New TB Regimens:
What Countries Want

The Value Proposition of Existing and New
First-Line Regimens for Drug-Susceptible Tuberculosis

TB ALLIANCE
GLOBAL ALLIANCE FOR TB DRUG DEVELOPMENT

Table of Contents

Executive Summary

The design and adoption of new tuberculosis (TB) regimens requires a close understanding of the opinions of those who approve, prescribe and receive TB treatments: what they like and dislike about current regimens and what they would value, tolerate or reject with regard to a new, shorter regimen. To assess these opinions regarding first-line regimens for drug-susceptible TB, we conducted interviews with 211 stakeholders in Brazil, China, India, Kenya and South Africa — five countries with high TB burdens — and with 11 global stakeholders.

Based on these interviews, efficacy, safety and side effects of current regimens were generally judged to be acceptable. A treatment frequency of five to seven days a week was common for current regimens and preferred for new regimens, with some exceptions in China and India. Avoiding interaction with antiretroviral drugs (ARVs) was a significant priority for African and global stakeholders, as was the availability of fixed-dose combinations (FDCs) in all but China and the Indian public sector.

Two international Phase III trials are currently testing whether the substitution of a fluoroquinolone into first-line TB regimens will allow these treatments to be shortened to four months. In the current study, with the exception of some stakeholders in China, the potential for a shorter (four- or two-month) regimen was positively received. Many stakeholders noted that a shorter regimen would increase the likelihood of adherence and listed several acceptable trade-offs, including increased drug costs. Shorter regimens including moxifloxacin would be welcomed for the same reasons, although there are concerns about whether primary fluoroquinolone resistance already exists and whether fluoroquinolone use for first-line treatment would lead to the loss of the fluoroquinolones as a viable option for second-line treatment.

Before adopting a new regimen to replace an existing one, stakeholders said they would require or prefer data including results from trials in their own countries (for Brazil, China, India and South Africa), cost and real-world effectiveness data, and efficacy data for various subgroups, including patients co-infected with HIV and TB.

The findings of this study are consistent with the target product profile used by the TB Alliance and with the organization's clinical trials strategy as currently implemented. Stakeholder feedback can guide the development of new TB drugs, but the diversity of opinions underlines the challenges ahead and the need for continued exchange of data and information.

Background

Despite notable treatment successes, there are still 1.8 million deaths from TB every year,[1] mostly among the poor and the marginalized. The United Nations has made the elimination of TB as a public health threat one of its global development goals for the millennium.[2]

Meeting this goal, especially in areas with high TB/HIV co-infection, will be difficult if not impossible without new tools, including new drugs for TB.[3–5] The current regimen recommended globally for drug-susceptible disease is lengthy, requiring a two-month intensive phase with four different drugs plus a four- to seven-month continuation phase with two drugs. Many patients are unable to adhere to this long regimen, even with the use of FDCs. Others are not cured because the failures in adherence and other misuses of these drugs, developed over 40 years ago, has generated widespread resistance.[6] Development of new strategies for second-line (drug-resistant) disease is of critical importance, given the rising rates of multidrug-resistant tuberculosis (MDR-TB). It remains true, however, that new, shorter first-line treatments will be vital in preventing the emergence of yet more drug-resistant disease.

For these reasons, the Stop TB Partnership in the Global Plan to Stop TB has called for the development of shorter, simpler therapies.[5] As part of the resulting effort, two international Phase III trials are currently testing whether the substitution of a fluoroquinolone into first-line regimens will allow these treatments to be shortened to four months.[7] The TB Alliance is a key participant in one of these trials, REMoxTB, which is investigating the efficacy of regimens containing the fluoroquinolone moxifloxacin.

To be truly successful, drug development must be aimed not just at regulatory approval (which is not examined in depth in this study) but also at subsequent adoption. Drug developers will benefit from considering local stakeholder opinions (e.g., what level of proof is required to initiate change). These opinions, along with international evidence, form the basis for local adoption decisions. In the shorter term, the opinions should also help inform target product profiles,[7] decisions about where to conduct pivotal drug trials, how the trials are designed, and the structure of clinical development programs.

