

## Journal Pre-proof

A cost comparison of amikacin therapy with bedaquiline, for drug-resistant tuberculosis in the UK

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## Highlights

- The WHO in 2018 replaced the injectable agents with bedaquiline for drug-resistant tuberculosis
- bedaquiline does not require intravenous administration and reduces culture conversion time.
- The cost of bedaquiline in the UK is close to cost neutral compared to injectable amikacin.

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## TITLE PAGE

**A cost comparison of amikacin therapy with bedaquiline, for drug-resistant tuberculosis in the UK.****Running title: Bedaquiline in the UK for drug-resistant tuberculosis****Highlights**

- The WHO in 2018 replaced the injectable agents with bedaquiline for drug-resistant tuberculosis
- bedaquiline does not require intravenous administration and may reduce culture conversion time.
- The cost of bedaquiline in the UK is close to cost neutral compared to injectable amikacin.

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## A cost comparison of amikacin versus bedaquiline, for the treatment of drug-resistant tuberculosis in the United Kingdom

**Comment [u1]:** This is 4 letters too long so United Kingdom could be shortened to UK.  
This was the preferred title by the reviewer.

### ABSTRACT

**Objectives:** Prioritisation of oral bedaquiline over the injectable agents in the treatment of multidrug-resistant Tuberculosis (MDR-TB) in the World Health Organisations (WHO) 2019 guidelines prompted this UK analysis of cost implications. The objective was to estimate the costs of amikacin versus bedaquiline in MDR TB treatment regimens using a historical cohort where the injectable agents were the standard of care.

**Methods:** This was a retrospective study using a known cohort of UK patients treated with an injectable agent, with data available on resource use, costs for the use of amikacin were compared with those for bedaquiline, based on recommended monitoring for bedaquiline.

**Results:** The estimated cost of treatment per patient had mean (sd) of £27236 (4952) for the observed injectable group, £30264 (3392) and £36309 (3901) for the 6 and 8 month amikacin groups, and £31760 (2092) for the bedaquiline group. The cost in the bedaquiline group was £30772 (1855) with a 10 % reduction and £27079 (1234) with a 33% reduction in in-patient stay.

**Conclusions:** In most scenarios, bedaquiline is close to cost neutral compared with injectable therapy, especially if, as expected, some reduction in duration of admission is possible as a result of bedaquiline's more rapid culture conversion.

### INTRODUCTION

Multidrug-resistant tuberculosis (MDR-TB) is a major public health concern in the UK and globally. Treatment is prolonged, more toxic and less effective compared to that for drug susceptible TB. In 2018 and then consolidated in 2019, the World Health Organisation (WHO) published major revisions to guidelines, prioritising the new drug bedaquiline and down-grading the injectable agents (aminoglycosides and polypeptides) which had played a major part in previous guidelines.<sup>[1, 2]</sup> Changes were based on meta-analysis data of efficacy, accumulating trial data supporting bedaquiline and ethical concerns regarding the side

effect profile of the injectable agents; most notably irreversible ototoxicity with the aminoglycosides and an association with increased mortality for capreomycin.<sup>[3-5]</sup> Furthermore, although phase three trial data is not available cohort data suggests that bedaquiline use within program conditions is associated with reduced mortality.<sup>(6)</sup> The revised guidelines have been adopted by many countries and this year NHS England published guidelines releasing funding for bedaquiline to be used in line with the most recent WHO guidelines.<sup>(7)</sup>

Although bedaquiline is currently expensive at £18700 for 6 months in high income countries, it has the potential to make treatment cheaper as a whole due to its oral formulation, reduced need for monitoring and potential to reduce time to sputum culture conversion and thus reduce inpatient stay.<sup>[5]</sup> We undertook this retrospective study to explore the cost implications of the change in policy from the injectable amikacin to bedaquiline in England.

## **METHODS**

The prior standard of care in the UK until July 2019 involved an inpatient stay until the patient is deemed non-infectious or was able to self-isolate, followed by a period under the outpatient parenteral antimicrobial therapy team (OPAT) where the injectable agent was delivered intravenously at home via a long line (PICC or HICKMAN) and then a period where only oral medications were given. The injectable agent was given for 6-8 months (stopped early if side effects occur, which they do in most cases)<sup>(9)</sup> and the total treatment duration was 18-24 months.<sup>[2]</sup> In comparison a patient on bedaquiline can go straight from hospital to the oral medication stage. Bedaquiline currently has licencing for 6 months of the total 18-24 months of treatment

