NHS England

Evidence review: Bedaquiline and/or delamanid for multi-drug resistant tuberculosis in children and young people

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Contents

1 Introduction

Existing guidance from the National Institute for Health and Care Excellence (NICE)

- We found no guidance from NICE about the use of bedaquiline and/or delamanid for multi-drug resistant tuberculosis in children and young people.

The indication and epidemiology

- Tuberculosis (TB) is an infection. In humans, the most common causal bacterium is *Mycobacterium tuberculosis* and the most usual site is the lung. There is great variation in distribution of TB in England; certain subgroups, such as new migrants, ethnic minority groups and those with social risk factors are disproportionally affected. The most deprived 10% of the population have an incidence of TB more than seven times higher than the least deprived 10%, and people born outside the UK have a rate 13 times higher than people born in the UK (Public Health England 2018).
- TB incidence in England peaked at 8,280 in 2011. Since then the number of people notified with TB has fallen by nearly 40% to 5,102 people in 2017. At 9.2 per 100,000, this was the lowest incidence of TB ever recorded in England and, for the first time, England is considered to be a low incidence country under current World Health Organisation (WHO) definitions (Public Health England 2018).
- TB in children is much rarer than in adults. A total of 180 cases were notified in children aged less than 15 years in 2017 (Public Health England 2018), compared with 207 the previous year. In 2017, the rate of TB in UK born children, a proxy for recent transmission in England, was 1.4 per 100,000, a 59% reduction from the peak of 3.4 per 100,000 in 2008.
- TB can be treated successfully with antibiotics. However, *M tuberculosis* has evolved resistance to many of the antibiotics to which it was previously susceptible, making treatment more difficult. Patients usually acquire drug-resistant disease either as a result of spread of a drug-resistant strain from another person or as a result of inappropriate or incomplete treatment.
- Multi-drug-resistant tuberculosis (MDR-TB) is diagnosed when the infecting bacteria fail to respond to rifampicin and isoniazid, two first-line antibiotics used to treat the illness. Treatment of MDR-TB requires second-line drugs such as fluoroquinolones and aminoglycosides, which in general are less effective, more toxic, require longer courses of treatment and are more expensive than first-line drugs. Also, aminoglycosides are given by injection, a further disadvantage of their use (NHS England 2015).
- Extensively drug-resistant tuberculosis (XDR-TB) is resistant to rifampicin, isoniazid, at least one fluoroquinolone and at least one injectable agent.
- Treatment of MDR- and XDR-TB is less likely to be successful. These conditions are more often fatal than infection with TB sensitive to rifampicin and isoniazid.
- MDR-TB in children is extremely rare in England. One person aged less than 15 years was diagnosed with MDR-TB or rifampicin-resistant TB in England in 2017. Public Health England does not publish data on XDR-TB by age, but in 2017 in England there were only three cases of any age of confirmed XDR-TB at diagnosis (Public Health England 2018). According to NHS England, “In 2017, 0 of 3 XDR-TB cases were in children, in 2016 this was 2 of 10 XDR-TB. So far during 2018, a total of 8 cases aged below 18 years have been presented to the BTS MDR Clinical Advice Service: 5 cases of MDR-TB, two of XDR-TB and one of other species of Mycobacteria.” (NHS England unpublished communication).

Standard treatment and pathway of care

- Standard treatment of children with pulmonary TB in England is with six months of isoniazid and rifampicin, along with pyrazinamide and ethambutol for the first two months of the six-month treatment period (NHS UK).
- MDR-TB and XDR-TB require treatment with at least six antibiotics to which the mycobacterium is likely to be sensitive. These may include aminosalicylic acid, amikacin, capreomycin, cycloserine, azithromycin, clarithromycin and moxifloxacin (British National Formulary).

The intervention

- Bedaquiline is a novel antibiotic, effective against strains of *M tuberculosis* resistant to other agents. It belongs to a new class of anti-mycobacterial drugs known as diarylquinolines, and exerts a bactericidal and sterilizing activity against *M tuberculosis* by inhibiting adenosine triphosphate synthase (Chahine et al 2014).
- Delamanid is also a new antibiotic with similar indications. It is a member of the nitroimidazole class. It acts by inhibiting the synthesis of methoxy-mycolic acid and keto-mycolic acid, both mycobacterial cell wall components (Xavier et al 2014).
- Both drugs are licensed in the UK for use in adults only, in combination treatment of MDR-TB (British National Formulary). Both licences are for 24 weeks treatment.

