Barriers and facilitators to early access of bedaquiline and delamanid for MDR-TB: a mixed-methods study

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Setting: Phase II trials for bedaquiline (BDQ) and delamanid (DLM) were completed by 2011 and the drugs were approved by stringent regulatory authorities for the treatment of multidrug-resistant tuberculosis (MDR-TB) between 2012 and 2014. Manufacturers established 'early access' mechanisms to provide drugs before local registration.

Objective: To inform improvements in early access, we explored experiences of providers and advocates in accessing BDQ and DLM before the end of 2015 using a mixed-methods design.

Design: We examined barriers and facilitators to early access through an electronic survey. Barriers and facilitators were classified as occurring at the manufacturer- or country-level. We identified themes using inductive content analysis and illustrated themes through case studies.

Results: We analysed 41 survey responses from 36 respondents reporting on 22 countries; early access was attempted in 30 (73%) survey responses. Eligibility restrictions (11/30, 37%) and complicated and slow processes (8/30, 27%) were manufacturer-level barriers; access to companion drugs (10, 33%) and importation difficulties (4, 13%) were country-level barriers. Previous experience with manufacturer (3/30, 10%) and country processes (2/30, 7%) facilitated access. Eight case studies show the human impact of barriers and facilitators.

Conclusion: Manufacturers and countries should develop transparent processes to permit early access, particularly for diseases that largely affect the poor, such as MDR-TB. Developers should plan for this need and rapidly register drugs with proven benefit, prioritizing high-burden settings.

Each year, more than half a million cases of tuberculosis (TB) resistant to the most important drugs in standard anti-tuberculosis treatment occur.¹ These forms of the disease, rifampin (RMP) resistant and multidrug-resistant TB (MDR-TB, defined as TB resistant to at least RMP and isoniazid [INH]), are difficult and expensive to treat.² Patients with MDR-TB are treated with toxic drugs for long durations, and treatment outcomes are often poor; success is achieved in only 50% of patients worldwide.^{3–5} The advent of two new drugs, bedaquiline (BDQ; SIRTURO, Janssen Therapeutics, Beerse, Belgium) and delamanid (DLM; Deltyba, Otsuka Pharmaceuticals, Tokyo, Japan), with novel mechanisms of action against *Mycobacterium tuberculosis* offer great hope to patients and providers worldwide who seek shorter, less toxic, and more ef-

fective treatment regimens. The story of their constrained uptake may be instructive for the introduction of other new drugs for TB and other diseases that disproportionately affect the poor.

As early as 2012, there was peer-reviewed, published evidence on the effectiveness of BDQ and DLM. Phase IIb trials for BDQ and DLM were completed in respectively 2011 and 2010.^{6–11} BDQ was conditionally approved by the US Food and Drug Administration in 2012 and DLM by the European Medicines Agency (EMA) in 2014.^{12,13} Following this, the World Health Organization (WHO) released interim guidance,^{14,15} more restrictive than the drug labels,^{12,13} to advise national TB programs on their use. The addition of 6 months of BDQ or DLM to a conventional regimen is recommended by the WHO for adults with pulmonary MDR-TB and extensively drug-resistant TB (XDR-TB; defined as MDR-TB with additional resistance to any fluoroquinolone and at least one of the three second-line anti-tuberculosis injectables) when an adequate regimen cannot be constructed (due to resistance or intolerance) or when there is increased risk of poor outcomes or comorbidities. WHO guidance further restricts BDQ and DLM in pregnant (or breast-feeding) women, children, those with certain comorbidities and those on concomitant medications.^{14,15}

It is estimated that as many as 250 000 people with MDR-TB each year could benefit from either drug if used according to the WHO interim guidelines.¹⁶ The drugs have been registered in only a small number of countries, and delayed registration of the drugs in high MDR-TB burden countries is one factor that has limited access.¹⁷ By the end of 2015, the time of the present study, both drugs were registered in the European Union, and BDQ was registered in 13 other countries, DLM in two.¹⁷ Pending regulatory approval and marketing, mechanisms such as compassionate use and expanded access were thought to facilitate access to a limited number of patients. These mechanisms are broadly defined as the means by which drugs can be distributed and used in patients outside of a clinical trial before regulatory approval or market access.¹⁸ Compassionate use generally involves granting of pre-marketing access to individual patients with an unmet medical need. Expanded access refers to the enrollment of a cohort of patients who meet specified eligibility criteria to receive a drug before regulatory approval or market access.¹⁸

It was hoped that compassionate use and expanded access would fill some of the treatment access gap. However, in late 2015, compassionate use or expanded

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FIGURE Explanatory sequential mixed-methods case study design.

access programs (hereafter, referred to as ‘early access’) had only provided access for approximately 700 patients to BDQ and 100 patients to DLM.¹⁷ Given the prodigious treatment gap between the estimated number of patients who require access—250 000 per year—and the number who actually received access to BDQ and DLM ($n = 800$), we sought to investigate experiences in attempting access to BDQ and DLM through early access before the end of 2015. Here, we present the results of a mixed-methods study that describes the experiences of providers and advocates in seeking access to BDQ or DLM through early access; barriers and facilitators encountered in the process; and case studies that illustrate how barriers obstructed or delayed and how facilitators enhanced access. This experience can inform early access to other drugs currently under development for TB and for other diseases that disproportionately affect people outside of high-income countries.

METHODS

We used an explanatory sequential mixed-methods case study design in which primarily quantitative data collection (survey) preceded and informed case studies.¹⁹

Survey

The survey assessed provider experiences attempting to access BDQ and DLM before regulatory approval (Figure). To include the full range of mechanisms for accessing investigational drugs before approval, we used the terms ‘compassionate use’, ‘expanded access’, and ‘pre-approval mechanism’, and asked respondents

to describe the mechanisms—and any experience with them—in the country for which they were reporting. We developed survey content in consultation with steering committee members of Research Excellence to Stop TB Resistance (RESIST-TB), a research-advocacy group for MDR-TB clinical trials. RESIST-TB steering committee members suggested survey content and provided feedback on survey drafts before the group agreed on a final version of the survey for distribution. The survey included standardized ‘closed’ and open-ended questions (Supplementary Material I). The survey captured basic demographic information on respondents, the number of patients for whom they cared or advocated, the estimated proportion of patients with whom they were familiar who would benefit from BDQ or DLM, familiarity or awareness of country-specific early access mechanisms, and any experience trying to access BDQ or DLM. Those who reported attempting early access were queried about the number of successful and unsuccessful applications for BDQ and DLM, as well as about barriers and facilitators to access. The survey was programmed in Qualtrics (Provo, UT, USA) and distributed in English by e-mail.