Knowledge about opinions of those who work in the field is limited. Clearly, there is concern about pill burden[8] and about the interaction between antiretrovirals (ARVs) for treatment of HIV/AIDS and current rifampicin-containing TB regimens[9] (which can be partially avoided by using more expensive efavirenz-based ARV regimens). Stakeholder attitudes to possible delivery via injection, a common and potentially overused drug delivery method[10] that is appealing to certain patient populations,[11] are unknown for TB drugs. Concerns might also be expected around side effects[12–15] and cost. Existing first-line TB drugs are inexpensive.[16] Depending on its duration and the cost of the new drug(s), a new regimen may be more expensive than the current one in terms of direct drug costs.

One especially important starting point for new TB drug retooling ("the process of preparing health systems at the country and global levels for the uptake of new TB tools"[17]) is World Health Organization (WHO) endorsement, since many national TB control programs (NTPs) rely on WHO treatment recommendations. An expert committee that the WHO convenes to review the evidence makes a recommendation to the WHO Stop TB Department for consideration. If recommended, the regimen is included in the standard treatment guidelines and the new drug is eligible for consideration for the essential medicines list (EML). Finally, recommended drugs can be considered for the WHO prequalification program, which aims to increase access to high-quality medicinal products for priority diseases.

Introduction of new tools for other indications has often been associated with a significant delay between global availability and local adoption,[18–20] and regimen change has presented significant challenges.[21–26] Aspects of this delay may have stemmed from a failure to understand current perceptions and needs in the field. Only with this understanding can drug developers correctly manage the drug development process (in terms of product profile and development pathway) and provide the information required by stakeholders so that they can evaluate new regimens for potential use in their programs. Many constituencies that are central to TB drug development may not be aware of certain field-level realities, so documenting them in a properly conducted study can have a significant impact.

We therefore undertook a study to understand the "value proposition" of new first-line TB treatment regimens, i.e., the features of various regimens that would be valued or not valued by key stakeholders and opinion leaders. This study also sought to identify what evidence from the testing of new TB regimens would be needed by decision makers to adopt a new regimen.

This study focused on new regimens that shorten TB treatment time for drug-sensitive, active disease, as the strategy of treatment shortening with new regimens is emphasized by the Global Plan to Stop TB, and treatment-shortening first-line regimens are currently being tested in two major Phase III trials. The results of the current study, described in the following report, should be helpful in guiding the development of new TB regimens so that they are appropriate for and adopted by countries with the highest burdens of TB disease.

To be truly successful, drug development must be aimed not just at **regulatory approval** but also at **subsequent adoption**.

Methods

Five countries with high TB burdens (Brazil, China, India, Kenya and South Africa) were selected for detailed investigations. More than 40% of new TB cases each year occur in these countries,[1] which are located in four distinct WHO regions. These five countries were chosen for the following reasons: India and China are the two countries with the highest TB burdens in the world; Brazil is the only high-burden country (HBC) in Latin America; and South Africa and Kenya are two high-burden countries in Africa that have a high degree of regional influence and are, respectively, less or more dependent on donor funding for TB control.

We focused on regimen change in the public sector, where a centralized decision-making process often leads quite directly to behavior change by individual public sector physicians. A broader survey methodology would likely be required to fully address the adoption determinants in the private sector and the full spectrum of patient perspectives.

In each country we first conducted an assessment of the process for public sector regimen change and produced a detailed mapping of stakeholders involved in this decision making. Stakeholders were classified into three categories, with their roles verified in initial interviews:

1. *Category A*: ***Main decision makers*** have direct responsibility for guideline change. These are chiefly Ministry of Health staff such as primary administrators of the NTP, and staff from the infectious disease control department.
2. *Category B*: ***Key influencers*** play a formal advisory role in the process of regimen change. They generally include members of standing or *ad hoc* expert committees whose advice and recommendations are sought in consideration of programmatic changes. These stakeholders generally have considerable technical expertise and belong to institutions such as reference centers, medical associations and research and academic institutions, any of which may be in a formal consultative status with the country's Ministry of Health or government. Stakeholders in this category and the next may overlap.
3. *Category C*: ***Other players*** have limited direct influence on the decision-making process for regimen change. These stakeholders can include provincial and municipal TB administrators, physicians working at public and private clinics and hospitals, staff of key non-governmental organizations (NGOs), patients and patient advocates. Only 14 individuals in these last two groups (referenced below as "patients") were interviewed (see Conclusions section). Patient advocates were identified as the leaders of the largest, most visible patient advocacy organizations within a country. Fewer patients were interviewed as it became apparent that in most situations they had little input into adoption decisions, and for the additional reasons cited in the Conclusions section. Other Category C stakeholders may also not be directly involved in adoption decisions, but they may be invited by the NTP to participate in broader community consultations. In addition, they are closer to patient care, so their opinions were considered important in the design of new regimens.