A cohort of 100 patients, for whom data were already available, was used to calculate the NHS costs of patients treated with an injectable agent in an observed cohort (in which median duration of injectable is less than 6 months).<sup>(8, 9)</sup> This was compared with a predicted cost with a minimum recommended treatment of 6 months of an injectable agent and a predicted model with bedaquiline substituted for the injectable used for 6 months. We chose 6 months for the ideal amikacin duration so as to maintain costs over a 6 month period and because amikacin use for over 6 months is rarely possible due to side effects.<sup>(4, 9)</sup>

As a comparison we also calculated the costs of the full 8 months of amikacin though we feel this is rarely used. A full costing of changing other oral medications as per the WHO 2019 guideline (e.g. prioritisation of linezolid which is now off patent) was not undertaken. 4 hospitals provided cost information for care (Table 1). The amount of monitoring required for each scenario was determined by UK guidance.<sup>(10)</sup> The injectable agents require the cost of the OPAT service, lines, weekly blood tests and monthly audiograms. In comparison, bedaquiline requires monthly electrocardiograms and monthly blood tests. The predicted model with bedaquiline was also analysed, with inpatient stay reduced by 10% and 33% of duration, based on the 33% reduction in time to sputum culture conversion observed with bedaquiline.<sup>[5]</sup> A multi-level Bayesian model was used for analysis. For the missing data across sites, mean costs were assumed (below) and analysis was also performed using minimum and maximum cost values.

## RESULTS

The expected cost of treatment per patient had mean (sd) of £27236 (4952) for the observed injectable group, £30264 (3392) and £36309 (3901) for the ideal 6 month and ideal 8 month amikacin group, and £31760 (2092) for the bedaquiline group (Table 2). The cost in the bedaquiline group was £30772 (1855) with a 10 % reduction and £27079 (1234) with a 33% reduction in in-patient stay. The findings are represented graphically in Figure 1. Figure 2 gives the expected difference in costs.

## DISCUSSION

We show that treatment with bedaquiline is close to cost neutral with current pricing of bedaquiline compared to treatment with an injectable, especially if, as predicted, in-patient stays are reduced by 10-33% with use of bedaquiline. Even in a worst case scenario, without any reduction in hospital stay, total costs to the NHS of first line use of bedaquiline for MDR TB, as recommended by the WHO, would be extremely modest, at a mean expected per patient extra cost of £3519 with only around 50 patients per year in the UK expected.

Furthermore, we may have underestimated the costs of amikacin usage, and have not performed a full cost-effectiveness analysis including quality of life assessment, or considered the ethical considerations of an inferior intravenous regimen with significant

side effects. Excluded costs include the cost of travel for OPAT administration and blood tests; staff time of TB nursing teams dealing with the complications of amikacin and its delivery; the morbidity and loss of earnings while needing a PICC line (particularly in those who are self-employed) and the cost to both the NHS and, most importantly, to the individual of significant and permanent hearing loss over the lifetime. Ototoxicity is estimated to be apparent in up to 61% of patients given prolonged amikacin and a significant proportion will require hearing replacement.<sup>[4]</sup> Furthermore, the hearing loss has an increased significance if we consider the ethical concept of reciprocity with regards to management for TB; all treatment has a dual purpose of treating the individual and protecting society.<sup>(11)</sup> With the duality in mind the infliction of hearing loss on an individual is even more questionable when there is an alternative.

We have predicted that inpatient stays in the UK are likely to reduce due to the importance placed on sputum culture conversion in discharge decisions. Many patients in the UK are admitted until sputum is culture negative in line with NICE guidance.<sup>(12)</sup> Although, there is some anecdotal evidence that a reduction in admission is already happening we have to wait to see if this becomes reality or not. Furthermore, admission duration may reduce further for extra-pulmonary cases as many patients were admitted to facilitate intravenous access and the initiation of OPAT and this admission is no longer required. Another area where we need to wait for further information is the conclusive evidence from phase 3 trials of bedaquiline's efficacy and safety, although the safety concerns from the phase 2 data has not been brought out in cohort and meta-analysis data.<sup>(3, 6)</sup>

Another issue we have not included is the pricing of bedaquiline and the potential for a reduction in the drug cost of bedaquiline with the transfer of bedaquiline to first line in UK guidelines and through further advocacy at a global scale. Low income countries receive bedaquiline at \$400 (USD) for a 6 month course through the Stop TB Partnership's Global Drug Facility. However, this is still high and unaffordable for many countries when combined with all the other drugs required to make an effective regimen. Furthermore, researchers at Liverpool University and other advocates who have calculated that \$1 (USD) per day would be a fairer price allowing drug companies to cover development costs while also recognising the huge public investment in the drug development.<sup>(13,14)</sup>

In summary, our retrospective cost analysis supports the recent changes in UK guidelines recommending bedaquiline in line with WHO guidelines rather than using toxic injectable medications of questionable efficacy. Further advocacy is required to help bring the cost of bedaquiline down to a feasible price for all who require it.