Rationale for use

- The addition of drugs to which MDR-TB is sensitive may increase the chances of cure. Treating patients with several antibiotics concurrently reduces the risk of the emergence of drug resistance. However, it is uncertain whether treating children and adolescents with bedaquiline and delamanid, separately or concurrently, would be effective, safe or cost-effective.

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2 Summary of results

- There is little published research within the scope of the questions identified for this review. We found three studies suitable for inclusion.

PICO I: Bedaquiline

One case series (Achar et al 2017, n=27)

Negative sputum culture results

- Achar et al 2017 reported that 23/23 (100%) of participants had negative culture results at the time the paper was prepared. 10/27 (37%) of participants were culture-negative at inception.

Electrocardiographic abnormalities

- Achar et al 2017 reported that 5/27 (19%) of participants had a corrected QT interval of more than 500ms, or more than 60ms change from baseline plus torsade de pointes, polymorphic ventricular tachycardia or signs/symptoms of serious arrhythmia. No

patient experienced symptoms attributable to prolongation of QTcF during treatment with bedaquiline.

PICO II: Delamanid

One case series (Tadolini et al 2016, n=16)

Negative sputum culture results

- Tadolini et al 2016 reported that 13/16 (81%) of participants had negative culture results at the time the paper was prepared. All had positive sputum culture when delamanid was started.

Adverse effects other than "mild"

- Tadolini et al 2016 reported that 1/16 (6%) had adverse effects other than "mild".

PICO III: Bedaquiline and delamanid

One systematic review (D'Ambrosio et al 2017)

D'Ambrosio et al 2017 was a systematic review of studies reporting the results of bedaquiline and/or delamanid use in children or adolescents with confirmed MDR- or XDR-TB. It included no evidence about the concurrent use of bedaquiline and delamanid.

3 Methodology

- The methodology to undertake this review is specified by NHS England in their 'Guidance on conducting evidence reviews for Specialised Commissioning Products' (2016).
- An initial description of the relevant Population, Intervention, Comparison and Outcomes (PICO) to be included in this review was prepared by NHS England's Policy Working Group for the topic. Unusually, this rapid evidence review covers three PICOs (see section 9) and was carried out using an accelerated timeline.
- The PICOs were used to search for relevant publications in Medline, Embase and Cochrane Library (see section 10 for search strategy).
- The search dates for publications were between 1 January 2008 and 19 December 2018.
- The titles and abstracts of the results from the literature searches were assessed using the criteria from the PICOs. Full text versions of papers which appeared potentially useful were obtained and reviewed to determine whether they were appropriate for inclusion.
- Evidence from all papers included was extracted and recorded in evidence summary tables, critically appraised and their quality assessed using National Service Framework for Long Term Conditions (NSF-LTC) evidence assessment framework (see section 7 below).
- The body of evidence for individual outcomes identified in the papers was graded and recorded in grade of evidence tables (see section 8 below).

4 Results

PICO I: Bedaquiline

One paper was included reporting the use of bedaquiline plus standard treatment. Achar et al 2017 was a case series reporting children and adolescents aged 10 to 17 years (median age 16 years) who received six months of bedaquiline (n=27).

1. In infants, children and young people aged 17 years and below with MDR-TB or XDR-TB, what is the evidence of clinical effectiveness for bedaquiline used in combination with other TB drugs compared to use of other TB drugs without bedaquiline?

The only clinical effectiveness outcome reported in the study was the rate of negative sputum culture results.

Negative sputum culture results
23/23 (100%) of participants were reported to have negative culture results at the time the paper was prepared. 10/27 (37%) of participants were culture-negative at inception.

2. In infants, children and young people aged 17 years and below with MDR-TB or XDR-TB, what is the evidence of safety for bedaquiline used in combination with other TB drugs compared to use of other TB drugs without bedaquiline?

The only safety outcome reported in the study was prolongation of the corrected QT interval of more than 500ms, or more than 60ms change from baseline plus torsade de pointes, polymorphic ventricular tachycardia or signs/symptoms of serious arrhythmia. These are electrocardiographic abnormalities associated with bedaquiline and delamanid.

Electrocardiographic abnormalities
5/27 (19%) of participants were reported to have a corrected QT interval of more than 500ms, or more than 60ms change from baseline plus torsade de pointes, polymorphic ventricular tachycardia or signs/symptoms of serious arrhythmia. No patient experienced symptoms attributable to prolongation of QTcF during treatment with bedaquiline.

3. In infants, children and young people aged 17 years and below with MDR-TB or XDR-TB, what is the evidence of cost effectiveness for bedaquiline used in combination with other TB drugs compared to use of other TB drugs without bedaquiline?

