Projected use of pretomanid, bedaquiline and linezolid in all-oral regimens for multi-drug resistant tuberculosis from 2021-2025

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Abstract

Background

The World Health Organization is urging countries to facilitate access to fully oral treatment regimens for patients with drug-resistant tuberculosis (DR-TB), which remains a public health crisis. TB Alliance has developed a new 6-month, all-oral regimen for DR-TB called BPaL (comprised of bedaquiline, pretomanid and linezolid), which is recommended by WHO for use under operational research conditions for patients with XDR-TB and in patients who are either unable to tolerate or who have failed MDR-TB treatment. The objective of this study is to project the use of BPaL, along with its components bedaquiline and linezolid, in DR-TB globally until the year 2025.

Methods

We conducted semi-structured interviews with National TB Programs in key countries to gather intelligence on country targets and planned regimens for DR-TB treatment for 2021-2025, and developed a deterministic model based on this data to project the use of these drugs globally.

Results

The study projects a consistent global growth in the use of bedaquiline, linezolid and BPaL, reaching 190,752, 137,712 and 103,122 patients respectively by 2025. Further, evidence from late-stage trials such as ZeNix, SimpliciTB and TB-PRACTECAL will inform the use of pretomanid-containing regimens.

Conclusion

This study can support global health stakeholders including donors, policy makers and manufacturers with planning and budgeting for DR-TB interventions. An estimation of future usage could help us estimate cost of the individual components of DR-TB regimens at different volumes. Above all, national efforts to scale up drug susceptibility testing and implement new treatments will be essential to ensuring they are accessible to all eligible patients in the coming years.

Introduction

The World Health Organization (WHO) is urging countries to facilitate access to fully oral treatment regimens for patients with drug-resistant tuberculosis (DR-TB).[1] Although some countries have accelerated their TB response, DR-TB remains a public health crisis. According to WHO estimates, about half a million people fall ill with DR-TB annually, of whom about 214,000 die. A 2017 mathematical modelling study that forecasted increasing rates for multidrug-resistant (MDR) and extensively drug-resistant (XDR) TB in four high DR-TB burden countries emphasized that additional efforts are required to reverse the epidemic of DR-TB.[2] Accelerating diagnosis and treatment of DR-TB are key components of WHO's End TB Strategy and a key target in the political declaration of the 2018 United Nations High Level Meeting (UNHLM) on TB.[3] However, these goals are at risk due to challenges in enabling access to diagnosis and care. Only one in three people with DR-TB are currently being detected globally. Of those, just over half are treated successfully.[1] Further, the global average success rate for XDR-TB [defined by WHO Global Tuberculosis Report 2020, and used for the purpose of this study as MDR-TB with additional resistance to any fluoroquinolone and at least one injectable drug] is even less, at 43%.[4]

The TB Alliance has developed a new 6-month, all-oral regimen for DR-TB called BPaL, containing three oral medications – bedaquiline, pretomanid, and linezolid. Research has shown that patients find it easier to complete the shorter, all oral DR-TB regimen compared to the longer regimens which last up to 20 months.[1] Additionally, all shorter regimens are likely lower in cost due to both reduction in drug cost as well as associated care cost. As an example, the cost of BPaL regimen is as low as USD 785 per treatment course at the Stop-TB Partnership's Global Drug Facility (Stop-TB/GDF) access prices which is approximately 2.5-10 times less than the cost for conventional regimens.[5,6,7] In 2019, WHO recommended BPaL to be used under operational research (OR) conditions for patients with XDR-TB and in patients who are either unable to tolerate or failed MDR-TB treatment.[8]

Evidence from TB Alliance's pivotal Nix-TB clinical trial (along with data from 18 additional clinical trials of pretomanid) was the basis for the United States Food and Drug Administration (USFDA), the European Commission, India and Uzbekistan approval of the BPaL regimen.[9] The BPaL regimen is being further evaluated for optimized dosing of linezolid in the ZeNix study.[10] Further, the new BPaMZ regimen consisting of bedaquiline, pretomanid, moxifloxacin and pyrazinamide is being studied by TB Alliance in the SimpliciTB trial as a potential treatment for both drug-sensitive tuberculosis (DS-TB) (four months) and DR-TB (six months).[11] Additionally, TB-PRACTECAL study tests a six-month regimen of bedaquiline, pretomanid, linezolid and moxifloxacin, against the locally accepted standard of care for MDR-TB in 7 sites in 3 countries.[12]

The objective of this study was to project the use of BPaL and its components bedaquiline and linezolid in DR-TB treatment globally until the year 2025. This information would be important for global health stakeholders including donors, policy makers, and manufacturers for planning resources and prioritization. The outputs of the study will also help determine future cost-volume equation for the individual components of DR-TB regimens.