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## FIGURE LEGENDS

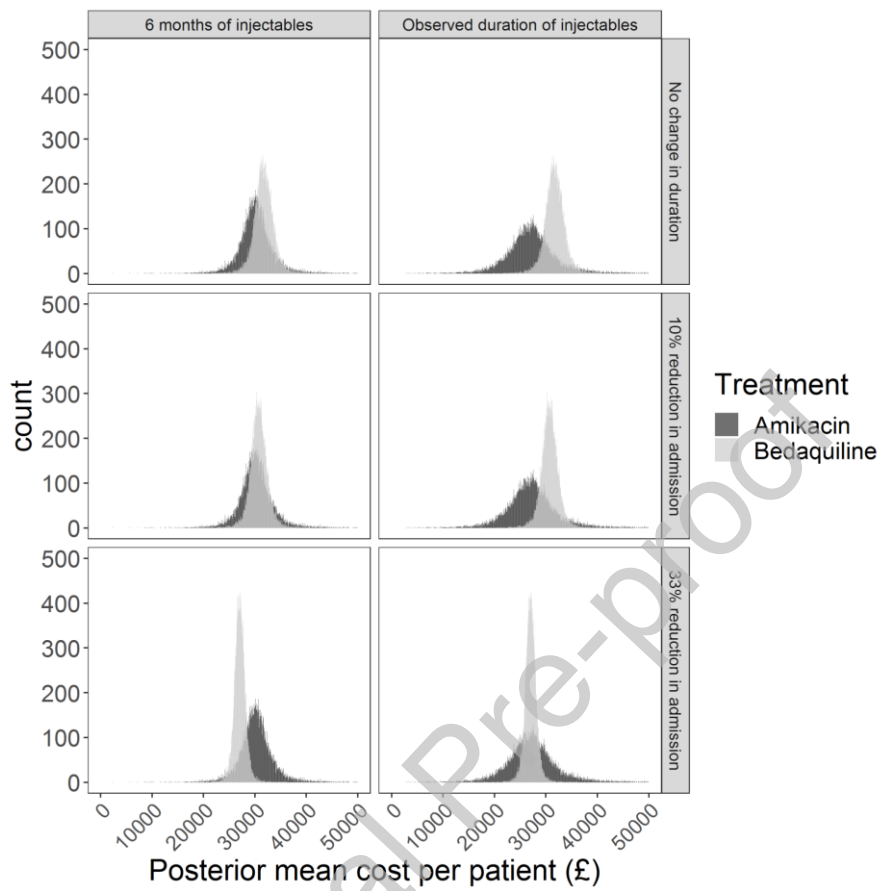
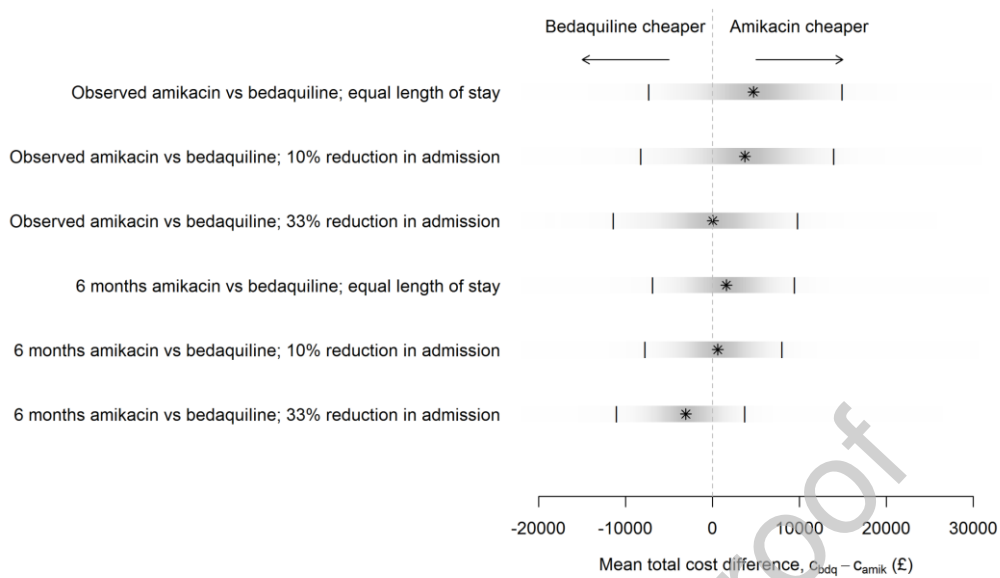


Figure 1

Costs for the observed and 6 month amikacin scenarios, versus bedaquiline, assuming either no reduction or a 10% or 33% reduction in in-patient stay with bedaquiline, compared to amikacin.