Survey population

Survey participants were MDR-TB treatment providers (defined as persons who participated directly in or consulted on the clinical care of people with MDR-TB) and advocates (defined as persons who liaised with, advised, or otherwise could have been involved in attempts to access BDQ or DLM). Members of RESIST-TB completed the survey and referred colleagues whom they believed had experience treating

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or working with individuals with MDR-TB. The survey was open from April 2015 to December 2015. Colleagues who were referred by RESIST-TB members were reminded by e-mail three times to complete the survey. A single respondent could complete the survey multiple times, once for each country in which s/he works.

We restricted our analysis to survey responses that described early access, defined as 1) the use of a drug before country regulatory approval outside of a clinical trial, and 2) in a named patient or cohort of patients. We excluded experiences that described access through clinical trials and drug donation programs after registration.

Survey analysis

From standardized questions, we describe respondent and country characteristics. We report the number of patients for whom an attempt was made to access each drug and the proportion of success. We examined the answers to open-ended survey questions as qualitative data through inductive content analysis, a method in which the data drive development of new theories and conclusions, which is best suited for situations when little previous evidence or knowledge exists.¹⁹ We read through the survey responses repeatedly to identify recurring themes and coded the data accordingly using QDA Miner Lite (Provalis Research, Montreal, QC, Canada). Similar codes were grouped to develop the reported theme areas. Barriers and facilitators were classified into two types: those related to the manufacturer (or product) and those specific to the country in which access was sought. Factors were linked to the manufacturer if they related to label or eligibility requirements that applied to all patients in all countries seeking access. Factors were linked to the country if they were specific to the experience of seeking approval in a given country to comply with country-specific regulatory requirements, such as approval from country clinical committees or institutional review boards and requirements related to the importation of the drug. We transformed qualitative data from open-ended survey questions to quantitative results by recording the frequency of responses by theme, barrier, facilitator and level.

Case studies

Case studies were used to explore providers' accounts of experiences attempting early access for patients (Figure).

Case study collection and sampling

We contacted a convenience sample of the survey population (providers and advocates) to request case studies of patients who attempted to access BDQ and/or DLM through early access. We used the diverse case method, an exploratory sampling method to select a subset of cases who represent experiences of interest: experience of country- and manufacturer-related facilitators and barriers, as well as timely and delayed access.²⁰ We selected cases illustrating experiences of both approved and rejected applications for both drugs which illustrate the themes identified in the survey.

Case analysis and integration

The case studies highlight the barriers that resulted in outright rejection or delay and facilitators that supported access.

Integration of survey and case study data

By connecting the two parts, we examined the ways in which the themes identified in the survey were reflected in individual experiences described in the case studies.

TABLE 1 Characteristics of survey respondents ($n = 36$) and countries ($n = 22$) for which they responded

Characteristic	n (%)
Respondent characteristics ($n = 36$)	
Sector respondent provides care	
Private sector only	2 (6)
Public sector only	27 (75)
Both private and public sectors	6 (17)
No response	1 (3)
Estimated number of people with MDR-TB whom respondent cares or advocates for annually	
<10	2 (6)
10–50	5 (14)
51–100	12 (33)
101–250	7 (19)
251–500	1 (3)
≥501	6 (17)
Not applicable	2 (6)
No response	1 (3)
Country characteristics ($n = 22$)	
High-burden country ¹	
TB	9 (41)
MDR-TB	11 (50)
World Bank income group ²¹	
Low	4 (18)
Lower-middle	10 (45)
Upper-middle	4 (18)
High	4 (18)
WHO region ¹	
Africa	7 (32)
Americas	1 (5)
Eastern Mediterranean	1 (5)
Europe	10 (45)
South-East Asia	2 (9)
Western Pacific	1 (5)

MDR-TB = multidrug-resistant TB; TB = tuberculosis; WHO = World Health Organization.

RESULTS

Survey

Between July and December 2015, we distributed the survey to 98 MDR-TB providers and advocates thought to have attempted early access to BDQ and/or DLM. We received 50 complete survey responses. We excluded nine survey responses that did not address early access. The 36 respondents who completed 41 surveys are described in Table 1. Nearly all (33, 92%) respondents reported working in the public sector. Most (26, 72%) reported caring or advocating for more than 50 MDR-TB or XDR-TB patients annually. The 41 survey responses reported experiences in 22 countries. Nine (41%) countries had high TB burdens and 11 (50%) had high MDR-TB burdens, as defined by the WHO.¹ Most countries belonged to the WHO Europe (10, 45%) and Africa (7, 32%) Regions. In nearly two thirds (26, 63%) of survey responses, respondents reported that early access was permitted in their country (Table 2). We received more than one response for eight (36%) countries; in four (50%) of these countries, responses were contradictory about the presence of a mechanism for early access (data not presented).

Respondents in 30 (73%) surveys reported attempting early access for a total of 458 patients: 384 for BDQ and 74 for DLM. Of

TABLE 2 Quantitative results of electronic survey on experience attempting to gain access to BDQ and/or DLM ($n = 41$, unless specified)

Question	<i>n</i> (%)
Eligible patients who would benefit from the addition of BDQ and/or DLM to regimen ($n = 41$)	
None	4 (8)
Few	6 (15)
Some	15 (37)
Most	14 (34)
All	2 (5)
Country permits access to drugs through early access ($n = 41$)	
Yes	26 (63)
No	7 (17)
Don't know	8 (20)
Attempt made to access to BDQ and/or DLM through early access ($n = 41$)	
Yes	30 (73)
No	11 (27)
Ease of early access process ($n = 30$)	
Easy	9 (21)
Moderately difficult	12 (42)
Difficult	9 (28)
Reported outcome attempting access to BDQ ($n = 30$)	
Accessed BDQ	354 (92)
Did not access BDQ	30 (8)
Reported outcome attempting access to DLM ($n = 30$)	
Accessed DLM	62 (84)
Did not access DLM	12 (16)
Reason for not attempting early access ($n = 11$)	
Respondent heard the process was too complex	7 (64)
Respondent believed they had to have a relationship with the manufacturer to enable access to drug(s) before regulatory approval	5 (45)
Respondent did not have the administrative support necessary to complete paperwork requirements	4 (36)
Lack of institutional support for use of drug(s) outside of a clinical trial	2 (18)
Respondents opted to access drug(s) through clinical trials	2 (18)
Respondent was not aware drugs could be accessed outside of a clinical trial	1 (9)

BDQ = bedaquiline; DLM = delamanid.

these, 354 (92%) patients successfully accessed BDQ and 62 (84%) patients successfully accessed DLM (Table 2). The remaining 11 (27%) surveys indicated that an attempt to access BDQ or DLM was not made. The most common reasons for not attempting access included believing that the process was too complex (7, 64%), that a relationship with the manufacturer was needed to access the drugs (5, 45%), and that the respondent did not have the administrative support to complete the required paperwork to access the drug(s) (4, 36%) (Table 2).

