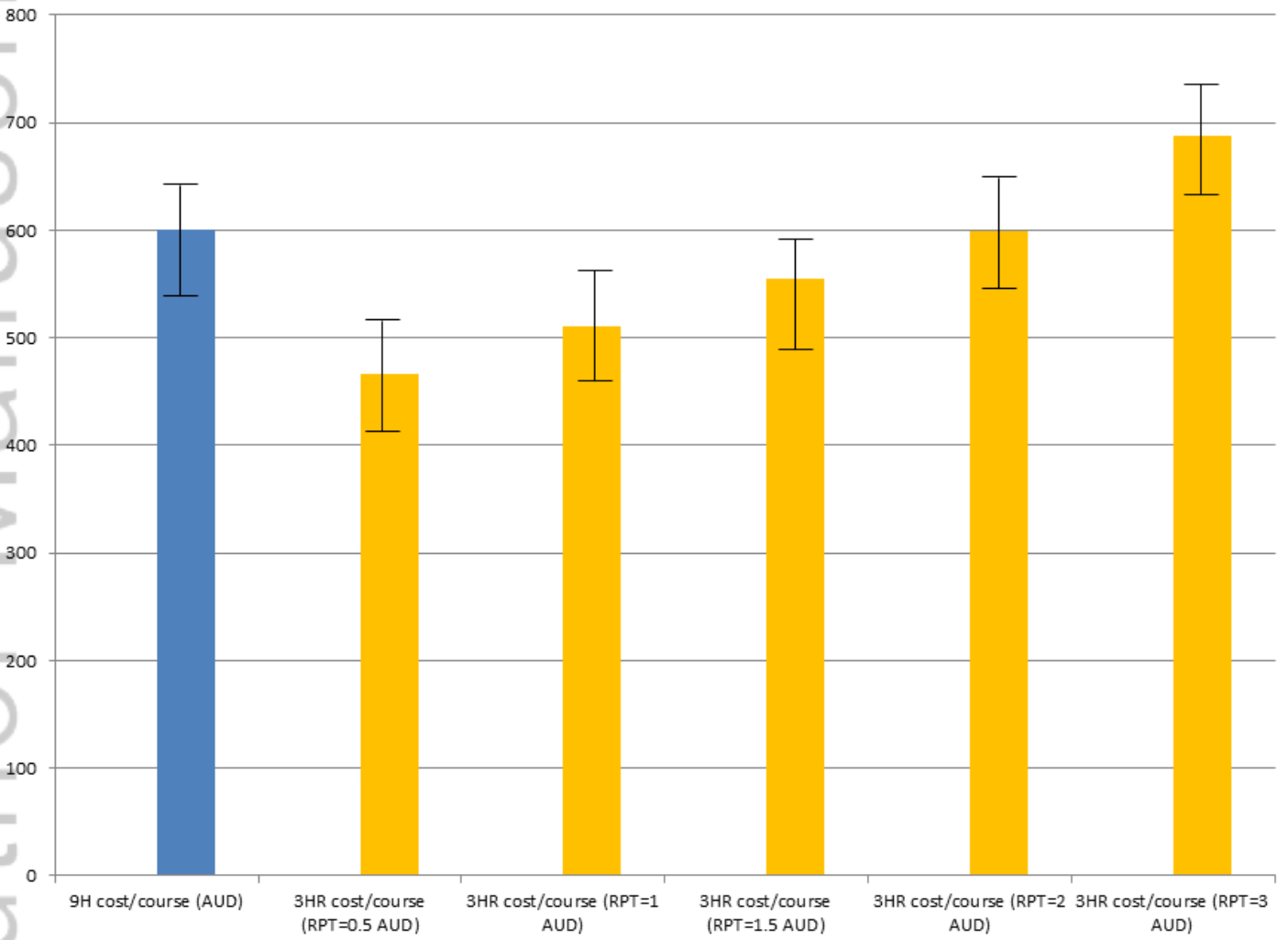


Figure 1b.tif

Introduction

Latent tuberculosis infection (LTBI) is a common condition, associated with increased lifetime risk of active disease¹⁻³. Current treatment for LTBI in Australia consists most frequently of a 9-month course of daily isoniazid (9H)⁴. While effective in reducing the risk of subsequent TB reactivation, the usefulness of isoniazid therapy is limited by prolonged duration and risk of adverse effects, particularly hepatotoxicity⁵. A three-month course of weekly isoniazid and rifapentine (a long-acting rifampicin derivative; 3HP) has been shown to be as effective as nine months of daily isoniazid, and associated with less hepatotoxicity⁶. This study has led to guidelines from both the US Centers for Disease Control and World Health Organization recommending this regimen for most LTBI treatment contexts^{7,8}; however, rifapentine is not currently commercially available in Australia.