We found no evidence relevant to this question.

4. From the evidence selected, are there any subgroups of patients that may benefit from bedaquiline used in combination with other TB drugs more than the wider population of interest?

We found no evidence relevant to this question.

PICO II: Delamanid

One paper was included reporting the use of delamanid plus standard treatment. Tadolini et al 2016 was a case series reporting children and adolescents aged 8 to 17 years (mean age 14

years) who received up to 24 weeks of delamanid (n=16). D'Ambrosio et al 2017 was a systematic review of studies reporting the results of bedaquiline and/or delamanid use in children or adolescents with confirmed MDR- or XDR-TB, and included results from Tadolini et al 2016.

1. In infants, children and young people aged 17 years and below with MDR-TB or XDR-TB, what is the evidence of clinical effectiveness for delamanid used in combination with other TB drugs compared to use of other TB drugs without delamanid?

The only clinical effectiveness outcome reported in the study was the rate of negative sputum culture results.

Negative sputum culture results
13/16 (81%) of participants were reported to have negative culture results at the time the paper was prepared. All had positive sputum culture when delamanid was started.

2. In infants, children and young people aged 17 years and below with MDR-TB or XDR-TB, what is the evidence of safety for delamanid used in combination with other TB drugs compared to use of other TB drugs without delamanid?

The only safety outcome reported in the study was adverse effects other than "mild".

Adverse effects other than "mild"
1/16 (6%) participants were reported to have adverse effects other than "mild".

3. In infants, children and young people aged 17 years and below with MDR-TB or XDR-TB, what is the evidence of cost effectiveness for delamanid used in combination with other TB drugs compared to use of other TB drugs without delamanid?

We found no evidence relevant to this question.

4. From the evidence selected, are there any subgroups of patients that may benefit from delamanid used in combination with other TB drugs more than the wider population of interest?

We found no evidence relevant to this question.

PICO III: Bedaquiline and delamanid

One paper was included reporting the use of bedaquiline and/or delamanid in children or adolescents. D'Ambrosio et al 2017 was a systematic review of studies reporting the results of bedaquiline and/or delamanid use in children or adolescents with confirmed MDR- or XDR-TB. All the participants whom it included received delamanid only, and were reported in Tadolini et al 2016 (see above). We found no evidence about the concurrent use of bedaquiline and delamanid.

1. In infants, children and young people aged 17 years and below with MDR-TB or XDR-TB, what is the evidence of clinical effectiveness for bedaquiline and delamanid used in combination with other TB drugs compared to use of other TB drugs without bedaquiline and delamanid?

We found no evidence relevant to this question.

2. In infants, children and young people aged 17 years and below with MDR-TB or XDR-TB, what is the evidence of safety for bedaquiline and delamanid used in combination with other TB drugs compared to use of other TB drugs without bedaquiline and delamanid?

We found no evidence relevant to this question.

3. In infants, children and young people aged 17 years and below with MDR-TB or XDR-TB, what is the evidence of cost effectiveness for bedaquiline and delamanid used in combination with other TB drugs compared to use of other TB drugs without bedaquiline and delamanid?

We found no evidence relevant to this question.

4. From the evidence selected, are there any subgroups of patients that may benefit from bedaquiline and delamanid used in combination with other TB drugs more than the wider population of interest?

We found no evidence relevant to this question.

5 Discussion

PICO I: Bedaquiline

Achar et al 2017 was a small case series, reporting only 27 participants. Being uncontrolled, it cannot help in assessing whether treatment which includes bedaquiline has different effects compared with treatment which does not.

Achar et al 2017's results indicate that the regime used in the case series results in high rates of negative sputum culture. However, 10/27 (37%) of participants were culture-negative at inception, so the 100% culture-negative rate after treatment does not imply that all these patients were rendered culture-negative by treatment, nor how important bedaquiline was in achieving that outcome.

Although electrocardiographic abnormalities occurred in five of the 27 participants, they did not lead to the withdrawal of bedaquiline from any of them.

The small size and lack of controls in Achar et al 2017 mean that it provides little useful information on the effectiveness and safety of bedaquiline in children and adolescents with MDR-TB.

PICO II: Delamanid

Tadolini et al 2016 was a smaller study than Achar et al 2017, reporting only 16 in-scope participants. Being uncontrolled, it cannot help in assessing whether treatment which includes delamanid has different effects compared with treatment which does not.

Tadolini et al 2016's results indicate that the regime used in the case series results in high rates of negative sputum culture (81% at the time of reporting), and that adverse effects other

than “mild” are uncommon. The authors do not define adverse effects more severe than “mild”.