Barriers and facilitators

Transformed qualitative data in Table 3 indicate the barriers and facilitators reported in the 30 survey responses where an attempt was made to access BDQ or DLM. These are divided into factors at the manufacturer level and factors at the country level.

At the manufacturer level, the most commonly cited barrier to early access was eligibility restrictions per drug label or WHO in-

terim guidance (11, 37%), including extra-pulmonary involvement or complex drug resistance, previous or concurrent use of BDQ or DLM, existing QTc prolongation, or age <18 years. Respondents described application and approval processes that were complicated, slow, and administratively burdensome (8, 27%), with one survey respondent recounting that,

...lots of forms and data required; lots of physician and nurse time; lots of emails back and forth and a very slow process...a wait time of months in critically ill patients (Table 3).

In contrast, facilitators included descriptions of clear and standardized application processes (2, 7%), with respondents describing the process as 'well established' and having 'clear criteria, standard forms and a transparent process for who could get the drug'.

A greater variety of barriers and facilitators was observed at the country-level. Lack of access to companion drugs to compose an adequate regimen was the most common country-level barrier (10, 33%). Respondents described that difficulty accessing companion drugs was due to prohibitive cost, drug shortages, lack of country support, and lack of registration for a TB indication, with one provider recounting that,

...the drugs (linezolid [LZD] and clofazimine [CFZ]) were still not allowed to enter the country due to bureaucratic issues surrounding registration....

CFZ, LZD, levofloxacin (LVX), and ethionamide (ETH) were the most frequently cited drugs for which access was an issue. Complex importation regulations and delays at customs were also common barriers for BDQ and DLM (4, 13%) and extended to unregistered companion drugs. Support from colleagues with previous experience in navigating the system (2, 7%) and the existence of country regulatory and importation frameworks (1, 3%) were highlighted as facilitators.

Suggestions for improvement

Suggestions from survey respondents on how the early access process could be improved are presented in Table 4. The most frequent recommendation was a call for a streamlined, electronic process for applications to both manufacturers and country authorities, which could minimize administrative burden and time from application to receipt of drugs (6, 20%). Furthermore, respondents suggested that support from international agencies, such as the WHO, in researching and guiding providers in the application (3, 10%) could aid in demystifying the otherwise complex process.

Case studies

Eight case studies were selected to illustrate the individual, human impact of these barriers and facilitators. Cases describe how these factors obstructed, delayed or enhanced access to BDQ and DLM. Four case studies are presented in full (Mariam, David, Calvin, Boris), with key excerpts from the remaining cases (Sandina, Tanvi, Raj, Valeri) presented in the text and in Table 3 (names changed).

Barriers and facilitators

The effect of manufacturer-level eligibility restrictions is described in case studies for Mariam, David, and Calvin and quotations from case studies for Raj and Sandina. Access to drugs was denied for Mariam due to extra-pulmonary disease and because of concurrent use of BDQ for David. In both cases, the patients ultimately recovered from MDR-TB but were disabled due to surgical

TABLE 3 Barriers and facilitators described in electronic survey and case studies

Theme	Survey (n = 30) n (%)	Quote ○ Case study • Survey
Manufacturer-level barriers		
Eligibility restrictions on disease characteristics, age, concomitant use of BDQ/DLM, previous use of BDQ/DLM, or use of BDQ/DLM for >6 months	11 (37)	<ul style="list-style-type: none"> ○ 'We kept hearing this criteria (concomitant BDQ/DLM) was going to be relaxed and that the company was going to no longer deny DLM to patients who needed BDQ as well. But that change had not been put into practice' (provider caring for Sandina) ○ 'It was almost universal among the compassionate use cases...they all had previous treatment with second-line drugs ...stopping an effective drug [BDQ] put the utility of using BDQ under compassionate use in question' (provider caring for Raj)
Complicated, lengthy, and/or slow application and approval process	8 (27)	<ul style="list-style-type: none"> • 'These steps are not publicly available anywhere and it is only because my organization told me all this that I was able to follow the process' • 'Lots of forms and data required; lots of physician and nurse time; lots of e-mails back and forth and a very slow process...a wait time of months in critically ill patients'
Companion regimen considered weak by manufacturer	4 (13)	<ul style="list-style-type: none"> • 'For BDQ, several requests have been made and most have been approved; those which were denied were either due to issues with QT or because an appropriate background regimen could not be provided due to unavailability of most Group 5 drugs...'
Manufacturer-level facilitators		
Previous experience or support from colleague with previous experience on manufacturer application process	3 (10)	<ul style="list-style-type: none"> • 'After the first few cases, the team became used to the process and the applications went smoothly – even the importation process...' ○ 'We knew how the system worked and had an excellent relationship with the manufacturer' (provider caring for Valeri)
Availability of clear, simple, and standardized process	2 (7)	<ul style="list-style-type: none"> • 'The process was very straightforward. There were clear criteria, standard forms, and a transparent process for who could get the drug'
Country-level barriers		
Lack of access to companion drugs due to absence of registration, prohibitive cost, stock out, or difficulty finding manufacturers	10 (33)	<ul style="list-style-type: none"> • 'The problem is providing the background regimen, particularly the cost of the Group 5 drugs' • 'The drugs (LZD and clofazimine) were still not allowed to enter the country due to bureaucratic issues surrounding registration and have been blocked by the antibiotic resistance commission due to (mostly unfounded) fears that introducing these drugs for anti-tuberculosis treatment would increase the amount of drug-resistant <i>C. difficile</i>, <i>E. coli</i> and other bacterial infections' ○ 'Most of their applications had been rejected because they did not have other drugs to add to the regimens with the BDQ; when we came, we came with LZD and imipenem...their applications were accepted, whereas before they had been rejected' (provider caring for Valeri)
Complicated, lengthy, and/or slow application and approval process	8 (27)	<ul style="list-style-type: none"> • 'Treatment for MDR-TB in the public sector is hampered by delays in getting access to drugs and appropriate diagnostic information needed to individualize treatment' • 'It requires signing many agreements, including with the Ministry of Health, and need for a competency and experience in using compassionate use. That means the Ministry of Health alone or any other organization with limited experience in using compassionate use would find it difficult getting it' ○ 'There are so many hurdles and bureaucratic delays. And people end up paying with their lives or their lungs or their sense of hope' (provider caring for Sandina)
Complex and logistically challenging importation regulations	4 (13)	<ul style="list-style-type: none"> • 'The initial approvals for permission to import BDQ were a long process, as it not clear how to do this legally. Finally, we imported through humanitarian goods cargo.' • 'No one in (country) was aware of the legal difficulties when BDQ became available via compassionate use. It was thought that if the drug was imported as a "humanitarian aid" donation it would be accepted, and Janssen was quite willing to cooperate, but ultimately the process proved unsuccessful' ○ 'The whole process for import was such a black box. Sometimes customs cleared these things quickly and sometimes they sat on packages for weeks (and sometimes there were extra 'fees' that needed to be paid to get the drugs out of customs)' (provider caring for Sandina)
Difficulty meeting requirements for use of BDQ/DLM including pharmacovigilance and DST	2 (7)	<ul style="list-style-type: none"> • 'Availability of extended DST for various drugs is a problem, often the regimen would include drugs with unknown DST results'
Lack of country and/or institutional political will for using BDQ/DLM	1 (3)	<ul style="list-style-type: none"> • 'They (country officials) believe that the only way to bring in these drugs via compassionate use is by changing legislation, which the TB program and advocates have no ability to do'
Country-level facilitator		
Previous experience or support from colleague with previous experience on country-level regulatory process	2 (7)	<ul style="list-style-type: none"> ○ 'We were lucky because we practice in an innovative environment where clinicians support one another. Once we had applied, we helped other colleagues apply for their patients and developed an application guide that was distributed nationally' (provider caring for Calvin)
Strong country support and political will to use BDQ/DLM	2 (7)	<ul style="list-style-type: none"> • 'We have a good system and experience for using these drugs and a very positive attitude from responsible institutions to introduce these drugs'
Existence of a national program or mechanism for approval and importation	1 (3)	<ul style="list-style-type: none"> • 'The (country) government's policy allowing importation of drugs for compassionate use for individual use makes accessing drugs fairly easy'