**Figure 2**

**Posterior distribution strip plots of the difference in mean costs between amikacin and bedaquiline scenarios. The 95% CrI is indicated by the vertical marks and the median by the asterisks.**

**Table 1:****Costs and usage of each item (£). Usage per patient (days/number of tests: median [IQR]).**

Name	Mean costs (£)** (per day/unit)	24 weeks treatment				
		Observed treatment AK	Ideal AK	0% reduction*** BDQ 24	10% reduction BDQ 24	33% reduction BDQ 24
Admission†	2865.43, 245.37	61[15.5,92]	61[15.5,92]	61[15.5,92]	54.9[13.95,82.8]	40.87[10.3,63.32]
Lines‡	117.25	1[1,1]	1.05[0.75,1.505]	0	0	0
ECG	20	3	3	7	7	7
Hearing test	33.75	3[1,6]	8	0	0	0
Blood tests	10.84	0*	0*	8	8	8
OPAT	116.67	91[0,149.5]	107[76,152.5]	0	0	0
AK (days)	23.04	160[91.5,187]	168	-	-	-
BDQ (days)	111.31	-	-	168	168	168

AK = amikacin for the observed duration of time with a median use of under 6 months, BDQ 24 = bedaquiline for 6 months (24 weeks), Ideal AK= amikacin for 6 months (24 weeks). \*\*\* X% reduction refers to the estimated reduction in inpatient stay due to the earlier sputum culture conversion predicted to happen with bedaquiline.

\*\* hospitals where data obtained were in London and the west midlands (St Mary's Hospital, The Royal Free Hospital, Birmingham Heartlands Hospital, and St Georges Hospital). Costs at 2018-2019 prices.

† Inpatient stays cost is fixed up to 19 days then per additional day. Although the inpatient tariff covers all items while an inpatient we have added the cost for items directly related to delivery of either amikacin or bedaquiline therapy: lines, ECGs, bloods and audiology tests while an in-patient, in order to fairly reflect the differences in cost of the 2 drugs to the service.

‡HICKMAN or PICC.

\*included within the OPAT tariff.

Costs excluded as estimated to be the same for all types of treatment: outpatient appointment; additional payments for co-morbidities, negative pressure rooms or ICU stay and choice of other drugs.

Table 2

Cost analysis results for each scenario, with posterior summary statistics.

	Scenario*	Cost AK (sd; £)	Cost BDQ (sd; £)	Cost BDQ- cost AK (sd; £)	P(BDQ cost- saving)	Max cost BDQ P(cost- saving) $\geq$ 0.95 (£)
Observed AK vs BDQ	0% reduction	27236 (4952)	31760 (2092)	4524 (5351)	0.16	5100
	10% reduction	27236 (4952)	30772 (1855)	3536 (5297)	0.2	6200
	33% reduction	27236 (4952)	27079 (1234)	-157 (5098)	0.5	10400
24 weeks AK vs BDQ	0% reduction	30264 (3392)	31760 (2092)	1496 (3991)	0.31	10400
	10% reduction	30264 (3392)	30772 (1855)	508 (3879)	0.42	11600
	33% reduction	30264 (3392)	27079 (1234)	-3185 (3623)	0.86	15800
32 weeks AK vs BDQ	0% reduction	36309 (3901)	31760 (2092)	-4549 (4420)	0.88	15600
	10% reduction	36309 (3901)	30772 (1855)	-5537 (4314)	0.92	16800
	33% reduction	36309 (3901)	27079 (1234)	-9230 (4089)	0.98	18000

BDQ = bedaquiline dosed for 24 weeks in all scenarios, AK = amikacin; sd = standard deviation. P(BDQ cost-saving) = probability that bedaquiline is cost saving under each scenario. \*0-33% reduction refers to the estimated reduction in inpatient stay due to the earlier sputum culture conversion predicted to happen with bedaquiline. Max cost BDQ P (cost-saving)  $\geq$  0.95 = the maximum cost of bedaquiline to ensure over or equal to 95% chance that bedaquiline would be cost saving over amikacin.