Introduction of this regimen would have apparent advantages for people with LTBI in Australia by safely shortening duration of LTBI therapy. However, the cost-benefit of this new therapeutic approach is uncertain. Cost-effectiveness modelling has suggested that short course therapy may be more expensive per course, although potentially cost-saving per case of TB averted⁹. Such modelling is sensitive to assumptions regarding cost of new therapies and practice variations regarding routine management¹⁰. Real-world data comparing different approaches to LTBI therapy are therefore required to inform cost comparisons.

Methods

Study design and participants

This was a pragmatic randomised controlled cost analysis trial comparing 3HP with 9H.

The protocol was registered prospectively with the Australian and New Zealand Clinical Trials Registry (www.anzctr.org.au; U1111-1142-8697) and approved by the Melbourne Health Human Research Ethics Committee (2013.036). Participants were recruited from clinics of a tertiary referral centre in Melbourne, Australia. Eligible participants were aged >18, diagnosed with LTBI and were willing to undergo randomisation. Potential participants were ineligible if they had a history of treatment for active/ LTBI, allergy/intolerance to isoniazid or rifamycins, a serum alanine aminotransferase (ALT) > 100 IU/L, were pregnant or breastfeeding or known to be contacts with a source case resistant to isoniazid or rifampicin.

Following randomisation, participants were managed according to local guidelines¹¹. Therapy for both study arms was self-administered by patients, with adherence counselling and review provided at clinic visits. Standard local practice includes baseline liver function testing (LFT). Clinicians had discretion to perform additional tests or clinical review as warranted. Participants who failed to attend scheduled clinic review had three attempts made to reschedule, with contact via phone and/or postal address.

Randomisation and blinding

1:1 randomisation was performed by computer-generated sequence made available only to investigators following individual participant enrolment. Due to the inherent differences in treatment duration, participants and investigators were not blinded to allocation.

Statistical analysis

Sample size was calculated to consider cost differences between intervention and control groups as the primary outcome. Based on local programmatic treatment data, 9H treatment was anticipated to cost 560 AUD. Assuming an expected difference of 200 AUD between regimen cost and variation of 50 AUD, it was calculated that 36 participants per group would have power of >80% to detect a difference with $\alpha=0.05$.

Costs were assessed at the level of the healthcare system, in AUD. Daily costs associated with hospitalisation were taken from previously published costing studies in the local context¹². The relevant Medicare Benefit Schedule fee for pathology or radiology tests was applied to tests performed in an outpatient setting. Tests performed prior to referral for consideration of LTBI diagnosis or treatment were not included in total costs.

At present, rifapentine is not registered in Australia. As cost of rifapentine in Australia was not available, and with note to commercial costs for the registered product in the USA and international discussion regarding price structures, the primary analysis assumed a cost of 1

AUD per 150mg tablet of rifapentine¹³. Secondary analyses were also performed with varying assumptions regarding market pricing of rifapentine, ranging from 0.5 to 3 AUD per 150mg tablet.

Statistical analysis was conducted using Stata 13.1 (College Station, USA) and Excel. Descriptive analyses were performed on demographic data, service utilisation and treatment completion. Primary analysis considered differences in cost per completed course for each group, by comparison of total costs for all randomised participants in each group divided by the number successfully completing treatment. Cost comparison was evaluated using t-tests and Mann-Whitney U tests. Secondary analyses were compared to consider differences in event frequency with inter-group comparisons made with χ^2 analysis or Fisher's exact test. P-values were calculated and considered significant if $p < 0.05$. All calculation of probabilities employed two-tailed tests.

Results

Between December 12, 2013 and June 16, 2015, 80 participants were enrolled, with 40 participants randomised to each treatment arm. The trial was ceased when complete planned cohort enrolment was achieved. Demographic data are presented in table 1.