Methods

In fifteen countries accounting for 81% of DR-TB incidence in 2019, we conducted semi-structured interviews with National TB Program (NTP) managers and their staff [respondents] between July 2020 and Jan 2021, to gather intelligence on country targets and planned regimens for DR-TB treatment for our project horizon 2021 to 2025. These countries are: China, India, Indonesia, Kazakhstan, Kyrgyzstan, Myanmar, Nigeria, Pakistan, Philippines, Russian Federation, South Africa, Tajikistan, Ukraine, Uzbekistan and Vietnam. In four of the countries, we conducted the interviews through KNCV and WHO. We complemented the data with additional information from country National Strategic Plans (NSP) where available.

For the countries which account for the rest of the 19% of DR-TB incidence in 2019, we extrapolated the data received through our interviews for 11 countries closest to them in the approach to adopting novel interventions.

First, we projected the number of patients in four categories: MDR-TB, MDR-TB treatment intolerant, MDR-TB treatment failed and MDR-TB with additional fluoroquinolone resistance who would be eligible for BPaL, or other bedaquiline or linezolid-based regimens (Table 1). Second, within each of these four categories, the respondents allocated the number of patients to respective drugs and regimens.

We have limited our study to use of BPaL, along with the individual use of two of its components bedaquiline and linezolid. Other Group C drugs in WHO guidelines such as delamanid were excluded from our analysis.

For MDR-TB patients, the respondents allocated the patients to either be using the shorter regimen recommended by WHO in 2016 [WHO2016] [not containing bedaquiline or linezolid] or the regimens recommended by WHO in 2019 [WHO2019] which includes a shorter all oral bedaquiline containing regimen [containing bedaquiline, levofloxacin/ moxifloxacin, ethionamide, ethambutol, isoniazid, pyrazinamide and clofazimine] or individualized longer regimens [containing a mix of levofloxacin, bedaquiline, linezolid, clofazimine, cycloserine and other Group C drugs].[13,7]

For MDR-TB treatment intolerant patients, we assumed an 8% intolerance based on the average between 2015-2017 as reported in the 2020 WHO report since most countries do not routinely capture data on MDR-TB treatment intolerant patients.[4] For India we have used the data available in the country NSP 2017-25.[14] Subsequently the respondents projected what proportion of the intolerant patients would be initiated on BPaL.

For MDR-TB treatment failed and MDR-TB with additional fluoroquinolone resistance patients, the respondents projected the percentage of patients likely to fail initial MDR-TB treatment and be re-treated during 2020-2025 as well as those on treatment for fluoroquinolone resistance. This was based on observed trends in their respective countries. We then obtained projected use of BPaL as well as bedaquiline and linezolid in WHO recommended regimens from the respondents (Table 1). Apart from the WHO recommended patient categories for BPaL, South Africa is investigating the regimen in MDR-TB. The country has projected BPaL use for patients with MDR-TB, assuming positive results from their BPaL

Conditional Access Programme. Another two countries have projected use of BPaL for MDR-TB patients based on similar assumptions.

While projecting the uptake for this new regimen, we have discussed key considerations with the respondents, and have defined timelines firstly on start and completion of the OR in respective countries and secondly the programmatic use in each country. For the programmatic uptake, we have considered need and time taken in countries for (i) national regulatory approval (which varies by country and can take 6-24 months), (ii) addition of the new regimen in national guidelines (which could be triggered either by inclusion in WHO Guidelines or successful results of the local OR) and (iii) availability of affordable generic drugs. We note that the ZeNix trial and TB-PRACTECAL will provide further data on BPaL in 2021 and may support the process for expansion of WHO guidelines to programmatic use for BPaL by late-2021 or early 2022. Additionally, OR in some key countries will start generating data by late 2021 to add to the evidence base for BPaL. Respondents have projected to start programmatic use of BPaL keeping these considerations and timelines in mind for their own respective countries. Certain countries plan to take a decision based on the results of their local OR and expect to start using BPaL programmatically from early 2022 onwards.

Sensitivity/Scenario Analyses

We conducted three one-way sensitivity analyses to estimate change in usage of bedaquiline, pretomanid, and linezolid if: (a) every year delay or expedited programmatic use of BPaL in each country; (b) change in uptake of BPaL ($\pm$10% from projected country plans); and (c) change in number of patients failing or intolerant to treatment ($\pm$10%).