A total of 172 interviews with 222 individuals (including 11 individual interviews with global stakeholders) were conducted by the study team between November 2006 and March 2007. Some interviews were conducted with multiple interviewees at a time.

Table 1 provides a categorization of interviewees by major job function. The entries in this list do not correspond precisely to Categories A, B and C, as the mapping of the country decision-making structures revealed variation among countries. In particular, organization and stakeholder categories that were critically involved in TB decision making in one country might be very remote from it in another.

Global interviewees were selected because they were members of key advisory bodies in TB control and therefore likely to be involved with the issuing of recommendations by the WHO. The group of interviewees included key individuals from the WHO Stop TB Department's Strategic and Technical Advisory Group for TB (STAG-TB), including representatives from the Stop TB Partnership and its functional Working Groups, and leaders from key technical and implementing agencies.

Stakeholders were interviewed, either individually or in small groups, by one to three members of the study team. Informed consent was obtained verbally, using a standard script. Interviews were exclusively in English in India, Kenya and South Africa. For Brazil and China, interviews were conducted in English if this was comfortable for the interviewee, but many interviews were conducted in Portuguese and Chinese, respectively, using interview guides that were translated before the interview. Simultaneous translation of answers was used so that those in the interview team who were not native speakers could participate. Interviews were conducted in person with the exception of telephone interviews with two provincial NTP officers and nine global stakeholders.

The interviews were structured to achieve the following objectives:

- To investigate stakeholder perceptions about current and future first-line TB therapy, including any major unmet needs in current first-line TB treatment;
- To understand what value, if any, a shorter treatment would offer; and
- To define the key success factors for adoption of new regimens.

Interview guides were developed and customized for each type of stakeholder in country (NTPs, NGOs, patient/advocacy groups and other stakeholders) and globally. Minor adjustments were made to account for country-specific differences in TB control, but the general outline is provided in Annex 1. After initial, open-ended questions, interviewers had the option of probing for specific responses.

Where there was a complete consensus among all interviewees, the responses were reported directly. If there was not a complete consensus, the opinions of Category A and B stakeholders were given greater weight in the reporting on adoption issues in order to reflect the likely importance of those parties' roles in the adoption process. The opinions of Category C stakeholders were given greater weight in reporting on drug design issues, reflecting the importance of their opinions in creating a regimen that fits well with patient and provider needs.

Table 1: Summary of Stakeholders Interviewed

TYPE OF STAKEHOLDER	BRAZIL	CHINA	INDIA	KENYA	SOUTH AFRICA	GLOBAL	TOTAL NUMBER OF PEOPLE INTERVIEWED (%)	TOTAL NUMBER OF DISTINCT INTERVIEWS (%)
COUNTRY STAKEHOLDERS:								
Ministry of Health and NTP staff	2	2	3	7	6		20 (9.0%)	20 (11.6%)
Government officials	0	4	2	5	1		12 (5.4%)	12 (7.0%)
Provincial TB control program administrators	2	0	0	3	5		10 (4.5%)	10 (5.8%)
Municipal TB control program administrators	5	0	0	0	10 (8)		15 (6.8%)	13 (7.6%)
Specialists, reference center staff, researchers and academics*	6	11	16 (11)	5	8		46 (20.7%)	41 (23.8%)
Medical association representatives	0	0	0	2	0		2 (0.9%)	2 (1.2%)
Providers, public and private	15(7)	12	29 (7)	11 (6)	2 (1)		69 (31.1%)	33 (19.2%)
Patients and patient advocates	2	0	6 (2)	6 (4)	0		14 (6.3%)	8 (4.7%)
NGO representatives	3	0	3	8 (7)	4		18 (8.1%)	17 (9.9%)
WHO country office staff	1	1	3	0	0		5 (2.3%)	5 (2.9%)
GLOBAL STAKEHOLDERS						11	11 (5.0%)	11 (6.4%)
TOTAL STAKEHOLDERS INTERVIEWED	**36**	**30**	**62**	**47**	**36**	**11**	**222 (100%)**	
TOTAL INTERVIEWS	**28**	**30**	**31**	**39**	**33**	**11**		**172 (100%)**

In the country columns, the number of people interviewed is listed, and the number of distinct interviews (if different) is listed in parentheses.