Overall, 34 of 40 participants in the 9H group (85%) completed therapy. No participant ceased therapy due to reported side effects, 4 participants cited duration of therapy as the basis for discontinuation and 2 failed to return for planned follow up. The mean time to discontinuation in this cohort was 30 days (range 0-60). No participant receiving 9H had a serious unexpected adverse event or was hospitalised during therapy.

In the 3HP group, 36 of 40 participants (90%) completed therapy. Three participants discontinued therapy due to side effects, including headache (2), nausea (1) and febrile illness (1). One patient discontinued therapy without adverse effects, citing pregnancy plans after initiation. Mean time to discontinuation following treatment initiation was 21 days (range 14-28).

One patient in the 3HP group was hospitalised during therapy, after developing a febrile illness within 24 hours of administration of the 3rd dose. Therapy was ceased and the participant recovered fully.

The number of outpatient reviews differed between study groups, with a median of 5 and 3 study visits in the 9H and 3HP groups respectively. Pathology and radiology testing did not differ between groups, with a median of 1 liver function test performed in both groups.

Cost

Overall, the median cost of treatment for the 9H group was 511 AUD (95% CI 464-558) and 3HP was 460 AUD (95% CI 392-527). The primary outcome was the mean cost of completed treatment course, which was 601 AUD (95% CI 555-647) for 9H, and 511 AUD (95% CI 448-547) for 3HP ($p<0.01$).

Comparison of cost distribution between groups and overall cost is shown in Figure 1a. 3HP was more expensive for inpatient costs, while outpatient and total costs was less for 3HP. In both regimens, outpatient physician visits were the most expensive component of treatment, accounting for 55-62% of total cost per completed course. While inpatient admission is associated with considerable cost, this occurred on a single occasion only. A sensitivity analysis was conducted by excluding this individual from primary analysis. The total cost of treatment for this participant was 1673 AUD, with 1173 AUD directly attributable to hospital stay. Exclusion of this participant resulted in a mean total cost of 452 AUD per completed course for 3HP (37/39 completing therapy). This remained significantly lower than 601 AUD (unchanged) total cost per completed therapy for 9H ($p<0.01$).

Secondary analyses were conducted to consider a range of rifapentine medication costs. Comparison was conducted from 0.5 AUD to 3 AUD per 150mg tablet, shown in Figure 1b. In our cohort, a rifapentine cost of 0.5 AUD would have resulted in a total cost of 467 AUD (95% CI 404-529) per completed course, which was also significantly lower than 9H ($p<0.01$). Alternatively, rifapentine costs of 2-3 AUD resulted in increased comparative cost in the 3HP arm ($p=0.1$ for 3 AUD when compared to 9H).

Discussion

This pragmatic randomised control trial demonstrated cost benefit with weekly rifapentine and isoniazid when compared with daily isoniazid therapy. We also found that both regimens were well tolerated, and completion rates were high, in keeping with previous local reports¹⁴. Given existing evidence suggesting statistically equivalent outcomes in prevention of subsequent active TB infection, these similarities in observed treatment acceptability provide further weight to implementation of short-course therapy for LTBI in an Australian context.

There are several limitations to this study. Most significantly, as rifapentine is not a commercially available product, assumptions regarding cost in an Australian context were required. While we have presented alternative analyses regarding medication cost, commercial variation in the future cost of rifapentine could impact on these results. We also chose to continue current approaches to medication adherence, particularly self-administration of doses between clinic visits. While initial trials of 3HP employed directly observed therapy (DOT), we note that subsequent studies in comparable settings have suggested no significant difference in adherence and completion with patient self-administration¹⁵.

The cost of both regimens was heavily influenced by tertiary outpatient visits. Alternative strategies involving less frequent review would have reduced costs, although this may have resulted in additional adverse effects and/or increased loss to follow up. While typical for Australian management of LTBI, this approach will likely be more expensive than community-based settings, and strategies to deliver LTBI therapy in alternative locations should be explored.

Table 1: Baseline demographic details

	<u>9H* (n=40)</u>	<u>3HP# (n=40)</u>
Female (%)	23 (58)	18 (45)
Age (median (range))	29 (18-63)	30 (21-77)
Weight (kg; median (range))	65 (53-90)	66 (52-114)
ALT (IU/mL; median (range))	19 (9-47)	25 (11-73)
HIV positive (%)	0(0)	0(0)
<u>Region of birth (%)</u>		
Australia	4(10)	3(8)
Indian subcontinent	8 (20)	14 (35)
Africa	15 (38)	7 (18)
Asia	6 (15)	7 (18)
Other	7 (18)	9 (23)
<u>Additional risk factors for progression to active TB*</u>		
Recent exposure to TB (%)	7(18)	6(15)
Current/planned immunosuppression (%)	6(15)	2(5)

*As reported by treating clinicians at enrolment.