Additionally, we conducted two scenario analysis to estimate the use of BPaL: (a) Country estimates on number of MDR-TB patients with additional fluoroquinolone resistance vary in the model between 0-50%. However, independent experts opine likely usage in this population to be 100% once BPaL regimen is used more widely. Our first analysis is based on the assumption that all MDR-TB patients with additional fluoroquinolone resistance will use BPaL from 2022 onwards.; and (b) During our interviews, respondents were asked to project the use of pretomanid in MDR-TB in their respective country, assuming positive clinical trial outcomes from SimpliciTB trial (more recently, also TB-PRACTECAL) and positive WHO recommendation for expanded usage of pretomanid to MDR-TB.

Ethical statement

Request for ethical approval or informed consent was not deemed necessary as the data collected were reflecting national projections. All respondents agreed with the publication of these data in an anonymized way.

Results

The absolute annual number of patients-courses for either bedaquiline, linezolid or BPaL is projected to increase from 189,501 in 2021 to 285,485 by 2025 globally (Figure 1).

Bedaquiline

We projected the use of bedaquiline to increase from 110,121 patients in 2021 to 190,752 patients by 2025, representing 40% and 71% respectively of the total MDR-TB treatments estimated in 2021 and 2025 (Figure 2). This increase is consistent with increasing trend of

orders for the drug serviced by Stop-TB/GDF as per their report of 2019 as well as the increased use reported by WHO TB Report 2020.[15,4]

All countries we interviewed are planning to use bedaquiline in the longer and shorter regimens, however, the extent of use varies between countries. Six of the fifteen countries we interviewed projected >70% of the MDR-TB patients will be using the WHO2019 recommended bedaquiline containing shorter regimens by 2023. The other nine countries interviewed project higher use (>50%) of the longer regimen, however, 30-90% of the patients on this regimen will be using bedaquiline. South Africa is providing almost all MDR-TB patients with a bedaquiline-containing shorter regimen.

Linezolid

We projected the use of linezolid to increase in the coming years to reach 137,712 patients by 2025, accounting for 51% of the MDR-TB treatments (Figure 3). Although linezolid is not recommended by WHO in the shorter regimen, it is being used in South Africa for a 2-month period within this regimen for all patients.[16] An additional six countries plan to use the drug in the shorter regimen from 2020 onwards for 30-90% of the patients. A higher number of patients (ranging from 50% to 90%) are expected to continue using linezolid in the longer regimen.

BPaL

In March 2021, 21 countries had already accessed pretomanid through direct procurement or via the Stop-TB/GDF to initiate the BPaL regimen[17,18] and some others have planned procurement. This is estimated to result in close to 2,000 patients accessing the new regimen by the end of 2021. Programmatic use will result in more than 42,000 patients using the regimen in the year 2025.

Of the total patients projected to use BPaL in 2025, 70% are those with MDR-TB and additional fluoroquinolone resistance, 14% who failed MDR treatment or are MDR treatment intolerant and the rest are new MDR-TB patients without additional resistance. Globally, 28% of the patients who are MDR treatment intolerant and 31% patients who fail MDR treatment are projected to use BPaL by 2025. Additionally, almost 50% MDR-TB patients with additional fluoroquinolone resistance globally are projected to use BPaL by 2025.

Scenario/Sensitivity Analyses

In our one-way sensitivity analyses a delayed or expedited programmatic use of BPaL by one-year results in reduction or increase by 40% cumulative use. Of the eligible population across patient categories, a change of $\pm$10% patients provided BPaL regimen would result in close to 30% change in cumulative use. Lastly, a $\pm$10% change in the population of patients who fail treatment or are intolerant to treatment would have little (<2%) impact on cumulative use, as the total number of such patients is low (Figure 5).

In the scenario analysis, the uptake of BPaL is most sensitive to the number of fluoroquinolone resistant patients using the regimen (Figure 5). If 100% of fluoroquinolone resistant patients were to use BPaL from 2022 onwards instead of the numbers projected by respondents, it would lead to an almost three-fold increase in the cumulative use of this regimen from 103,122 to 280,745 patients by 2025. For pretomanid use in MDR-TB patients, three countries

projected initiation in 2023, ten in 2024 and two in 2025 – based on their country experience of implementing new regimens, including administrative or operational delays such as availability of the products in country, updates in national guidelines and time taken for training for clinicians. We estimate that 16,500 MDR-TB patients would be using pretomanid in 2025 (3 years post introduction) which is equivalent to 9% of MDR-TB treated patients, and >25,000 cumulatively in the three years (Figure 5). Although pretomanid is being evaluated for use in DS-TB as well, we have not included projected use in this category since our study is limited to DR-TB.