* Some of these specialists and researchers may also provide medical treatment to TB patients.

Results

Stakeholders expressed their opinions on three main areas: the perceived value of current regimens and how this affected preferences for future first-line regimens of any kind; the value specifically of shorter regimens; and requirements for adoption of a new regimen.

Perceived value of current and future first-line regimens

Presented below are features that stakeholders valued in current first-line regimens and wished to see in future first-line regimens. Opinions on what was valued for either current or future regimens were often similar and addressed together in a single answer.

Efficacy

All stakeholders interviewed believe that the current regimen is efficacious and that a new regimen should have efficacy equal to or better than the current treatment.

Safety

Stakeholders believe that the current regimen is mostly safe, but may require additional monitoring in diabetic patients, the elderly, heavy alcohol users and patients co-infected with hepatitis C or HIV. Safety in these subpopulations is seen as an area for potential improvement. In countries with high HIV prevalence, such as Kenya and South Africa, safety and efficacy for patients co-infected with HIV (on and off ARVs) were of high priority.

Stakeholders said that new regimens should be devoid of additional safety issues, particularly those requiring renal, hepatic or cardiac monitoring, because such monitoring would be burdensome for both patients and health systems and could increase the cost of care.

Side effects

Most Category A and B stakeholders reported that the side effects of the current regimen are manageable through counseling or low-cost vitamins or medicinal supplements. Category C stakeholders, however, noted that the significance of these side effects is often understated, and that they contribute to decreased adherence to the regimen and should be avoided if possible.

All stakeholders stated that side effects to be avoided in new regimens include photosensitivity, skin pigmentation (which contributes to negative stigma), and any irreversible side effects. In India, nausea and vomiting were noted as a problem associated with current TB treatment. Category C stakeholders in India and Brazil noted that dizziness and fatigue should be avoided, as these side effects prevent patients from working while on treatment.

In China, stakeholders noted that the cost for adjuvant therapies to mitigate the effect of certain side effects is often borne by patients. Therefore, side effects requiring additional therapies should be avoided.

Fixed-dose combinations were felt to be critical for adoption of new regimens.

Pill burden

In general, Category A and B stakeholders perceived the pill burden of the current regimen (the number of pills required on a daily basis) as being high, but not a significant barrier for the correct use of current or new regimens. For these stakeholders, any reduction in pill burden or size of pills would therefore be welcomed but was generally not seen as critical with regard to adoption, even in countries with high HIV rates and many patients with oral thrush. However, most providers and patients felt that the current pill burden is a significant area for improvement.

Fixed-dose combinations (FDCs)

FDCs[27–29] were felt to be critical for adoption of new regimens according to global stakeholders and stakeholders in the three study countries (Brazil, Kenya and South Africa) that currently use FDCs containing two or more drugs. This was most strongly emphasized by government officials in these three countries.

FDCs were favored in these countries because of the perception, consistent with global guidance,[29] that they can help curb resistance and reduce the *ad hoc* modification of regimens by patients or providers. FDCs should aim to include at least two, if not all four, drugs in a single pill. Most stakeholders at the NTP level in Brazil, Kenya and South Africa felt strongly about the need, where possible, for "one size fits all" regimens that are appropriate for all age groups and patient populations. Some stakeholders noted that loose drugs are needed in addition to FDCs to allow physicians to modify regimens for patients with side effects.

In China and India, however, FDCs are not in wide use and at the time of the study were not preferred. In these countries, although there is some use of FDCs in their private sectors, the government TB control programs use specially-designed patient treatment boxes containing blister strips of single-agent drugs grouped into daily doses. In China, physicians prefer the flexibility of loose drugs, although some piloting of FDC usage has occurred, and there are recent indications that FDC usage is spreading and becoming more popular.