BDQ = bedaquiline; DLM = delamanid; LZD = linezolid; MDR-TB = multidrug-resistant tuberculosis; DST = drug susceptibility testing.

TABLE 4 Suggestions to improve early access process ($n = 30$)

Suggestion	Survey n (%)
Fast, electronic process with minimal administrative burden	6 (20)
Clear eligibility criteria and instructions on process from manufacturers and country regulatory authorities	4 (13)
Create national stocks of drugs that are released upon necessary approvals	3 (10)
Support from international agencies on country-specific legal and regulatory processes	3 (10)
Improve attitudes and increase political will around use of drugs	1 (3)
Lower drug costs and increase resources for procurement	2 (7)
Release manufacturers from responsibility for patient outcomes and adverse events	1 (3)
Eliminate or reduce burden of pharmacovigilance training	1 (3)

intervention at the disease site and drug toxicity, respectively. Limiting use of BDQ to a maximum of 6 months was also a major barrier:

It was almost universal among the compassionate use cases...they all had previous treatment with second-line drugs and many of them were failures of second-line drugs...stopping an effective drug [BDQ] put the utility of using BDQ under compassionate use in question (provider caring for Raj).

Calvin and Sandina suffered from complicated, slow, and lengthy processes that obstructed or delayed access to drugs at the manufacturer- and country-levels. A provider caring for Sandina described it this way:

There are so many hurdles and bureaucratic delays. And people end up paying with their lives or their lungs or their sense of hope.

Case 1: Mariam: bedaquiline in patient with extra-pulmonary XDR-TB

In April 2013, we sought alternative treatment options for a 24-year old female in Georgia with an extensive history of treatment for extra-pulmonary TB of the right knee joint and abdominal lymph nodes. She was first diagnosed in 2005 and received three courses of first-line treatment and two surgical interventions on the knee over the course of 3 years. Drug susceptibility testing (DST) in 2008 on surgical specimens confirmed XDR-TB. Between 2008 and 2011, she received treatment with second- and third-line anti-tuberculosis drugs. Despite good treatment adherence, the disease persisted and she had two more surgeries in 2011 and 2012. Further testing confirmed resistance to all drugs tested.

With no other therapeutic options available in Georgia at the time, in May 2013 we applied to Janssen Therapeutics for BDQ on grounds of compassionate use. The request was denied on the grounds that the program was limited to patients with pulmonary disease and safety and efficacy data on BDQ use in extra-pulmonary cases were lacking.

We subsequently contacted the Médecins Sans Frontières-Partners In Health (MSF-PIH) Medical Committee for Compassionate Use of Investigational New Drugs for MDR-TB—a consultative group of experienced MDR-TB clinicians from around the world—for further input. The committee strongly supported the use of BDQ, given that the young patient had no other hope of successful treatment. A revised application to Janssen in July 2013 included a letter of support from the MSF-PIH Medical Committee. Our request was denied again with the same rationale: the pro-

gram was limited to patients with pulmonary pre-XDR-TB and XDR-TB, that extra-pulmonary disease had not been studied, that the compassionate use program was restricted to areas in which there were data, and thus, that the compassionate use program could not be extended to extra-pulmonary disease.

No further chemotherapeutic treatment could be provided; in the face of continued infected fistulas, we performed a palliative surgical intervention that concluded with immobilization for 3 months. Non-specific antibacterial treatment, plus antifungal and symptomatic treatment was given for 1 year. As a result, the fistulas closed and signs of infection resolved. Partial recovery of the locomotor function of the knee was achieved. At the time of writing, the general condition of the patient is satisfactory, with no signs of active TB.

Case 2: David: delamanid in XDR-TB patient with concurrent bedaquiline use

This 38 year-old man with MDR-TB living in the United States had originally been diagnosed with pulmonary MDR-TB in December 2013. The patient, David, was treated with a series of empiric regimens pending full DST results. By late December 2013, he was being treated with a customized regimen comprising nine drugs, including an intravenous agent. When testing revealed continued presence of the bacterium, additional resistance, and disease progression apparent through chest computer tomography scan, expert consultation was requested to assist with interpretation of discordant DST results and treatment recommendations.