Discussion

By combining the interviews with NTP staff from 15 high DR-TB countries with deterministic modelling, we projected an increase in the uptake of bedaquiline, linezolid and BPaL over the coming 5 years.

The use of bedaquiline has been increasing since 2015 and is expected to increase further in the coming years.[15] Eight of the fifteen countries we interviewed intend to transition from the previously WHO2016 recommended injectable-containing shorter regimen or the longer regimen to treat MDR-TB patients to the WHO2019 recommended bedaquiline-containing shorter regimen for >50% patients by 2023. The transition period varies between countries and depends on each country's individual acceptance of the updated WHO guidelines, local policy development, funding, training of clinical staff and health workers in the field, procurement of bedaquiline for new regimen and in some cases liquidation of the stockpile of existing injectables. The major driver of increase in uptake of bedaquiline is in fact its use in shorter regimens, including the BPaL regimen (Figure 2). This implies that bedaquiline will continue to be a key drug in MDR-TB as well as XDR-TB regimens.

For the projected use of linezolid most countries indicated that while the drug is recommended for the full course of the WHO2019 longer treatment, patients only use it for as long as it is tolerable. The use of linezolid in the shorter regimen (not including BPaL) is not recommended by WHO. However, in 2018 South Africa included linezolid in the shorter all-oral bedaquiline-containing regimen in country-wide enrolment for 2 months.[16] Seven of the fifteen countries have projected use of the drug in a shorter regimen in anticipation of further evidence of success of this treatment. Figure 3 shows that up until 2022, 90% of linezolid use would be in the longer MDR-TB regimens, and from 2023 onwards, the major driver of linezolid growth is use in the BPaL regimen. Based on respondent feedback, we also project a greater use of linezolid in the shorter MDR-TB regimen from 2023 onwards, thereby increasing the use of linezolid globally.

As with any new drug or regimen, the programmatic uptake is largely dependent on the efforts to facilitating access to the drugs. The bedaquiline Donation Program showed how support from a large institutional donor (USAID) catalyzed access to a new drug and helped change DR-TB treatment landscape, improving quality of the entire DR-TB care paradigm, gathering additional effectiveness and safety data in programmatic settings, and identifying programmatic challenges associated with new TB drug introduction.[19] In the case of BPaL, the TB Alliance-led LIFT-TB project and other efforts including Stop-TB/TBREACH funded projects to provide technical assistance or accelerate commencement of OR in multiple highest DR-TB burden countries is expected to spark the uptake of pretomanid containing novel regimens

starting with several pathfinder countries.[20] Enrollment of patients in OR has so far commenced in 5 countries with several others expected to start soon. To ensure speedy and affordable access to quality assured pretomanid, TB Alliance has licensed the drug for use as part of the BPaL regimen to its global commercialization partner Viatris in addition to the generic manufacturers Macleods and Hongqi Pharmaceuticals thus far. Since October 2019, the product has been available through Stop-TB/GDF to 150 countries at a price of $364 for a full six-month treatment course.[5] To accelerate initiation of OR, Viatris and in some cases TB Alliance, have agreed to donate catalytic quantities of pretomanid in a few countries. These efforts are expected to speed access to pretomanid. Moreover, respondents in our interviews have indicated that the all-oral nature, short treatment duration, and reported high efficacy of the BPaL regimen will likely result in faster uptake than experienced with other regimens in the past. We anticipate the ZeNix trial results will be available in mid-2021, which may enable WHO guidelines to be updated, leading to a higher use of BPaL within fluoroquinolone resistant MDR treatment. Additionally, we anticipate MSF would be sharing data from TB-PRACTECAL in 2021, which may enable WHO to include a BPaL-based regimen for use in MDR-TB patients.[21]

Figure 4 shows use of BPaL is mainly in patients with MDR-TB and additional fluoroquinolone resistance. However, a few countries such as South Africa have indicated the readiness to use BPaL for newly diagnosed MDR-TB patients as well, which we have added in our model. It is possible that this would increase the chances of successful treatment and reduce the number of patients progressing to XDR-TB.