The small size and lack of controls in Tadolini et al 2016 mean that it provides little useful information on the effectiveness and safety of delamanid in children and adolescents with MDR-TB.

PICO III: Bedaquiline and delamanid

We found no evidence about the concurrent use of bedaquiline and delamanid.

Larger well-designed comparative studies, ideally randomised controlled trials are needed to test hypotheses about the safety and effectiveness of bedaquiline and delamanid used outside their product licences.

6 Conclusion

There is very little available evidence about the use of bedaquiline and delamanid in children and adolescents, with a total of 43 participants reported within the scope of the PICOs. This makes it impossible to draw conclusions about the drugs’ effectiveness, safety and suitability for use in this age group.

7 Evidence Summary Table

For abbreviations see list after last table

I Bedaquiline in multi-drug resistant tuberculosis no comparator									
Study reference	**Study Design**	**Population characteristics**	**Intervention**	**Outcome measure type**	**Outcome measures**	**Results**	**Quality of Evidence Score**	**Applicability**	**Critical Appraisal Summary**
Achar et al 2017 South Africa, Tajikistan, Uzbekistan and Belarus	P1: Case series	27 children and adolescents. Median age 16 years (range 10 to 17 years), 15 (56%) female. Median weight 50 kg (range 35 to 76 kg). No patients were HIV positive. 26/27 (96%) had pulmonary TB and 1/27 (4%) had intrathoracic lymph node TB. Diagnoses for 17/27 (63%) patients were confirmed by mycobacterial culture. Baseline sputum smears from 19 (70%) patients were positive for acid-fast bacilli. One participant had concomitant spinal TB osteomyelitis. 18/27 (67%) had XDR TB; 6/27	26 participants received adult dose bedaquiline (400mg/day for 2 weeks, then 200mg 3 times/day for 6 months). One 10-year-old weighing 35 kg received 300 mg/day (recommended on the basis of expert opinion) during her loading phase. The mean duration of bedaquiline treatment of the 20 children and adolescents who completed therapy was 172 days.	Primary outcome Clinical effectiveness	Culture negative sputum when reported	23/23 (100%)	5	Direct	A small case series. Only 23 participants were still on treatment with sputum culture data available when the study reported. Since 10/27 (37%) of participants were culture-negative at inception, the 100% culture-negative rate after treatment does not imply that all these patients were rendered culture-negative by treatment, or indicate how important bedaquiline was in achieving that outcome. No patient experienced symptoms attributable to prolongation of QTcF during treatment with bedaquiline. No participant had bedaquiline withdrawn because of adverse effects.
				Primary outcome Safety	Prolongation of the corrected QT interval[1] of more than 500ms, or >60ms change from baseline plus torsade de pointes, polymorphic ventricular tachycardia or signs/symptoms of serious arrhythmia	5/27 (19%)			

[1] An electrocardiographic abnormality associated with bedaquiline and delamanid.

I Bedaquiline in multi-drug resistant tuberculosis no comparator									
Study reference	**Study Design**	**Population characteristics**	**Intervention**	**Outcome measure type**	**Outcome measures**	**Results**	**Quality of Evidence Score**	**Applicability**	**Critical Appraisal Summary**
		(22%) had MDR TB with fluoroquinolone resistance; and 3/27 (11%) had MDR TB with resistance to a second-line injectable drug. Baseline sputum smears from 19/27 (70%) patients were positive for acid-fast bacilli. For the 10 patients without positive mycobacterial cultures, drug susceptibility was presumed. from contact history.							

