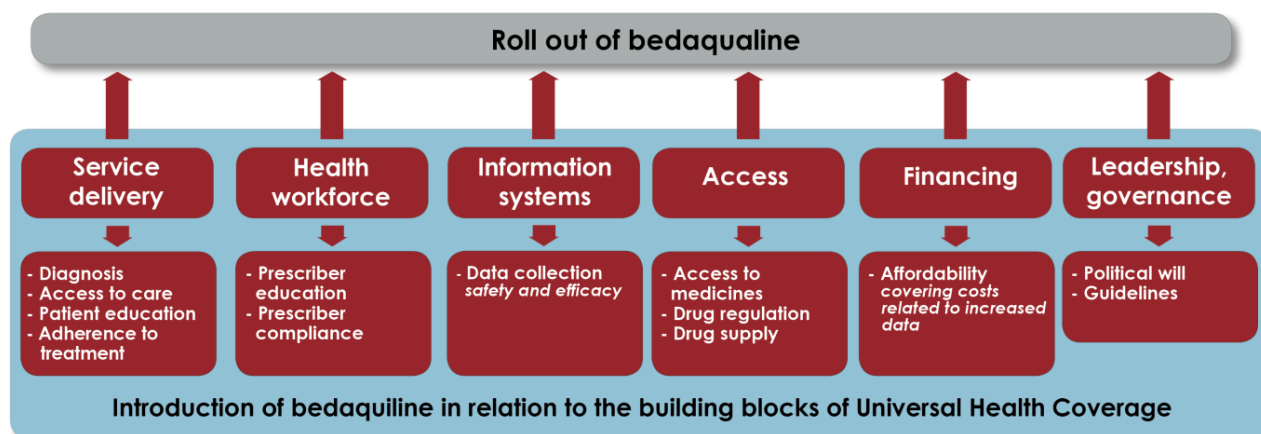


Learning from Experiences: Introducing Bedaquiline in South Africa

Executive summary

How should a new antibiotic be introduced to a new market or country to ensure sustainable access and appropriate use? Looking at what has been done in other countries is one way to learn from experiences and to constantly improve practices. In this paper, we have done desktop research and interviewed key stakeholders that have insight into how the anti-tuberculosis (TB) drug bedaquiline (Sirturo) was introduced to South Africa.



The key take-aways that arose from the research and interviews were the importance of will to do it right, or at least as good as possible, at all levels and that there is a structured health system that can accommodate both access and stewardship. Given the increasing focus on universal health coverage and health system strengthening, putting the experiences from the introduction of bedaquiline into the WHO health system framework provides a way to structure the building blocks needed for a controlled introduction of a new antibiotic:

1. Service delivery

Access to healthcare and diagnostics coupled with clear clinical routines are instrumental. South Africa started by rolling out bedaquiline in few centers of excellence to ensure appropriate use.

2. Health Workforce

Healthcare staff needs to be sufficient and adequately trained. Once clinical routines for a new medicine are established, healthcare staff on all levels, but also patients, need to be educated in how to use the new medicine.

3. Health information systems

Health information systems are increasingly important as antibiotics reach markets in low- and middle-income countries (LMICs), and especially so after fast-track approval. As the safety profile of a new drug is not known, and developers need to gather this data, requirements of data collection and monitoring are higher than usual.

4. Access to essential medicines

Sustainable and equitable access to medicines may be challenging, not only due to high costs. Procurement, distribution and storage are factors that need consideration – more often than not, patients cannot wait long periods to access an antibiotic, and the antibiotic needs to be available for the whole length of treatment.

5. Financing

Especially for LMICs, the cost of therapy is an important factor that may limit access to a new antibiotic. Antibiotics need to be priced so as to be affordable, but other factors, such as need for diagnostics, hospital stay or visits to get injectable medicines also contribute to the affordability of a new medicine.

6. Leadership and governance

Perhaps the most prominent feature of the South African introduction is the role of political will. The Ministry of Health took leadership and created a program for stewardship that made a controlled roll-out of bedaquiline possible.

Perspective

The rapidly increasing rates of antibiotic resistance and slow development of new antibiotics put antibiotic stewardship into an even more important position. Since not many new antibiotics are brought to market, it is increasingly important to use those few in a responsible manner to conserve their efficacy from the very beginning while still ensuring access for those who really need it. To “get it right” from the start, it is important to investigate and analyze what has been done before in other fields of medicine such as TB, HIV or even oncology, to learn what works and what the challenges are. A recent and closely related drug introduction is bedaquiline into South Africa beginning in 2012.