It should be noted that the UNHLM Political Declaration on TB targets aims at treating a higher number of MDR-TB patients than is projected by respondents.[22] If we were to assume a similar proportion of uptake with the UNHLM targets as projected by respondents for all regimens, it would translate to a 70% increase of cumulative use in bedaquiline and linezolid, and a two-fold increase in BPaL by 2022 itself.

Additionally, it is noted in this study that there is an increasing level of drug susceptibility testing (DST) over the last few years – from 9% to 26% between 2015-2018 for first line DST and 22% to 56% between 2015-2018 for second line DST.[4] However, this is an area on which all countries need urgent additional focus and investments. With new drugs for TB coming to market for the first time in decades, there is an increased need for such testing, as well as for developing tests for products like bedaquiline, linezolid and pretomanid. Respondents have projected an increase in number of patients treated, as a result of likely increase in testing.

The COVID-19 pandemic has highlighted the limitations of TB care and prevention services around the world. The response has disrupted TB services worldwide, including in highest burden countries and reduced access to TB and MDR-TB diagnosis.[23] However, all the countries we interviewed intend to increase the number of notifications and treatments in the coming years to make up for the shortfall in 2020.

Limitations

The countries included in this study accounted for 81% of the global MDR-TB incidence, and therefore 19% of the projections were extrapolated to reach global projections.

As mentioned earlier, most countries do not capture data on MDR-TB treatment intolerant patients routinely. Hence, we have used the global average of reported intolerant patients and projected the number of patients using this average in each country. We believe this is a conservative estimation, and there may be additional patients who would be eligible to use BPaL once it is made available in countries.

Additionally, if new data from ZeNix suggest that lower doses or shorter durations of linezolid retain high efficacy along with a more favourable safety profile, there might be greater projected uptake of BPaL in the study period.

Conclusion

The study projects a consistent growth in the use of bedaquiline from 110,121 patients in 2021 (40% of MDR-TB treatments) to 190,752 patients in 2025 (71% of MDR-TB treatments). Similarly, 137,712 patients are projected to use linezolid in 2025 (51% of MDR-TB treatments). Additionally, BPaL is projected to be used for treating cumulatively more than 100,000 DR-TB patients globally by 2025 (16% of MDR-TB treatments in 2025). Further, evidence from trials such as SimpliciTB and TB-PRACTECAL will add to the use of pretomanid-containing regimens. The timely availability and affordability of these new regimens will be crucial for uptake and the global health community should prepare for introduction. This includes alignment of all stakeholders, scale-up of drug susceptibility testing, patient engagement, education of clinicians, health workers and affected communities on the safety and efficacy of such regimens, as well as procurement and distribution of the drugs. The completion of the ZeNix study will further inform and strengthen our assumptions around the usage of BPaL if new data suggest that lower doses or shorter durations of linezolid retain the high efficacy seen in the Nix-TB trial with a more favorable safety profile.

We believe this study would be informative for global health stakeholders including donors, policy makers and manufacturers by supporting planning and budgeting for DR-TB interventions. An estimation of future usage could help in volume-based pricing of these key DR-TB medicines. Above all, national efforts to scale up drug susceptibility testing and implement new treatments will be essential to ensuring they are accessible to all eligible patients in the coming years.