II Delamanid in multi-drug resistant tuberculosis no comparator									
Study reference	**Study Design**	**Population characteristics**	**Intervention**	**Outcome measure type**	**Outcome measures**	**Results**	**Quality of Evidence Score**	**Applicability**	**Critical Appraisal Summary**
Tadolini et al 2016 Italy, South Africa, Georgia, India, Namibia, Swaziland, Russia and Armenia	P1: Case series	16 children and adolescents. Mean age 14 years, range 8 to 17 years, 6/16 (38%) female. Three patients (16%) were HIV positive. All had pulmonary TB and 1/16 (6%) also had extra-pulmonary disease. 11/16 (69%) had XDR-TB; 4/16 (25%) had "pre-XDR-TB"[2] and 1/16 (6%) had MDR-TB.	15 participants received delamanid 100 mg twice daily (adult dosage), one received 50 mg twice daily due to a body weight of 22 kg. Treatment was for 24 weeks.	Primary outcome Clinical effectiveness	Culture negative sputum when reported	13/16 (81%)	6	Direct	A small case series. All participants reported here had positive sputum culture when delamanid was started. Only one participant had completed TB treatment. Six had completed 24 weeks of delamanid and ten were still receiving delamanid, of whom three had recently started on delamanid, so the interim treatment responses are not yet available. The paper describes a further three participants approved to receive delamanid who had not started the drug. These are not reported here. The authors do not define adverse effects more severe than "mild". They report that all but one participant showed good tolerability to delamanid with no or mild adverse events. One participant receiving a combination of delamanid-capreomycin-ethionamide-cycloserine-clofazimine-imipenem-amoxicillin/clavulanate-pyrazinamide experienced severe vomiting, renal impairment and severe electrolyte disturbances (hypokalaemia and hypomagnesaemia) with a corrected QT interval prolongation >500 ms. Delamanid was discontinued. After management of vomiting and electrolyte imbalance correction, the patient was able to complete delamanid treatment without further QT prolongation.
				Primary outcome Safety	Adverse effects other than "mild"	1/16 (6%)			

[2] Not defined by the authors, but this may mean disease was due to MDR-TB strains with additional resistance not sufficient to constitute XDR-TB.

III Bedaquiline and delamanid in multi-drug resistant tuberculosis									
Study reference	**Study Design**	**Population characteristics**	**Intervention**	**Outcome measure type**	**Outcome measures**	**Results**	**Quality of Evidence Score**	**Applicability**	**Critical Appraisal Summary**
D'Ambrosio et al 2017	R1: Systematic review Search date 31 December 2016.	Children or adolescents (age range not reported) with confirmed MDR- or XDR-TB	Treatment regimes containing delamanid and/or bedaquiline	Any	Any	No studies found of concurrent use of bedaquiline and delamanid	8	Direct	A methodologically robust systematic review, confirming the extent of research on this topic. The authors searched for studies of children or adolescents (age range not reported) with confirmed MDR- or XDR-TB who received treatment regimes containing delamanid and/or bedaquiline. They found no studies of concurrent use of the two drugs and noted that "The information identified is really scarce".

MDR-TB = multi-drug resistant tuberculosis. XDR-TB = extensively drug-resistant tuberculosis.

8 Grade of Evidence Table

For abbreviations see list after last table

I Bedaquiline in multi-drug resistant tuberculosis no comparator					
Outcome Measure	**Reference**	**Quality of Evidence Score**	**Applicability**	**Grade of Evidence**	**Interpretation of Evidence**
Culture negative sputum when reported	Achar et al 2017	5	Direct	C	Culture negativity occurs when mycobacteria are not grown when sputum from a patient is cultured. Achar et al 2017 reported a rate of culture negativity of 23/23 (100%). Culture conversion indicates the elimination of viable mycobacteria from sputum, and may be associated with earlier remission of symptoms. If so, it is of value to patients. It may also indicate an earlier end to a patient's infectivity to others. This small uncontrolled study suggests that treatment regimes that include bedaquiline for 6 months are effective in eliminating viable mycobacteria from sputum. Since 10/27 (37%) of participants were culture-negative at inception, the 100% culture-negative rate after treatment does not imply that all these patients were rendered culture-negative by treatment, or indicate how important bedaquiline was in achieving that outcome.
Prolongation of the corrected QT interval of more than 500ms, or >60ms change from baseline plus torsade de pointes, polymorphic ventricular tachycardia or signs/symptoms of serious arrhythmia	Achar et al 2017	5	Direct	C	Prolongation of the corrected QT interval of more than 500ms or >60ms change from baseline plus torsade de pointes, polymorphic ventricular tachycardia or signs/symptoms of serious arrhythmia is an electrocardiographic (ECG) abnormality associated with bedaquiline and delamanid. Achar al 2017 reported a rate of this ECG abnormality of 5/27 (19%) in children and adolescents treated with bedaquiline. No patient experienced symptoms attributable to prolongation of QTcF during treatment with bedaquiline. Prolongation of the corrected QT interval or other ECG abnormalities may lead to symptomatic cardiac arrhythmias, so its avoidance is likely to be of value to patients. This small uncontrolled study indicates a possible rate of QT interval prolongation in children and adolescents treated with bedaquiline. However, the absence of controls and the potential role of other drugs in causing this adverse effect limit what can be concluded.