In 2014, when the introduction of Bedaquiline had started, the WHO issued a policy implementation package for the introduction of new TB drug introduction. This package provides countries with a roadmap, focusing on the system-wide requirements needed for a successful and controlled introductionⁱ. The roadmap relied partly on experiences from South Africa.

Bedaquiline is an anti-TB antibiotic discovered by Janssen in 1997. It represents a whole new class of antibiotics, and is a welcome addition to treatment of multidrug-resistant (MDR)-TB. Janssen acquired a fast-track approval for bedaquiline by the FDA in 2012 and EMA in 2014. The fast-track approval was given prior to having clinical safety and efficacy data from larger phase III clinical trials, and is conditioned to Janssen providing these data. A specific concern raised in Phase II studies was the risk of sudden cardiac death. While a rare event that was not ascribed with certainty to bedaquiline, the seriousness warranted extra precautions and heart monitoring via ECG. Continuous, biennial follow-up of current safety data is required until the necessary trial results are delivered to the FDA and EMA.

While FDA and EMA are the world's largest regulatory bodies, they do not have jurisdiction in for example Africa. Thus a regulatory approval from the Medicines Control Council was needed for introduction of bedaquiline to South Africa. However, many LMICs lack regulatory capacity and thus FDA and EMA have a key role also outside their actual jurisdiction.

While this case studyⁱⁱ takes South Africa as an example case, it is in no way intended as a critique or endorsement of what was done in South Africa. Rather, the paper should be considered as a positive example of controlled introduction of a new drug. In retrospect, and from an outside point of view, it

is easier to see what could have been done differently and these lessons can provide valuable insights when designing introductions of antibiotics. Also, the paper does not consider problems related to access that have been reported from other countries in the case of bedaquilineⁱⁱⁱ.

Introduction of bedaquiline

During the past few years, universal health coverage (UHC) has grown to be an area of focus in global level discussions related to access and quality health care. These efforts also align well with issues of access to antibiotics and rational use of antibiotics to ensure that new antibiotics remain effective as long as possible. The structure of health system building blocks^{iv} needed to achieve UHC can therefore be used as a framework for analyzing the introduction of bedaquiline. Indeed, the introduction of bedaquiline into South Africa emphasizes the need of a structured healthcare system.

The South African health system

South Africa is divided into nine provinces that are further subdivided into a total of 52 districts. The province is the major administrative level in the South African health care system; each province has a health budget to comply with and run operations in. Drug procurement to health care facilities is also handled at province level, as each province has a central medicines depot that distributes medicines to the facilities based on needs and projections of future needs. This means that there may be large regional variations between the provinces, not only in patient population sizes and demographics, but also in health care resources and delivery as well as access to medicines.

The South African health care system is composed of both public health care – government owned and financed hospitals and health care centers – and private general practitioners and specialists. In the case of TB, medicines are expensive when purchased privately, but free when treatment is within the national healthcare system. As a consequence, private health care providers rarely treat TB patients; any patients presenting with TB are generally diagnosed by the private provider and then referred to a national center for further evaluation and treatment. TB patients in the government facilities would receive first-line treatment, but if multidrug resistance is suspected, the patients would be transferred to a center with more experience. Non-Governmental Organizations (NGOs) like Médecins Sans Frontières have some activity in parts of South Africa with their own channels of distribution, but mainly comply with the local guidelines.

The role of the national level is policy, coordination, monitoring and evaluation. The Department of Health has allocated funds for a conditional grant that is earmarked for antiretroviral drugs, the purchase of GeneXpert instruments and both new and repurposed TB drugs, including bedaquiline. The former Medicines Control Council, now South African Health Products Regulatory Authority (SAHPRA), is responsible for regulatory approval of all new drugs to be marketed in the country. However, there is a route for special approval on mainly individual patient basis. One of these so called Section 21 drugs is the anti-leprosy drug Clofazimine, increasingly used also against multidrug-resistant TB.

1. Service delivery

Bedaquiline was introduced into the health care system gradually, beginning from four centers in Johannesburg, Durban, Klerksdorp and Cape Town. As the program was expanded, centers of excellence that were able to treat MDR-TB in the provinces also gained access to bedaquiline. Thus, patients needed to be referred to these centers to access the treatment. These centers received training and were assessed for readiness to start using bedaquiline. As experience grew, more facilities received the training and were granted access to bedaquiline. Many facilities also needed to be supplied with equipment for ECG and audiometric testing as these were specific areas for concern regarding adverse reactions connected to bedaquiline treatment, and aminoglycoside use was widespread.