The regimen was changed to include the addition of BDQ plus two second-line drugs and replacement of the intravenous agent. The treating clinicians and consultants remained concerned about the effectiveness of almost all of these drugs. Only BDQ and two other drugs were likely to be effective, given the DST profile. Four months into treatment, painful peripheral neuropathy developed. Despite a 2-week interruption and dose reduction of the offending drug, the neuropathy progressed.

Given the limited treatment options, in April 2014, David's treating physician requested access to PA-824 (pretomanid) from the Global Alliance for TB Drug Development and DLM from Otsuka Pharmaceuticals. The request for PA-824 was denied because there was no designated compassionate use program at the time. Repeated requests to Otsuka—including at least two conference calls with the company's clinical resource person and support from international experts to use DLM in this case—were denied. Otsuka's policy at the time was not to provide DLM to patients who were currently on BDQ or who had received BDQ in the past 6 months. Although the patient was willing to sign an informed consent form documenting that he understood the risks and benefits associated with the combined use of the two drugs, the company continued to deny access. His physicians had no choice but to refer him for surgical resection, which was not ideal given his extensive burden of pulmonary disease. Although he was ultimately cured of his XDR-TB, he is now oxygen-dependent with severe mobility limitations due to his poor respiratory reserve and permanent peripheral neuropathy.

The benefit of previous experience or support from colleagues with experience in accessing drugs was highlighted in Calvin and Valeri (manufacturer-level) and Boris's (country-level) experiences. In reference to pursuing access a second time, Valeri's provider described it:

We knew how the system worked and had an excellent relationship with the manufacturer.

In rare instances, existing country regulatory and importation frameworks were cited in the survey as both a facilitator and a suggestion for how compassionate could be improved. Through *Autorisation temporaire d'Utilisation* (ATU), a unique mechanism for early access in France, providers were able to access BDQ and DLM simultaneously and use drugs for more than 6 months (Boris), two separate eligibility restrictions that were cited as barriers in other countries.

Case 3: Calvin: support from colleagues facilitates access to delamanid

A 34 year-old, HIV-negative male with diabetes and MDR-TB resistant to INH, RMP, and ofloxacin and susceptibility to amikacin came into my care in August 2015. He had been first diagnosed with MDR-TB in 2013 and was treated with several regimens—including a LZD-based regimen—but he never experienced sustained response. In January 2014, he was offered treatment with BDQ, which was available through an expanded access program in South Africa. Despite excellent adherence, no microbiologic response occurred, and BDQ was discontinued in June of 2014 after the allowed 24 weeks of treatment. He stayed on a 6-drug ‘suppression’ regimen. His X-ray revealed minimal disease. His diabetes was well controlled, despite limited access to monitoring tools.

In November 2015, we planned a salvage regimen containing DLM and four other drugs. The national clinical advisory committee hesitated to use DLM because it reported that the drug had not been used in the country before. The company's website provided no information about compassionate use of DLM; it offered a generic e-mail address for inquiries.

Seeking information from colleagues, we learned that two children at a large teaching hospital had received DLM via compassionate use. The treating clinicians provided us with the forms that they had used, and recommended we seek regimen guidance and an endorsement from the European Respiratory Society/World Health Organization (ERS-WHO) TB Consilium, an independent international committee. Within days of its submission, the ERS-WHO TB Consilium replied in agreement with our DLM-containing salvage regimen. Completing the company forms provided to us by colleagues, the country's importation form for unregistered drugs, and request for ethics approval to administer the drug required time-consuming, inefficient repetition of similar information. We also had to pay the regulatory agency for filing the application. We received DLM within 6 weeks of application. Although we had already been trained in pharmacovigilance for BDQ, and the majority of us were trained in Good Clinical Practice for clinical trials, the company required clinician participation in a 3-hour pharmacovigilance training. In the context of a clinic with extremely high demand for care, the process consumed considerable clinician time.

Case 4: Boris: a unique country mechanism eases access to concomitant and prolonged use of bedaquiline and delamanid

A 30-year old, HIV-negative male with hepatitis C virus from the Russian Federation came into our care in July 2015. The patient had a long, tragic history of unsuccessful anti-tuberculosis treatment. He had first been diagnosed and treated for pulmonary TB in Chechnya in 2002. In 2012, he was again diagnosed with pulmonary TB. Soon after initiating treatment, he left Chechnya to seek care in Germany. DST conducted in Germany revealed MDR-TB. The patient began a third course of treatment comprising seven drugs. From Germany, he was transferred to a hospital in Brest, France, where treatment was cut short after 18 months

due to side effects. We first encountered the patient on his referral to the Bligny Hospital in Briis-sous-Forges, France, for relapse of sputum smear-positive, pulmonary MDR-TB.

The existence of a unique early access mechanism was a critical factor in the patient's subsequent care. In 1986, France's *Agence Nationale de Sécurité du Médicament et des produits de Santé* (ANSM) enacted an ATU, a regulatory mechanism to ensure access to non-approved drugs for terminally ill patients or those with rare diseases. In March 2011, France introduced one of the first compassionate use programs for BDQ through the ATU mechanism. A treating physician applies for BDQ directly to the ANSM and not to the drug company.

It was clear that the patient needed BDQ due to his previous treatment history and resistance to eight drugs. In August 2015, with support from the French TB Consilium, we requested BDQ through the ATU. Access was granted immediately and the patient started a new, seven-drug regimen containing BDQ. By September 2015, the final results of new DST suggested that the strain had grown resistant to two of the drugs in the regimen; these and several others in the current treatment had been previously administered to the patient. We re-examined the regimen with the French TB Consilium. Although we had limited experience in the concomitant use of BDQ and DLM, we agreed that the best chance for the patient's cure was the addition of DLM. Similar to BDQ, our request for DLM was addressed directly to the ANSM and not to the drug company. ANSM promptly approved the application; importation from Germany engendered a 20-day delay. We replaced the agents to which resistance had been documented with DLM and an intravenous companion drug. We monitored the patient's safety with the greatest attention and reassured the patient that this was the best option for him. Early microbiological response occurred in November 2015 and was confirmed in February 2016.

Hearing loss, a known side effect of one of the drugs in the regimen, led to the discontinuation of a companion drug in February 2016. The discontinuation of BDQ and DLM after 24 weeks of treatment, as prescribed by the manufacturers, would have left the patient with a weak treatment regimen. With the French Consilium, we agreed to continue the use of both drugs for the full treatment duration. A companion drug was stopped due to transient, asymptomatic QT interval prolongation. At the time of writing, Boris's condition has clearly improved and he has only a few months of treatment left before the end of the planned 24 months of treatment.