II Delamanid in multi-drug resistant tuberculosis no comparator					
Outcome Measure	**Reference**	**Quality of Evidence Score**	**Applicability**	**Grade of Evidence**	**Interpretation of Evidence**
Culture negative sputum when reported	Tadolini et al 2016	6	Direct	C	Culture negativity occurs when mycobacteria are not grown when sputum from a patient is cultured. Tadolini et al 2016 reported a rate of culture negativity of 13/16 (81%). Culture conversion indicates the elimination of viable mycobacteria from sputum, and may be associated with earlier remission of symptoms. If so, it is of value to patients. It may also indicate an earlier end to a patient's infectivity to others. This small uncontrolled study suggests that treatment regimes that include delamanid are effective in eliminating viable mycobacteria from sputum. Of the 16 participants, only one participant had completed TB treatment. Six had completed 24 weeks of delamanid and ten were still receiving delamanid, of whom three had recently started on delamanid. The results do not indicate whether these patients were rendered culture-negative by treatment, or how important delamanid was in achieving that outcome.
Adverse effects other than "mild"	Tadolini et al 2016	6	Direct	C	The authors do not define adverse effects more severe than "mild". Tadolini et al 2016 reported that one participant (out of 16 children and adolescents treated with delamanid) receiving eight anti-TB drugs experienced severe vomiting, renal impairment and severe electrolyte disturbances with a corrected QT interval prolongation >500 ms. Delamanid was discontinued. After management of vomiting and electrolyte imbalance correction, the patient was able to complete delamanid treatment without further QT prolongation. The avoidance of severe adverse effects is of high value to patients. This study indicates the potential for severe adverse reactions from anti-TB drugs, though it is unclear the extent to which delamanid caused the reported effect.

III Bedaquiline and delamanid in multi-drug resistant tuberculosis					
Outcome Measure	**Reference**	**Quality of Evidence Score**	**Applicability**	**Grade of Evidence**	**Interpretation of Evidence**
Any	D'Ambrosio et al 2017	8	Direct	B	A methodologically robust systematic review, confirming the extent of research on this topic. The authors searched for studies of children or adolescents (age range not reported) with confirmed MDR- or XDR-TB who received treatment regimes containing delamanid and/or bedaquiline. They found no studies of concurrent use of the two drugs and noted that "The information identified is really scarce".

MDR-TB = multi-drug resistant tuberculosis. XDR-TB = extensively drug-resistant tuberculosis.

9 Literature Search Terms

PICO I: Bedaquiline

Search strategy	
P – Patients / Population Which patients or populations of patients are we interested in? How can they be best described? Are there subgroups that need to be considered?	Young people, children and infants aged 17 years and below who have any one of the following (1, 2, 3 or 4): 1.Laboratory confirmed MDR or XDR TB with resistance to fluoroquinolones or second-line injectable drugs (kanamycin, amikacin, capreomycin) 2. Where microbiological evidence is lacking but compelling circumstantial evidence indicates very likely MDR/XDR-TB aetiology (e.g. sputum smear negative active disease in a close contact of a patient with laboratory confirmed MDR/XDR-TB- This is important because PHE data show that only 23% of children with TB have a confirmed positive culture, as opposed to 62% of adults. This is because of the nature of TB disease in children, with a smaller number of bacteria present (paucibacillary as opposed to multibacillary disease) and the greater difficulty of obtaining samples in children. As the majority of TB disease in children is diagnosed clinically without microbiological confirmation, and the majority of drug-resistant disease in children is transmitted from an infectious adult (usually in the household) it is essential that children with clinically diagnosed drug resistant TB are eligible for appropriate treatment.) 3.'Functional' MDR or XDR TB which may arise as a result of intolerance or contraindication of first line or second line TB medications. 4.Cases of non-pulmonary MDR-TB
I – Intervention Which intervention, treatment or approach should be used?	Bedaquiline plus standard treatment- fluoroquinolones or second-line injectable drugs (kanamycin, amikacin, capreomycin)
C – Comparison What is/are the main alternative/s to compare with the intervention being considered?	• Standard treatment without the use of bedaquiline • No comparison
O – Outcomes What is really important for the patient? Which outcomes should be considered? Examples include intermediate or short-term outcomes; mortality; morbidity and quality of life; treatment complications; adverse effects; rates of relapse; late	Critical to decision-making: • Disease free survival • Safety – adverse effects resulting in drug discontinuation (liver toxicity/ nausea and vomiting), cardiac adverse events (most importantly QT prolongation on ECG)

morbidity and re-admission; return to work, physical and social functioning, resource use.	Important to decision-making: • Positive treatment outcome – sputum culture conversion, treatment completion or cure • Sparing of hearing loss • Reduction in use of drugs with potential adverse effects • Cost effectiveness
Assumptions / limits applied to search The search for peer reviewed published evidence will be conducted using standard search engines and the criteria specified in this PICO table. Standard exclusion criteria will usually be applied unless otherwise discussed and approved with NHS England Clinical Effectiveness Team. Standard Exclusion criteria: • Studies which are not able to be identified and retrieved via one of the following search engines: PubMed, MEDLINE, Embase, Cochrane. • Studies not available in the English language • Studies published more than 10 years ago • Grey literature including conference papers, abstracts, posters, letters, internet publications, manufacturer documents • Case reports	