Depending on the patient's condition, bedaquiline is used both in inpatient and outpatient care. For outpatients at the first visit, a baseline ECG is performed and the patient is given medication for the first two weeks (the loading dose). At two weeks, a first follow-up includes a repeat ECG, and the patient is provided with another two weeks of bedaquiline. At the one-month follow-up, ECG is again repeated and blood samples are taken. After that, once monthly follow-ups are made. In general, this procedure has not resulted in significant delays or interruptions of therapy on the part of the health care system.

Diagnostic capacity

An instrumental component of introducing bedaquiline was access to diagnostics and rapid susceptibility testing in the form of the GeneXpert platform that started to be used in 2010. While monthly cultures and smears are still made to follow-up treatments, the GeneXpert platform provides the basis for detection of MDR-TB. It provides results within hours (instead of two months with prior methods) and is also more sensitive – detected cases of MDR-TB doubled after its introduction. South Africa has a strong national reference laboratory and sufficiently equipped provincial laboratories to meet the needs of the TB program. Currently, GeneXpert is used to diagnose TB and rifampicin resistance. Additional genetic tests are then used to identify additional resistance markers to first- and second-line drugs to confirm extensively drug-resistant (XDR) or pre-XDR strains.

Reflections

Access to healthcare is of prime importance for controlled introduction of new medicines. This means not only access to medicines, but also diagnosis

and care to ensure that the new medicine is used judiciously. The less acute nature of TB makes it possible to have a system of referral to TB centers that have stronger diagnostic capacity. But for the more acute infections, such as pneumonia, diagnosis and treatment should be available closer to the patient at the primary care level. This creates a larger demand for diagnostic capacity and surveillance of resistance to select the patients that are eligible to use a new antibiotic, but also to restrict use in other patients. In both cases, adequate financial and human resources to ensure both access to care and surveillance of resistance development are critical.

Clinical routines are equally important. In South Africa, a panel of experts created guidelines based on available information about bedaquiline and a mandatory case review ensured that patients were selected accordingly. Such an expert panel could also periodically assess the development of resistance to be able to adjust the guidelines if necessary. This also adds a level of control, as the review process will validate that cases have been managed according to these guidelines and allows for monitoring of treatment quality and resistance development.

Since clinical trials in phase II and III are done on adults, special populations like children are only studied in post-marketing phase IV studies. The lack of information on pharmacokinetics, safety and efficacy, and lack of e.g. pediatric formulations impedes access to vital drugs in already vulnerable populations. This puts an added burden on service delivery as safety must be monitored and reported more rigorously.

An often-forgotten part of service delivery is also education of patients. Good healthcare should strive to enable patients to regain and maintain their health. This includes educating about the disease in question, how to prevent it from spreading, and how it should be properly treated. In the case of bedaquiline, this need was accentuated by the less orthodox dosage regimen, highlighting the need to give clear guidance on how the medicine should be taken. Still, defaulting is a significant problem in TB care that needs to be addressed with innovative interventions that motivate the patient to follow through on the treatment.

2. Health Workforce capacity

Introducing a drug requires that all relevant healthcare staff – physicians, nurses and pharmacists, is sufficient and are updated on how to use the new drug appropriately. This process requires creation of new guidelines and policies, training of staff and, as an extension, educating patients and the general public. Initial sites had their staff undergo Good Clinical Practice (GCP) courses.

Creating guidelines and education

To facilitate the new program for bedaquiline introduction, the Ministry of Health engaged with clinicians, academic researches and NGOs to create a group of experts to develop guidelines for the introduction and use of bedaquiline and to review all cases that were considered for bedaquiline therapy. The National Clinical Advisory Committee was established in 2010 to support the National TB Program in developing treatment guidelines for drug-resistant TB and providing technical advice regarding management of difficult cases of drug-resistant TB. A year later, the committee started discussing bedaquiline and this became the key activity. The expert committee collected available knowledge and created partnerships to engage with the provinces to disseminate the guidelines and train clinical staff. When bedaquiline use expanded the knowledge base regarding both clinical effect and safety of bedaquiline, the committee used its network of partners to communicate the updated knowledge, increasing the general confidence in the safety and efficacy of bedaquiline.