DISCUSSION

Our study reveals that a small, select population of providers and advocates was able to obtain access to BDQ or DLM through early access for a limited subset of the 250 000 patients annually who would benefit from these drugs.¹⁶ Nevertheless, the study indicates that the fate of individual patients without (marketed) treatment options is dependent on the policies and practices of the country in which they are being treated and of the manufacturer of the product to which they seek access. Patients experiencing denied or delayed access faced protracted illness, likely continued transmitting resistant disease, sustained irreversible injury due to toxicities from older treatments and unchecked disease, and even death. The success stories, however, reveal that it does not have to be this way. Starkly different experiences were reported across countries, drugs, and contexts, revealing that opportunities for improvements to the mechanism are possible.

The shortage of information on country- and manufacturer-level processes governing early access to the drugs resulted in confusion and uncertainty. This manifested in conflicting reports about whether a mechanism existed in a single country. Establishing and clearly communicating country requirements for early access and importation of drugs could potentially resolve this barrier.²² Regional or other supranational mechanisms could support countries to develop country processes where they otherwise do not exist, or serve as a clearinghouse to distribute information on existing country processes. Limited application and approval information from manufacturers also obstructed early access. In some cases, informal networks countered this by providing guidance to colleagues in need. National legislation requiring that manufacturers have publicly accessible policies and procedures for early access, such as the US 21st Century Cures Act,²³ could both inform providers who are attempting early access and ease manufacturer's concerns that disseminating such information would be construed as marketing.

Restrictions on eligibility criteria were a major reason cited for rejection from manufacturers. Early access eligibility criteria mirrored the drug labels of marketed BDQ and DLM. Applying these conditions to desperate patients in settings of high MDR-TB burden goes against the purpose of early access, which is intended to provide access to investigational drugs for serious conditions when patients are not otherwise eligible for inclusion in a clinical trial. While criteria have been relaxed over time—DLM was extended for use in children aged 6–17 years in 2016²⁴—a 2017 report on DLM does not mention exclusion for concomitant use of BDQ,²⁵ and the 2018 WHO rapid communication defers to best practices for 'off label use' when considering treatment beyond 24 weeks with either drug^{26,27}—compassionate use criteria should reflect the realities of patients with severely constrained treatment options. However, manufacturers need not have total control over who is eligible for early access. As demonstrated by France's ATU program, national governments can take legal responsibility for harms experienced by patients, in turn releasing manufacturers of liability and providing countries with the ability to use drugs in the patients they deem eligible.

Manufacturers should plan early access programs at the early stages of clinical development, long before labels are developed. The benefit of changing criteria for compassionate use access to BDQ and DLM is limited at the time of writing, as marketing authorizations are more common, if still far from universal. However, with six drugs in Phase I trials and 12 drugs or regimens in Phase 2, the time to plan for early access for these agents is now. Developers of several drugs tested in late Phase 2, and even Phase 3 trials, such as pretomanid and sutezolid, have announced no early access plan despite repeated calls for early access during extremely lengthy development and marketing processes.²⁸ Furthermore, fear that clinical trials or marketing authorization will be derailed or hindered in the event poor outcomes or adverse events are observed in early access patients are unfounded and should not be a reason to avoid developing programs.²⁹ National governments also have a role in ensuring early access mechanisms are in place. In the example of France, the long established ATU mechanism was rapidly leveraged for BDQ in 2011, a year before the drug's first approval by a regulatory authority. Established early access mechanisms will avoid the need for countries to develop frameworks in response to specific drugs.

While important, early access should be only a temporary solution to meet needs of patients with limited treatment options. This study reveals that early access, even when well exe-

cuted, does not greatly increase access to new anti-tuberculosis drugs. Prompt registration in high-burden countries and affordable pricing of drugs shown to be effective are of utmost priority. Once drugs have an indication, countries and manufacturers should immediately register the drugs or determine and act upon the evidence gaps impeding registration. This is particularly true for drugs that are developed for conditions disproportionately affecting the poor; a plan should be in place to promote access to products with proven effectiveness where the greatest burden exists. Companies typically prioritize registration by stringent regulatory authorities such as the EMA and US Food and Drug Administration but recently, registration of the first vaccine for dengue was prioritized in Latin America and Asia where the burden of disease is highest.³⁰ However, it should be noted that expeditious registration to promote access should be balanced with appropriate evidence of safety and efficacy. While manufacturers hold responsibility for securing marketing authorization in each sovereign nation according to its regulations, there is untapped potential to strengthen existing regional and global mechanisms, and additional innovations to facilitate the registration process should be explored. As an example, one mechanism on which additional efforts could be built is the Collaborative Procedure for Accelerated Registration, which has been piloted since 2015. This aims to speed registration of finished pharmaceutical products that have been approved by stringent regulatory authorities. Initial efforts have resulted in LVX and ETH being registered for TB in high-burden countries such as the Philippines, Ukraine, and Kenya.³¹ Similarly in 2016, Ukraine passed Law No 1350 (known as Bill N° 4484), which recognizes assessments conducted by stringent regulatory authorities and expedites registration of drugs for public health priority diseases to less than a month.³² Steps have also been made to establish the African Medicines Agency, a supranational regulator which will be responsible for providing regulatory guidance, harmonizing registration, and monitoring adverse effects post-marketing in countries of the African Union.³³ Early access is a continuum and post-marketing monitoring for safety concerns can ease regulatory authority and provider concerns of introducing new drugs. For TB, systematic post-marketing pharmacovigilance around safety exists for the first time in many countries as a way to safeguard patients while increasing access to treatment options.³⁴

This mixed-methods study provides an overview of the experiences of respondents and some common themes that affected success or failure of attempts to access BDQ or DLM through early access. Nevertheless, there are limitations. Survey respondents and cases were reported largely from middle- and high-income countries. Barriers and facilitators identified in our study may underrepresent those experienced in low-income settings, where limited access to adjunctive therapies and companion drugs are likely to further compromise patient care. Due to the nature of the standardized, electronic survey, we did not have the ability to probe respondents on their answers. Although drugs acquired through compassionate use mechanisms are generally free of charge, additional labor and monitoring requirements may result in additional costs. We did not inquire directly about whether associated costs, in addition to the operational demands, were considered to have further limited access these drugs. The sampling method for the survey may have resulted in selection bias, favoring English speaking providers and advocates with the most (successful) experiences. Furthermore, we cannot rule out that persons who did not respond to the electronic survey had different experiences than those who did reply, which

could also introduce selection bias. The sample size was small, further limiting our ability to draw inferences, and multiple respondents in the survey may have reported on the same case. Nevertheless, this study details significant challenges to successful early access to the first new anti-tuberculosis drugs in about 50 years.