PICO II: Delamanid

Search strategy	
P – Patients / Population Which patients or populations of patients are we interested in? How can they be best described? Are there subgroups that need to be considered?	Young people, children and infants aged 17 years and below who have any one of the following (1, 2, 3 or 4): 1.Laboratory confirmed MDR or XDR TB with resistance to fluoroquinolones or second-line injectable drugs (kanamycin, amikacin, capreomycin) 2.Where microbiological evidence is lacking but compelling circumstantial evidence indicates very likely MDR/XDR-TB aetiology (e.g. sputum smear negative active disease in a close contact of a patient with laboratory confirmed MDR/XDR-TB- This is important because PHE data show that only 23% of children with TB have a confirmed positive culture, as opposed to 62% of adults. This is because of the nature of TB disease in children, with a smaller number of bacteria present (paucibacillary as opposed to multibacillary disease) and the greater difficulty of obtaining samples in children. As the majority of TB disease in children is diagnosed clinically without microbiological confirmation, and the majority of drug-resistant disease in children is transmitted from an infectious adult (usually in the household) it is essential that children with clinically diagnosed drug resistant TB are eligible for appropriate treatment.)

	3.'Functional' MDR or XDR TB which may arise as a result of intolerance or contraindication of first line or second line TB medications. 4.Cases of non-pulmonary MDR-TB
I – Intervention Which intervention, treatment or approach should be used?	Delamanid plus standard treatment- fluoroquinolones or second-line injectable drugs (kanamycin, amikacin, capreomycin)
C – Comparison What is/are the main alternative/s to compare with the intervention being considered?	• Standard treatment without the use of delamanid • No comparison
O – Outcomes What is really important for the patient? Which outcomes should be considered? Examples include intermediate or short-term outcomes; mortality; morbidity and quality of life; treatment complications; adverse effects; rates of relapse; late morbidity and re-admission; return to work, physical and social functioning, resource use.	Critical to decision-making: • Disease free survival • Safety – adverse effects resulting in drug discontinuation (liver toxicity/ nausea and vomiting), cardiac adverse events (most importantly QT prolongation on ECG) Important to decision-making: • Positive treatment outcome – sputum culture conversion, treatment completion or cure • Sparing of hearing loss • Reduction in use of drugs with potential adverse effects • Cost effectiveness

Assumptions / limits applied to search

The search for peer reviewed published evidence will be conducted using standard search engines and the criteria specified in this PICO table. Standard exclusion criteria will usually be applied unless otherwise discussed and approved with NHS England Clinical Effectiveness Team.

Standard Exclusion criteria:

- Studies which are not able to be identified and retrieved via one of the following search engines: PubMed, MEDLINE, Embase, Cochrane.
- Studies not available in the English language
- Studies published more than 10 years ago
- Grey literature including conference papers, abstracts, posters, letters, internet publications, manufacturer documents
- Case reports

PICO III: Bedaquiline and delamanid

Search strategy	
P – Patients / Population Which patients or populations of patients are we interested in? How can they be best described? Are	Young people, children and infants aged 17 years and below who have any one of the following (1, 2, 3 or 4): 1.Laboratory confirmed MDR or XDR TB with resistance