NGOs in partnership with the national TB program in turn arranged 1-5 days training sessions in the different provinces to train healthcare staff. Two important aspects were to educate clinicians about the need to switch from fixed dose antiretrovirals to avoid efavirenz in patients with HIV coinfection, and about the correct dosing of bedaquiline.

Adherence to therapy has been a long-standing problem with TB treatment with a relatively high rate of patients lost to follow up. Often cited reasons for this include the total length of treatment, toxicity and affordability and access to drugs. In the case of bedaquiline, the irregular dosing schedule is a cause of concern and requires education of both patients and healthcare staff. Adherence problems have been addressed by increasing knowledge about the effect of the treatment and its lower toxicity. The impression of some clinicians is however still that adherence to treatment is suboptimal and follow-up could be improved.

Reflections

One important part of an introduction program is to ensure that healthcare staff is sufficient and well trained to use the new drug. In South Africa, the expert committee was responsible for creating guidelines, collecting and disseminating information and engaging partners in the provinces. The importance increases with the degree of novelty – a “me too” drug requires less extra thought from the workforce, compared with if diagnostics, monitoring of therapy or dosage calculation are different from what is customary. Naturally, the collected information and created guidelines need to be effectively disseminated to clinical practitioners. A well-functioning case review system with an independent committee of experts can also function as a gate-keeper, ensuring correct use of the new drug.

3. Health information systems

As bedaquiline had received conditional fast-track approval from FDA and EMA, Janssen is required to provide these regulatory authorities with additional information on bedaquiline safety and efficacy. Also, in the case of antibiotics, development of resistance needs to be monitored by including resistance patterns in the data that is collected. Due to this sparsity of data, additional pharmacovigilance and efficacy reporting was required from prescribing facilities. This added reporting proved difficult for the health care facilities to manage. All adverse events were mandatory to record in the patient records, and all serious adverse events (SAEs), i.e. events that resulted in hospitalization, disability or were life-threatening, had to be reported. As more data than usual was required and fields were added to the electronic data systems, physicians struggled with the added administrative burden. Even though Janssen provided administrative support to collect the information, and Aurum Institute hired data capturers to major treatment facilities, collection was still lagging.

Reflections

The system of fast-tracking new drug approvals provides market access faster and cheaper with the cost of limited data on safety and efficacy. The first introductions of the new drug would therefore, in a sense, resemble phase III clinical trials with a need to collect more data, both on patients and on adverse events, and require closer clinical monitoring. The collected data needs to be processed and analyzed and results need to be fed back to the health care staff.

This not only places a burden on the health staff, patients and finances, but also health information systems that need to be able to accommodate the extra data collected. As a result, fast-tracking transfers parts of the burden and costs of clinical development from the drug developer to the health systems that first start using the new drug. This added burden needs to be considered in planning and execution of an introduction.

4. Access to essential medicines

In order to be eligible for bedaquiline therapy, patients needed to meet a number of criteria. Exclusion criteria included age, weight and previous exposure to bedaquiline. Originally, the inclusion criterion was XDR or pre-XDR TB as per laboratory diagnosis. Later, inclusion was expanded to also cover patients with severe side effects of TB treatment (ototoxicity and nephrotoxicity) or pregnancy. As of 2020, South Africa has transitioned to non-injectable anti-TB therapy for all patients, which effectively means that all patients are eligible for bedaquiline. This development has also been driven by civil society, for example by using the hashtag #Kanamustfall and with messaging stating that it is unethical to force someone to take a toxic medication when there is a less toxic alternative available.

Ensuring medicine supply on individual level is also a means to improve adherence to therapy. In practice, when a patient is approved for bedaquiline therapy, the whole treatment course is procured and stored at the treatment center, making sure that shortages do not interrupt therapy and increasing patient confidence in accessibility to the medicine.

Drug distribution and stock management

In South Africa the drug distribution is managed through provincial medical depots, and these had strong control of bedaquiline stocks and distribution and controlling access to medicines. Currently, the process of medicines procurement and distribution in the public sector is highly dependent on the ten provincial medical depots (with the Eastern Cape province operating two such stores). Some provincial depots have strong control themselves, but in some depots like the KwaZulu-Natal central medical depot, control was delegated to the Centre of Excellence, the second largest DR-TB treatment facility in South Africa. Provinces are increasingly arranging for direct delivery of medicines from manufacturers to health facilities, bypassing the depots. The medicines ordering forms were adapted for ordering bedaquiline, in order to integrate bedaquiline into the existing systems.