Most importantly, this work highlights the need for earlier, concerted action on the part of developers to make drugs available and for countries to develop transparent, simple processes to permit clinician-supervised access to new treatments for patients with limited options. Developers of drugs in early to middle stages of clinical development should be anticipating and planning for this need. The study reinforces urgency in the rapid registration of drugs with proven safety and efficacy benefits in settings where the need is greatest.

References

- World Health Organization. Global tuberculosis report, 2017. WHO/HTM/TB/2017.23. Geneva, Switzerland: WHO, 2017.
- Diel R, Rutz S, Castell S, Schaberg T. Tuberculosis: cost of illness in Germany. *Eur Resp J* 2012; 40: 143–151.
- Falzon D, Gandhi N, Migliori G B, et al. Resistance to fluoroquinolones and second-line injectable drugs: impact on multidrug-resistant TB outcomes. *Eur Resp J* 2013; 42: 156–168.
- Migliori G B, Sotgiu G, Gandhi N R, et al. Drug resistance beyond extensively drug-resistant tuberculosis: individual patient data meta-analysis. *Eur Resp J* 2013; 42: 169–179.
- Sotgiu G, Centis R, D'Ambrosio L, et al. Efficacy, safety and tolerability of linezolid containing regimens in treating MDR-TB and XDR-TB: systematic review and meta-analysis. *Eur Resp J* 2012; 40: 1430–1442.
- Gler M T, Skripconoka V, Sanchez-Garavito E, et al. Delamanid for multidrug-resistant pulmonary tuberculosis. *N Engl J Med* 2012; 366: 2151–2160.
- Diacon A H, Pym A, Grobusch M, et al. The diarylquinoline TMC207 for multidrug-resistant tuberculosis. *N Engl J Med* 2009; 360: 2397–2405.
- Diacon A H, Donald P R, Pym A, et al. Randomized pilot trial of eight weeks of bedaquiline (TMC207) treatment for multidrug-resistant tuberculosis: long-term outcome, tolerability, and effect on emergence of drug resistance. *Antimicrob Agents Chemother* 2012; 56: 3271–3276.
- Diacon A H, Pym A, Grobusch M P, et al. Multidrug-resistant tuberculosis and culture conversion with bedaquiline. *N Engl J Med* 2014; 371: 723–732.
- ClinicalTrials.gov, US National Library of Medicine. To evaluate the safety, tolerability, and efficacy of TMC207 as part of an individualized multidrug-resistant tuberculosis (MDR-TB) treatment regimen in participants with sputum smear-positive pulmonary MDR-TB. NCT00910871. Bethesda, MD, USA: US National Library of Medicine, 2015. <https://clinicaltrials.gov/ct2/show/NCT00910871>. Accessed February 2019.
- ClinicalTrials.gov, US National Library of Medicine. A placebo-controlled, Phase 2 trial to evaluate OPC 67683 in patients with pulmonary sputum culture-positive, multidrug-resistant tuberculosis (TB). NCT00685360. <https://clinicaltrials.gov/ct2/show/NCT00685360>. Accessed February 2019.
- US Food and Drug Administration. Sirturo (bedaquiline) product insert. Silver Spring, MD, USA: FDA, 2012. https://www.accessdata.fda.gov/drugsatfda_docs/label/2012/204384s000lbl.pdf. Accessed February 2018.
- European Medicines Agency. Deltyba (delamanid) product insert. London, UK: EMA, 2014. http://www.ema.europa.eu/docs/en_GB/document_library/EPAR_-_Product_Information/human/002552/WC500166232.pdf. Accessed February 2019.
- World Health Organization. The use of bedaquiline in the treatment of multidrug-resistant tuberculosis. WHO/HTM/TB/2013.6. Geneva, Switzerland: WHO, 2013.
- World Health Organization. The use of delamanid in the treatment of multidrug-resistant tuberculosis: interim policy guidance. WHO/HTM/TB/2014.23. Geneva, Switzerland: WHO, 2014.
- Bonnet M, Bastard M, du Cros P, et al. Identification of patients who could benefit from bedaquiline or delamanid: a multisite MDR-TB cohort study. *Int J Tuberc Lung Dis* 2016; 20: 177–186.
- Furin J, Brigden G, Lessem E, Rich M, Vaughan L, Lynch S. Global progress and challenges in implementing new medications for treating multidrug-resistant tuberculosis. *Emerg Infect Dis* 2016; 22: e151430.
- Horsburgh C R, Jr, Haxhaire-Theeuwes M, Lienhardt C, et al. Compassionate use of and expanded access to new drugs for drug-resistant tuberculosis. *Int J Tuberc Lung Dis* 2013; 17: 146–152.
- Creswell J W. Designing and conducting mixed-methods research. 3rd ed. Los Angeles, CA, USA: Sage Publications, 2018.
- Seawright J, Gerring J. Case selection techniques in case study research: a menu of qualitative and quantitative options. *Polit Res Q* 2008; 61: 294–308.
- The World Bank. World Bank: country and lending groups. Washington DC, USA: World Bank, <https://datahelpdesk.worldbank.org/knowledgebase/articles/906519-world-bank-country-and-lending-groups> Accessed February 2019.
- Masini T, Hauser J, Kuwana R, Nhat Linh N, Jaramillo E. Will regulatory issues continue to be a major barrier to access to bedaquiline and delamanid? *Eur Resp J* 2018; 51: 1702480.
- Congress.gov. H.R.6-21st Century Cures Act. 114th Congress (2015–2016) July 13, 2015. Washington DC, USA. www.congress.gov/bill/114th-congress/house-bill/6/text. Accessed February 2019.
- World Health Organization. The use of delamanid in the treatment of multidrug-resistant tuberculosis in children and adolescents: interim policy guidance. WHO/HTM/TB/2016.14. Geneva, Switzerland: WHO, 2016.
- Hafkin J, Hittel N, Martin A, Gupta R. Early outcomes in MDR-TB and XDR-TB patients treated with delamanid under compassionate use. *Eur Resp J* 2017; 50: 1700311.
- World Health Organization. Rapid communication: key changes to treatment of multidrug- and rifampicin-resistant tuberculosis (MDR/RR-TB). WHO/CDS/TB/2018.18. Geneva, Switzerland: WHO, 2018.
- World Health Organization. WHO best-practice statement on the off-label use of bedaquiline and delamanid for the treatment of multidrug-resistant tuberculosis. WHO/HTM/TB/2017.20. Geneva, Switzerland: WHO, 2017.
- Lessem E, Cox H, Daniels C, et al. Access to new medications for the treatment of drug-resistant tuberculosis: patient, provider and community perspectives. *Int J Infect Dis* 2015; 32: 56–60.
- McAnaw S, Rodriguez C A, Muller A, Mitnick C, Horsburgh C R. Has compassionate use ever sunk a drug? *Int J Tuberc Lung Dis* 2018; 22: 119–120.
- Access to Medicine Foundation. The world's first dengue and malaria vaccines: what can we learn about access? Amsterdam, The Netherlands: Access to Medicine Foundation, <https://accessstovaccinesindex.org/cross-cutting/first-dengue-and-malaria-vaccines-what-can-we-learn-about-access/> Accessed February 2019.
- World Health Organization. Accelerated registration of prequalified FPPs. Geneva, Switzerland: WHO, 2019. <https://extranet.who.int/prequal/content/collaborative-registration-faster-registration>. Accessed February 2019.
- Verkhovna Rada of Ukraine. Draft Law on Amendments to Article 9 of the Law of Ukraine 'On Medicines' on Facilitation of State Registration of Medicinal Products. Kiev, Ukraine: Government of Ukraine, 2016. http://w1.c1.rada.gov.ua/pls/zweb2/webproc4_1?pf3511=58807. Accessed February 2019.
- Ndomondo-Sigonda M, Miot J, Naidoo S, Dodoo A, Kaale E. Medicines regulation in Africa: current state and opportunities. *Pharmaceut Med* 2017; 31: 383–397.
- Lachenal N, Hewison C, Coutissou S, et al. Setting up an active pharmacovigilance system for the endTB Project. Presented at the 48th Union World Conference of Lung Health, Guadalajara, Mexico, 13 October 2017. *Int J Tuberc Lung Dis* 2017; 21: S205. [Abstract: OA-160-13]