Figure 1a: Comparative cost of isoniazid (9H) versus isoniazid/rifapentine (3HP) by category, in Australian dollars (AUD)

Figure 1b: Total cost of isoniazid (9H*) versus isoniazid/rifapentine (3HP#) per completed course, with sensitivity analysis of varied assumptions regarding rifapentine (RPT) cost, in Australian dollars (AUD)

*9H = Daily isoniazid therapy for 270 doses. # 3HP = Weekly isoniazid and rifapentine therapy for 12 doses.

** Medication cost shown assumes 72 AUD per course

All costs rounded to nearest 0.1 AUD

References

1. Trauer JM, Moyo N, Tay E-L, Dale K, Ragonnet R, McBryde ES, et al. Risk of active tuberculosis in the five years following infection... 15%? *CHEST* 2016;**149**(2):516-25.
2. Taylor WC, Tsevat J, Pauker SG. Priorities for the treatment of latent tuberculosis. *N Engl J Med* 2004;**351**(8):832-4
3. McBryde E, Denholm JT. Risk of active tuberculosis in immigrants: effects of age, region of origin and time since arrival in a low-exposure setting. *Med J Aust* 2012;**197**(8):458-61.
4. Denholm JT, McBryde ES. Management of latent tuberculosis infections in Australia and New Zealand: a review of current practice. *Tuberc Res Treat.* 2010;**2010**:1-5
5. Saukkonen JJ, Cohn DL, Jasmer RM, Schenker S, Jereb JA, Nolan CM, et al. An official ATS statement: hepatotoxicity of antituberculosis therapy. *Am J Respir Crit Care Med* 2006;**174**(8):935-52.
6. Sterling TR, Villarino ME, Borisov AS, Shang N, Gordin F, Bliven-Sizemore E, et al. Three months of rifapentine and isoniazid for latent tuberculosis infection. *N Engl J Med* 2011;**365**(23):2155-66.
7. Recommendations for use of an isoniazid-rifapentine regimen with direct observation to treat latent Mycobacterium tuberculosis infection. *MMWR* 2011;**60**(48):1650-3.
8. Getahun H, Matteelli A, Abubakar I, Aziz MA, Baddeley A, Barreira D, et al. Management of latent Mycobacterium tuberculosis infection: WHO guidelines for low tuberculosis burden countries. *Euro Resp J* 2015:ERJ-01245-2015.
9. Shepardson D, Marks S, Chesson H, Kerrigan A, Holland D, Scott N, et al. Cost-effectiveness of a 12-dose regimen for treating latent tuberculous infection in the United States. *Int J TB Lung Dis* 2013;**17**(12):1531-7.
10. Shepardson D, MacKenzie WR. Update on cost-effectiveness of a 12-dose regimen for latent tuberculous infection at new rifapentine prices. *Int J Tuberc Lung Dis* 2014;**18**(6):751.
11. Street AS, McBryde ES, Denholm JT, Eisen DP, editors. Management of tuberculosis. 1 ed. Parkville: Victorian Infectious Diseases Service; 2012.
12. Hannan L, Steinfors D, Irving L, Hew M. Direct ultrasound localisation for pleural aspiration: translating evidence into action. *Intern Med J* 2014;**44**(1):50-6.
13. DeLuca A, Frick M, Lessem E, Kanouse J, Wegener D, Mingote LR. Activism on rifapentine pricing: removing cost barriers to improve the uptake of tuberculosis research innovations. *Pub Health Action* 2014;**4**(4):238.

14. Denholm JT, McBryde ES, Eisen DP, Penington JS, Chen C, Street AC. Adverse effects of isoniazid preventative therapy for latent tuberculosis infection: a prospective cohort study. *Drug Healthcare Patient Safety*. 2014;**6**:145.
15. Belknap R, Borisov A, Feng P, et al. Adherence to once-weekly self-administered INH and rifapentine for latent TB: iAdhere. Abstract 827LB. Conference on Retroviruses and Opportunistic Infections Seattle, Washington, USA; 2015.