One particular challenge was forecasting the need of bedaquiline to ensure availability to patients. From national level, statistics are requested from the provinces in a web-based system and were initially checked via requests for manual reporting. In many cases, the requests for statistics were directed to the treating facilities where a few engaged physicians and pharmacists would estimate the need of bedaquiline based on their clinical experience. Sometimes estimates were too low, and sometimes the estimates were too high, much due to the fact that bedaquiline was reserved to patients with limited treatment options. As clinical experience accumulated, use of bedaquiline increased and eventually led to a national tender on bedaquiline. At times, drugs were necessary to redistribute between provinces to ensure access as the projections failed. One problem with decentralizing to health care facilities is that as the number of facilities able to prescribe bedaquiline increases, the level of control of stocks decreases and the need for a national consensus on bedaquiline use increases.

Reflections

An efficient introduction requires timely forecasting and management of medicine supply and ensuring affordability. Hospital and pharmacy order forms need to be updated and functioning logistics systems need to be ensured. In the beginning of an introduction, forecasting of needs may prove challenging: as the number of patients receiving the antibiotic may fluctuate, or as in the South African case increase rapidly, supply systems may not be able to keep up with the changing demands. This may in turn lead to either lack of access to medicines or that preordered medicines expire on the shelf. Coordination of supplies is needed along the whole supply chain, from manufacturer or importer to patient.

A critique raised in relation to the introduction of bedaquiline is the lack of access to the new medicine and the slow adoption. However, a controlled introduction of a new drug takes time as all the components need to be built and put into place, healthcare staff needs to be trained and data need to be collected. In addition, the lack of clinical safety data combined with the expressed safety concerns are also rate-limiting factors for roll-out. A faster adoption could have risked both antibiotic stewardship and patient safety.

5. Financing

Bedaquiline prices were initially tiered according to the income level of the country where it was sold: a six month course of treatment in high income countries would cost USD 30,000, USD 3,000 in middle income countries and USD 900 in low income countries^v.

Introduction of bedaquiline to South Africa was initiated as a donation program covering 200 patients in 2013-2015 by Janssen pharmaceuticals prior to final approval by MCC/SAPHRA.

Beginning mid-March 2015, South Africa started purchasing bedaquiline at USD 1,000 per course. When bedaquiline use was expanded to all patients with drug-resistant TB in 2018, prices were negotiated down to USD 400. However, thanks to changes in currency exchange rates, the current price is USD 337 for a six-month course. The price negotiated by the South African Minister of Health was subsequently extended also to the Global Drug Facility. To date, more than 25,000 patients have received bedaquiline under programmatic conditions in South Africa.

Reflections

To ensure equitable access to care, the treatment cost per patient needs to be kept low enough to ensure affordability.

However, the cost of medicine is only a part of the total cost of a controlled introduction. The end cost is of course dependent on what health system investments are needed to ensure a controlled introduction. Relatively obvious costs relate to diagnostics, such as new instrumentation and consumables or increased need of human and infrastructural capacity and associated staff time. Critical but less obvious costs for a successful roll-out of new treatment regimen are for example costs for the creation of guidelines, training of existing and new staff, printing training materials, clinical guidelines and adapting diagnostic order forms and or electronic record systems.

All of these hidden costs need to be considered along with procurement supply plans and the introduction timeline, but there may also be costs that decrease. These potentially decreasing societal costs include in-patient care costs related to morbidities, such as loss of income or loss of ability to work and support oneself and family. Cost analyses can be complicated as several factors need to be weighed in, but are necessary to form a realistic basis for understanding the financial impact of introducing a new drug to the country.

6. Leadership and governance

An orderly introduction of a new medicine will require an organization that takes responsibility for the whole chain of events. In the case of bedaquiline in South Africa, the introduction was driven by the Ministry of Health that coordinated actions and created a program for bedaquiline use through the drug-resistant TB directorate and ensured bedaquiline availability. The expert committee was initially formed with a mandate to create guidelines, help the DR-TB directorate and facilities manage difficult DR-TB cases. Later the mandate included review of applications for bedaquiline use, clinical guidance to clinicians on DR-TB matters and publications.