Contexte : La bédaquiline (BDQ) et le delamanide (DLM) ont terminé leurs essais de Phase II en 2011 et ont été approuvés par des autorités réglementaires strictes pour le traitement de la tuberculose multirésistante (TB-MDR) entre 2012 et 2014. Les fabricants ont mis en place des mécanismes d'accès anticipé afin de fournir les médicaments avant les enregistrements au niveau national.

Objectif : Pour mettre en lumière les améliorations nécessaires en matière d'accès anticipé, nous avons examiné les expériences des fournisseurs et des promoteurs de l'accès à la BDQ et au DLM avant fin de 2015 en utilisant un modèle multi-méthodes.

Schéma : Nous avons analysé les obstacles et les facteurs facilitants de l'accès rapide via un sondage électronique. Les obstacles et les facteurs facilitants ont été classés comme survenant au niveau du fabricant ou du pays. Nous avons identifié des thèmes à l'aide d'une analyse inductive de contenu et les avons illustrés à l'aide d'études de cas.

Résultats : Nous avons analysé 41 réponses à une enquête auprès de 36 répondants de 22 pays; l'accès anticipé a été tenté dans 30 (73%) des réponses au sondage. Les restrictions d'éligibilité (11/30, 37%) et la complexité et la lenteur des démarches (8/30, 27%) étaient des obstacles au niveau du fabricant ; l'accès aux médicaments associés (10, 33%) et les difficultés d'importation (4, 13%) constituaient des obstacles au niveau des pays. Une expérience préalable avec les démarches au niveau du fabricant (3/30, 10%) et du pays (2/30, 7%) étaient des facteurs facilitants. Huit études de cas illustrent l'impact humain des obstacles et des facteurs facilitants.

Conclusion : Les fabricants et les pays doivent mettre au point des procédures transparentes permettant un accès rapide, en particulier pour les maladies qui touchent principalement les personnes pauvres, telles que la TB-MDR. Les développeurs doivent planifier la réponse à ce besoin et enregistrer rapidement les médicaments dont les bénéfices sont avérés, en donnant la priorité aux régions les plus touchées.

Marco de Referencia: La fase II de los ensayos clínicos con bedaquilina (BDQ) y delamanid (DLM) se completaron en el 2011 y estos fármacos recibieron la aprobación por parte de organismos de regulación rigurosos para el tratamiento de la tuberculosis multirresistente (TB-MDR) entre el 2012 y el 2014. Los fabricantes crearon mecanismos de 'acceso precoz' destinados a proveer los fármacos antes de haber obtenido su registro local.

Objetivo: Con el propósito de documentar los progresos en el acceso precoz, se examinaron las experiencias de los proveedores de atención y los facilitadores del acceso a la BDQ y el DLM antes de fines del 2015 en un estudio de métodos mixtos.

Método: Mediante una encuesta electrónica se analizaron los obstáculos y los factores que facilitaron el acceso precoz. Estos factores se clasificaron según que se presentaran a nivel del fabricante o del país. Se reconocieron los temas principales mediante un análisis inductivo de contenido y se ejemplificaron los temas con estudios de casos.

Resultados: Se analizaron 41 respuestas a las encuestas aportadas por 36 entrevistados con experiencias de 22 países; el intento de

obtención de un acceso precoz se refirió en 30 de las respuestas (73%). Entre los obstáculos a nivel del fabricante se encontraron las restricciones de las condiciones exigidas (11/30, 37%) y la complejidad y la lentitud de los procedimientos (8/30, 27%); las barreras referidas a escala nacional fueron el acceso a los medicamentos utilizados en asociación (10, 33%) y las dificultades de importación. La experiencia previa con el fabricante (3/30, 10%) y con los procedimientos del país (2/30, 7%) facilitó el acceso. Ocho estudios de casos aclaran el impacto humano de los obstáculos y los factores facilitadores.

Conclusión: Es primordial que los fabricantes y los países elaboren procedimientos transparentes que faciliten el acceso precoz, en especial para las enfermedades que afectan en gran medida a las personas pobres como es el caso de la TB-MDR. Los encargados del desarrollo galénico deberían prever esta necesidad y acelerar el registro de los medicamentos cuyo beneficio se ha demostrado, dando prioridad a los entornos con alta carga de morbilidad.