there subgroups that need to be considered?	to fluoroquinolones or second-line injectable drugs (kanamycin, amikacin, capreomycin) 2. Where microbiological evidence is lacking but compelling circumstantial evidence indicates very likely MDR/XDR-TB aetiology (e.g. sputum smear negative active disease in a close contact of a patient with laboratory confirmed MDR/XDR-TB- This is important because PHE data show that only 23% of children with TB have a confirmed positive culture, as opposed to 62% of adults. This is because of the nature of TB disease in children, with a smaller number of bacteria present (paucibacillary as opposed to multibacillary disease) and the greater difficulty of obtaining samples in children. As the majority of TB disease in children is diagnosed clinically without microbiological confirmation, and the majority of drug-resistant disease in children is transmitted from an infectious adult (usually in the household) it is essential that children with clinically diagnosed drug resistant TB are eligible for appropriate treatment.) 3.'Functional' MDR or XDR TB which may arise as a result of intolerance or contraindication of first line or second line TB medications. 4.Cases of non-pulmonary MDR-TB
I – Intervention Which intervention, treatment or approach should be used?	Bedaquiline and delamanid plus standard treatment-fluoroquinolones or second-line injectable drugs (kanamycin, amikacin, capreomycin)
C – Comparison What is/are the main alternative/s to compare with the intervention being considered?	• Standard treatment without the use of bedaquiline and delamanid in combination • No comparison
O – Outcomes What is really important for the patient? Which outcomes should be considered? Examples include intermediate or short-term outcomes; mortality; morbidity and quality of life; treatment complications; adverse effects; rates of relapse; late morbidity and re-admission; return to work, physical and social functioning, resource use.	Critical to decision-making: • Disease free survival • Safety – adverse effects resulting in drug discontinuation (liver toxicity/ nausea and vomiting), cardiac adverse events (most importantly QT prolongation on ECG) Important to decision-making: • Positive treatment outcome – sputum culture conversion, treatment completion or cure • Sparing of hearing loss • Reduction in use of drugs with potential adverse effects • Cost effectiveness •

Assumptions / limits applied to search
The search for peer reviewed published evidence will be conducted using standard search engines and the criteria specified in this PICO table. Standard exclusion criteria will usually be applied unless otherwise discussed and approved with NHS England Clinical Effectiveness Team. Standard Exclusion criteria: • Studies which are not able to be identified and retrieved via one of the following search engines: PubMed, MEDLINE, Embase, Cochrane. • Studies not available in the English language • Studies published more than 10 years ago • Grey literature including conference papers, abstracts, posters, letters, internet publications, manufacturer documents • Case reports

10 Search Strategy

We searched PubMed, Embase and Cochrane Library, limiting the search to papers published in English between 1 January 2008 and 19 December 2018. We excluded conference abstracts, commentaries, letters, editorials and case reports.

Search date: 19 December 2018

Embase search:

1	drug resistant tuberculosis/ or extensively drug resistant tuberculosis/ or multidrug resistant tuberculosis/
2	*Tuberculosis/
3	(((multi* or extensive*) adj2 drug resistan*) and (tb or tuberculosis)).ti,ab.
4	(mdr-tb or mdrtb or xdr-tb or xdrtb).ti,ab.
5	(drug resistan* adj5 (tb or tuberculosis)).ti,ab.
6	(tb or tuberculosis).ti.
7	1 or 2 or 3 or 4 or 5 or 6
8	bedaquiline/ or delamanid/
9	(bedaquiline or sirturo or tmc207).mp.
10	(delamanid or deltyba or opc-67683).mp.
11	8 or 9 or 10
12	7 and 11
13	(exp animals/ or nonhuman/) not human/
14	12 not 13
15	conference*.pt.
16	14 not 15
17	limit 16 to (english language and yr="2008 -Current")

References from the PWG supplied by in the PPP		Paper selection decision and rationale if excluded
1	Elizabeth P. Harausz, Anthony J. Garcia-Prats et al (2017) on behalf of the Sentinel Project. New and Repurposed Drugs for Pediatric Multidrug-Resistant Tuberculosis Practice-based Recommendations. Am J Respir Crit Care Med Vol 195, Iss 10, pp 1300–1310, May 15, 2017	Excluded. This paper reports clinical practice recommendations without including a systematic literature review on which they were based. The literature review cited by the authors (their reference 12) does not describe a systematic review methodology. The article is therefore out-of-scope.
2	H. Simon Schaaf, Anthony J. Garcia-Prats, et al (2018) Challenges of using new and repurposed drugs for the treatment of multidrug resistant tuberculosis in children, Expert Review of Clinical Pharmacology, 11:3, 233-244, DOI: 10.1080/17512433.2018.1421067	Excluded. This is a non-systematic review and is therefore out-of-scope.
3	Jay Achar, Cathy Hewison, et al, (2017). Off-Label Use of Bedaquiline in Children and Adolescents with Multidrug-Resistant Tuberculosis. Emerging Infectious Diseases • www.cdc.gov/eid • Vol. 23, No. 10, October 2017	Included.

11 Evidence Selection

- Total number of publications reviewed: 9
- Total number of publications considered potentially relevant: 3
- Total number of publications selected for inclusion in this briefing: 3

12 References

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Xavier AS, Lakshmanan M 2014. Delamanid: A new armor in combating drug-resistant tuberculosis. *Pharmacol Pharmacother* 5: 222–224.