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References

1. World Health Organization. WHO urges countries to enable access to fully-oral drug-resistant TB treatment regimens. Geneva: Departmental news, 15 June 2020. Available: https://www.who.int/news-room/detail/15-06-2020-who-urges-countries-to-enable-access-to-fully-oral-drug-resistant-tb-treatment-regimens
2. Dr Aditya Sharma MD, Andrew Hill PhD, Ekaterina Kurbatova MD, et al. (2017). Estimating the future burden of multidrug-resistant and extensively drug-resistant tuberculosis in India, the Philippines, Russia, and South Africa: a mathematical modelling study. The Lance Infectious Diseases, Volume 17, issue 7, P707-715. DOI: 10.1016/S1473-3099(17)30247-5
3. General Assembly of the United Nations. Resolutions of the 73rd session. Available: https://www.un.org/en/ga/73/resolutions.shtml
4. Global Tuberculosis Report 2020. Geneva: World Health Organization; 2020. Licence: CC BY-NC-SA 3.0 IGO. Available: https://www.who.int/tb/publications/global_report/en/
5. The Stop TB Partnership. Announcement, 28 October 2019. The Stop TB Partnership's Global Drug Facility catalog now lists the first-ever, all-oral regimen for highly resistant forms of drug-resistant tuberculosis at US $1,040 per treatment course. Available: http://www.stoptb.org/news/stories/2019/ns19_025.html
6. Stop TB Partnership. Press release. Stop TB Partnership and Johnson & Johnson, with support from USAID and The Global Fund, Announce Price Reduction for bedaquiline for Treatment of DR-TB in Low- and Middle-Income Countries. Available: http://www.stoptb.org/news/stories/2020/ns20_024.html
7. Reuters; Healthcare and Pharma. New tuberculosis treatment for developing countries to cost $1,040; 2019 Oct 28. Available: https://www.reuters.com/article/us-tb-alliance-tuberculosis-idUSKBN1X713X
8. World Health Organization. WHO consolidated guidelines on drug-resistant tuberculosis treatment. Geneva: World Health Organization; 2019. Available: https://www.who.int/tb/publications/2019/consolidated-guidelines-drug-resistant-TB-treatment/en/
9. Francesca Conradie, M.B., B.Ch., Andreas H. Diacon, M.D., Nosipho Ngubane, M.B., B.Ch., et al. (2020). Treatment of Highly Drug-Resistant Pulmonary Tuberculosis. N Engl J Med 2020; 382:893-902; DOI: 10.1056/NEJMoa1901814
10. ClinicalTrials.gov [Internet]. Bethesda (MD): National Library of Medicine (US) 2000. Identifier NCT03086486, Safety and Efficacy of Various Doses and Treatment Durations of Linezolid Plus Bedaquiline and Pretomanid in Participants with Pulmonary, XDR-TB, Pre- XDR-TB or Non-responsive/Intolerant MDR-TB (ZeNix); 2017 Mar 22 [cited 2021 May 10]; [about 17 screens]. Available: https://clinicaltrials.gov/ct2/show/NCT03086486
11. ClinicalTrials.gov [Internet]. Bethesda (MD): National Library of Medicine (US) 2000. Identifier NCT03338621, Trial to Evaluate the Efficacy, Safety and Tolerability of BPaMZ in Drug-Sensitive (DS-TB) Adult Patients and Drug-Resistant (DR-TB) Adult Patients; 2017 Nov 9 [cited 2021 May 10]; [about 13 screens]. Available: https://clinicaltrials.gov/ct2/show/NCT03338621

12. ClinicalTrials.gov [Internet]. Bethesda (MD): National Library of Medicine (US) 2000. Identifier NCT02589782, Pragmatic Clinical Trial for a More Effective Concise and Less Toxic MDR-TB Treatment Regimen(s) (TB-PRACTECAL); 2015 Oct 28 [cited 2021 May 10]; [about 13 screens]. Available: https://clinicaltrials.gov/ct2/show/NCT02589782
13. WHO treatment guidelines for drug-resistant tuberculosis, 2016 update. October 2016 revision. Available: https://www.who.int/publications/i/item/9789241549639
14. National Strategic Plan for Tuberculosis Elimination 2017-2025, Central TB Division, Directorate General of Health Services, Ministry of Health with Family Welfare, India. Available: https://tbcindia.gov.in/index1.php?lang=1&level=2&sublinkid=5450&lid=3266
15. Stop TB Partnership. Information on Bedaquiline. Bedaquiline Order Status Report - 6 March 2019, accessed on 10 May 2021. Available: http://stoptb.org/gdf/drugsupply/bedaquiline.asp
16. Programmatic data from South Africa, recorded in the Electronic Drug-Resistant Tuberculosis Register (EDRWeb). Referenced in WHO consolidated guidelines on tuberculosis. Module 4: treatment - drug-resistant tuberculosis treatment. Geneva: World Health Organization; 2020
17. Stop TB Partnership. Press release: Important News: Increased access to pretomanid/BPaL. Available: http://www.stoptb.org/news/stories/2020/ns20_018.html
18. Viatris. Unpublished data
19. E Rutta, C Kambili, Y Mukadi (2020). The Bedaquiline Donation Program: progress and lessons learned after 4 years of implementation. Int J Tuberc Lung Dis. 2020 Oct 1;24(10):1039-1045. DOI: 10.5588/ijtld.20.0134.
20. TB Alliance. Press release: TB Alliance with the Support of the Republic of Korea Announce Initiative to Broaden Adoption and Scale Up of New Treatments for Drug-Resistant Tuberculosis. Available: https://www.tballiance.org.za/news/lift-tb-press-release-english
21. Medicines Sans Frontieres. Press release: Drug-resistant TB clinical trial ends enrolment early after positive initial data. Available: https://www.msf.org/drug-resistant-tuberculosis-trial-ends-enrolment-after-positive-initial-data
22. Stop TB Partnership. Country Targets for The UNHLM Political Declaration on TB. Available: http://www.stoptb.org/resources/countrytargets/
23. Suvanand Sahu, Lucica Ditiu, Kuldeep Singh Sachdeva, Alimuddin Zumla (2021). Recovering from the Impact of the Covid-19 Pandemic and Accelerating to Achieving the United Nations General Assembly Tuberculosis Targets. International Journal of Infectious Diseases 2021 Mar 11; DOI: 10.1016/j.ijid.2021.02.078