Treatment frequency

The countries studied differ with regard to dosing schedules and the practice of direct observation.[30–32] We confirmed that, at the time of the study, five- or seven-day-per-week dosing was standard in Brazil, Kenya and South Africa, generally reported by private sector physicians in India, and an option recently introduced by the NTP in China. However, NTP guidelines in India and China are based on intermittent dosing (three times a week in India, and every other day in China). In India, stakeholders at the national TB control program strongly believe that an increased frequency of dosing would be unacceptable even with a shorter regimen because more frequent dosing would significantly increase the number of patient-provider interactions and thus increase the cost of care and potentially complicate the provision of directly observed treatment. Currently in India, patient-provider interactions occur three times a week for eight weeks followed by once a week for 16 weeks, for a total of 40 interactions.

Global stakeholders were particularly concerned about intermittent dosing in countries struggling to fully implement directly observed treatment because it increases the potential impact of each missed dose in the development of resistance. Most country stakeholders also preferred five- or seven-day dosing for both current and future regimens to an intermittent schedule "in order to prevent relapse." However, in India the public program has achieved a high cure rate with direct observation using intermittent dosing, and national stakeholders were concerned that a new daily regimen option might threaten this achievement. For example, the new regimen might complicate the current DOTS system or provide an additional draw to the private sector, where formal supervision of treatment is rare.

Drug delivery

Overall, global and country stakeholders were comfortable with the current method of oral administration via tablet or capsule.

In general, concerns about alternative drug delivery options outweighed any perceived benefits:

- Inhalable drugs are being studied based on the possibility of local and sustained drug delivery.[33] However, this delivery method raised concerns (in all study countries but Brazil) about product wastage and the need for additional training of healthcare workers and patients to use the device.
- Injectable delivery systems (e.g., for patients with difficulty swallowing, such as the elderly and TB/HIV co-infected patients suffering from oral thrush) were seen as unappealing for patients, more dangerous for healthcare workers, potentially costly, requiring special storage, disposal and formulation requirements, and a potential barrier to treatment access if they could be given only in a health care facility with appropriately trained personnel.
- Chewable/liquid formulations (e.g., for children) raised questions about storage and the potential for added complexity in procurement and distribution, although stakeholders noted that easy-to-swallow formulations would be beneficial for pediatric patients.

These concerns about alternative delivery mechanisms were particularly strong in China and India, where stakeholders felt that these mechanisms would be prohibitively expensive and too difficult to implement on the wider national scale.

Drug interactions

All stakeholders noted that any new regimen should avoid introducing new drug-drug interactions with ARVs. Global stakeholders noted that data proving the lack of these drug-drug interactions would be necessary for adoption.

Drug interactions between the current regimen and ARVs were noted as a particular problem by stakeholders in Kenya and South Africa. Brazilian and Chinese stakeholders noted particular concern about possible interactions with medicines for diabetes.

Stakeholders were **comfortable** with the current method of oral administration **via tablet or capsule**.

Stakeholders noted that a **four-month therapy** would be of **significant value** compared to the current regimen.

Other issues

In China, the most important unmet need in current TB therapy was thought to be consistency in TB drug quality. Formulation impurities exist in many countries[34] and were considered a major concern by many stakeholders in China and India.

For any new antimicrobial drug there is a potential for the emergence of drug resistance. Many stakeholders were concerned about this potential for new TB drugs. This issue was felt to be particularly acute for antibiotics that might be broadly available and given as monotherapy either by self-administration or after a misdiagnosis. In addition, a new drug introduced for first-line treatment was expected to be lost to resistance more rapidly than a new drug for second-line treatment, which would be used by many fewer patients.

Perceived value of shorter regimens

A globally stated goal of TB drug development is to shorten TB treatment duration. We therefore investigated how stakeholders perceived the value of shorter regimens, specifically a four-month regimen, as this length of regimen is the subject of two current, large Phase III trials for TB. Questions regarding a possible two-month regimen elicited similar responses.