Reflections

A successful program needs to be designed to cover the whole system from ministry level to health care levels, with elements of oversight, engagement of relevant actors and training of staff. A functioning governance structure is therefore instrumental for a controlled roll-out.

Another interesting aspect of introducing new antibiotics, especially from an LMIC perspective, is related to fast-track approvals. Fast-tracking the approval of new drugs is seen as a means to stimulate drug development by elongating the period of market exclusivity. The two components of fast-tracking are to speed up the time for regulatory authorities decisions, but also to reduce the demands for phase III clinical trials. However, the data still needs to be collected and reported to the relevant authorities. For new antibiotics, the greatest need to access the drug (and consequently, most use can be expected) is in LMICs. Unless care/precaution is taken, fast-tracking may lead to that new drugs with unfavorable safety profiles are released to markets where monitoring of adverse events and possibility to counter the events are limited. Alternatively, if market access is conditioned to collecting the missing safety and effectiveness data, this can incur major costs and strains to health systems in LMICs.

Interestingly, the indication of bedaquiline was expanded relatively quickly. Starting out as a last option treatment for multidrug resistant TB, it was soon demanded to be used more widely. Its utility as a non-injectable drug, advantageous safety profile (compared with e.g. kanamycin) and good efficacy paved the way for demands of making bedaquiline a first-line therapeutic. Similarly, an expansion of indication can be expected also for other new antibiotics – possibly to an even greater extent depending on the spectrum of activity. A new antibiotic approved and marketed for example

with the indication complicated urinary tract infection could easily be expanded to cover not only uncomplicated urinary tract infections but also bacteremia and sepsis and, if the pharmacokinetic profile allows for it, also other infections such as pneumonia caused by the same species of bacteria – especially in areas where resistance is common to the first and second line antibiotics. Slowing down this type of expansion of indication is very difficult, and often not even desirable as the case for bedaquiline clearly shows. However, any expansion of indication should be done in a controlled manner, and unnecessary expansions should be curtailed.

Final remarks

TB is in many aspects different from other infectious diseases, but the experiences from the introduction of bedaquiline can be applied to other antibiotics as well. Common ground for any other new antibiotics is the need for responsible use within developed stewardship programs, diagnostics and treatment guidelines and timely access to the medicine for those patients who need it.

Unlike other infections, antibiotics for TB have the “advantage” of often being used in larger programs where the medicines are distributed to patients, rather than patients buying them from a local pharmacy. Other antibiotics tend to be made available to the general market, sometimes without a requirement of a prescription, making the control of use much more difficult within a national program.

The example of South Africa highlights the importance of a functioning health system for a controlled roll-out of a new antibiotic. The case of bedaquiline involved a number of stakeholders – the national regulatory agency, Ministry of health, academic researchers and clinical experts. The program was also heavily reliant on healthcare facilities, staff and access to diagnostics to provide access to those in need of the new therapy.

In the context of other antibiotics, there are no clear programs similar to TB. Rather antibiotics are used all over the health systems and communities, in some cases without any oversight from medical or pharmaceutical professionals. So controlled introduction of a new non-TB antibiotic appears to be difficult unless health systems are strengthened, for example through the auspices of universal health coverage.

References

ⁱ Policy implementation package for new TB drug introduction. WHO. <https://www.who.int/tb/PIPnewTBdrugs.pdf?ua=1>

ⁱⁱ This case study builds on a desktop review and interviews with stakeholders. The desktop review was based on published materials online: scientific literature, stakeholder websites, reports and articles. Relevant stakeholders were identified by internal brainstorming, web searches and referrals from contacts.

Interviews were held with stakeholders working on different aspects of the introduction of bedaquiline: Clinton Health Access Initiative (CHAI) (access, regulatory affairs, distribution), a Clinician in Kwazulu Natal (clinical experiences and applications), an academic from Cape Town (introduction programming and overview) and a representative of the Ministry of Health (introduction programming and overview).

ⁱⁱⁱ Countries Raise Concerns about Access to Affordable Drug-Resistant TB Treatment. Third World Network. <https://twn.my/title2/health.info/2019/hi190601.htm>

^{iv} Everybody's business : strengthening health systems to improve health outcomes : WHO's framework for action. https://www.who.int/healthsystems/strategy/everybodys_business.pdf?ua=1

^v South Africa ensures reduction of prices for Bedaquiline to benefit the world. Stop TB Partnership. http://www.stoptb.org/news/stories/2018/ns18_053.asp