Table 1. The four patient categories and drugs and regimens projected for each

Patient category	Bedaquiline	Linezolid	BPaL
MDR-TB	X	X	X*
MDR-TB Intolerant			X
MDR-TB Failed			X
MDR-TB + FQ resistant	X	X	X

*Applicable for three countries which projected use of BPaL for MDR-TB patients

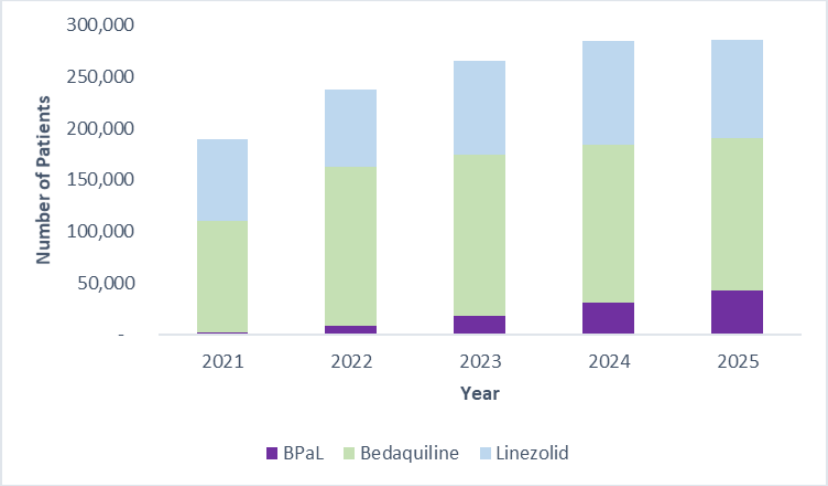

Figure 1. The projected use of bedaquiline, linezolid and BPaL globally between 2021-2025

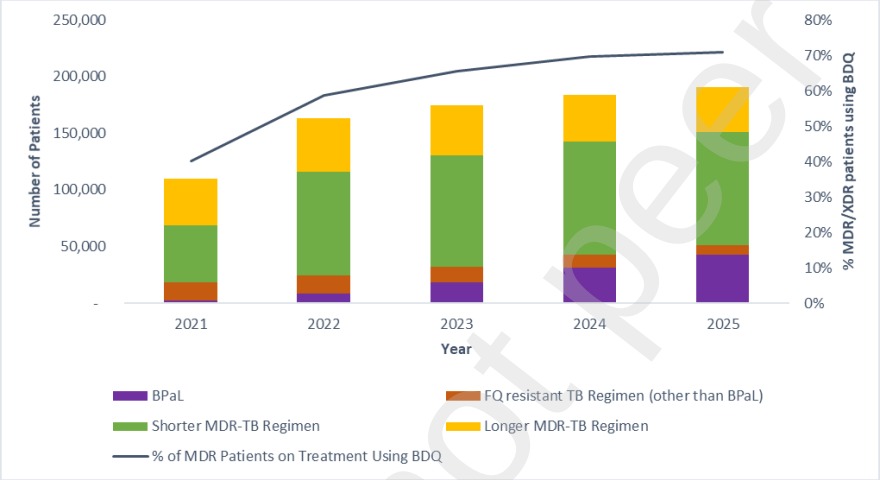

Figure 2. The projected use of bedaquiline in various regimens globally between 2021-2025

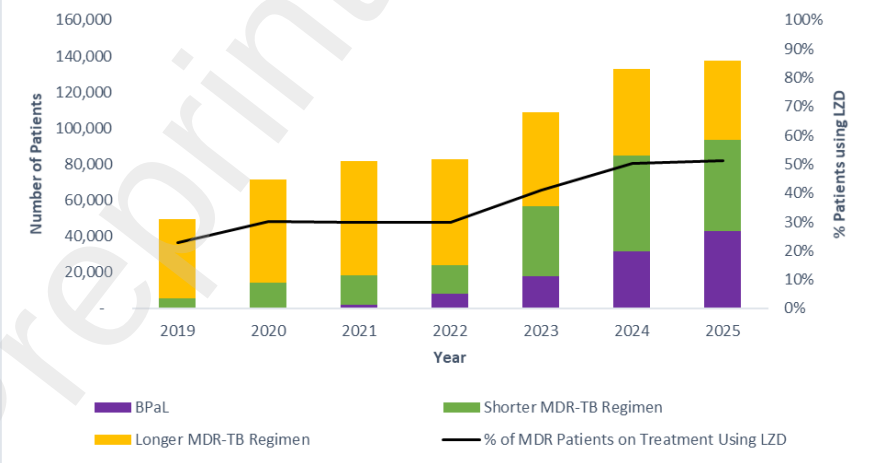

Figure 3. The projected use of linezolid in various regimens globally between 2021-2025

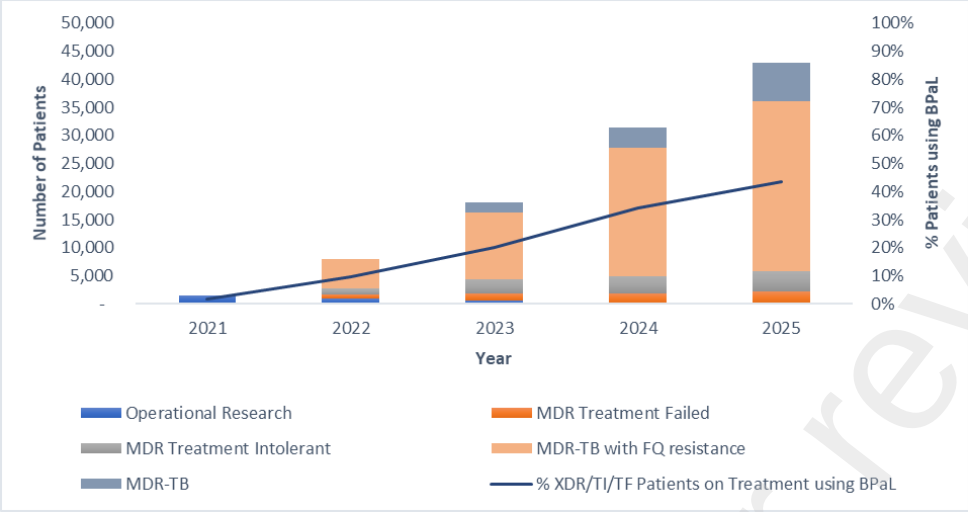

Figure 4. The projected annual use of BPaL in various regimens globally between 2021-2025

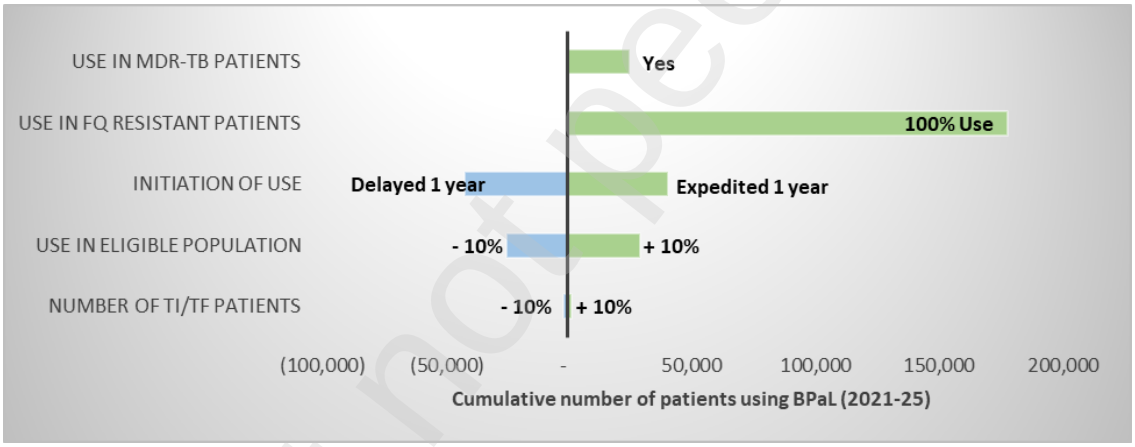

Figure 5: Sensitivity/Scenario analyses on cumulative use of BPaL