Global stakeholders and stakeholders in Brazil, Kenya, India and South Africa all noted that a four-month therapy would be of significant value compared to the current regimen (although in India this value would be decreased if the number of patient-provider interactions had to increase above current levels). In fact, public physicians and patients in India and Kenya and some stakeholders in South Africa felt that a reduction in treatment time of even one month would be an improvement. The stakeholders in Kenya and South Africa noted that default typically occurs after the two-month intensive phase, so motivation of patients to complete their treatment should be easier if it involved only a two-month rather than the current four-month continuation phase. The few patients interviewed put additional emphasis on possible benefits that shortening would have in terms of increased adherence and reduced travel costs for clinic visits.

At least some stakeholders in China also welcomed the idea of a shorter regimen but, based on results from locally-initiated studies, they were skeptical that shorter regimens could be sufficiently efficacious and viable in real-world situations. Stakeholders at the hospital level were also skeptical, and some physicians already lengthen regimens beyond the WHO-approved six-month regimen that is officially recommended by the national TB program.

Many private physicians interviewed in India also treat TB for longer (eight to ten months), and noted that they would wait for two to three years to see the results of "real world" clinical experience before switching to a shorter regimen. In addition, many respondents in India and China said they would want clinical trial data that demonstrate two-year relapse rates as equal to or better than the current rates.

Acceptable trade-offs

Some Category A and B stakeholders interviewed in countries other than China felt that an increase in pill burden or in manageable and reversible side effects would be an acceptable trade-off for a shorter regimen. However, patients and their direct healthcare providers felt that increases in pill burden or side effects may decrease adherence and quality of life.

Global WHO endorsement of a new regimen appears to be necessary but **not sufficient for local adoption.**

All stakeholders noted that an increase in direct drug costs would be acceptable. Their reasons were as follows. First, they stated that drugs are a small portion of the overall costs of TB control programs (e.g., first-line drugs are ~12% of the NTP's costs in China[1]). Second, they believe that shorter regimens would improve adherence and decrease the incidence of MDR-TB, which is considerably more expensive to treat.

For a four-month regimen, allowable drug cost increases cited in China and India ranged widely, from 50% to 400%, which reflects the difficulty of obtaining accurate cost-sensitivity data when future financing constraints and exact cost-benefit scenarios remain unknown. In Kenya, stakeholders noted that increased costs were acceptable given that most drugs are purchased using donor funds.

Injections, which were otherwise seen as undesirable, were perceived as having some value for all stakeholders if they could reduce treatment frequency to once a week or treatment duration to less than two months.

Unacceptable trade-offs

Trade-offs that stakeholders noted as unacceptable for a shortened regimen were similar to those listed above as being unacceptable for any new regimen.

Perceived value of a shorter regimen containing moxif oxacin

As noted earlier, a Phase III trial (REMoxTB) is currently underway to investigate whether a four-month regimen containing the fluoroquinolone moxifloxacin has equal efficacy to the current six-month first-line regimen. We therefore asked stakeholders whether they would value such a regimen.

Stakeholders noted several advantages of a four-month regimen containing moxifloxacin, including those noted above for shorter regimens in general. Lack of interactions between moxifloxacin and ARVs were noted as an advantage by stakeholders in Brazil, India, Kenya and South Africa, and in South Africa some stakeholders saw the potential for scaling up isoniazid preventive therapy if moxifloxacin replaced isoniazid as a first-line drug.

However, stakeholders were concerned that widespread use of fluoroquinolones for other indications may have led, already, to primary resistance to fluoroquinolones in some strains of *Mycobacterium tuberculosis*. All categories of stakeholders noted that moxifloxacin use in first-line treatment might lead to new resistance and thus loss of the fluoroquinolone class as an option for second-line treatment. In Brazil, Kenya and South Africa, stakeholders were concerned about the lack of information on moxifloxacin use in people with low CD4 counts or in patients concurrently on ARVs.

Perceived requirements for new regimen adoption

Category A and B stakeholders and global stakeholders were asked what would be required for the adoption of a new regimen either globally or in their country. Aside from the properties of regimens (described above), stakeholders outlined a variety of evidence that would be needed for adoption.

Local clinical trials

National stakeholders in Brazil, China, India and South Africa identified local (in-country) clinical trials as an absolute requirement for adoption. These trials would need to be held within the respective countries and may require control regimens and protocols relevant to existing local treatment guidelines.

There were some calls for a Brazilian trial that would evaluate the new regimen against the Brazilian standard of care, which at the time of this investigation excluded ethambutol (although Brazil is, in 2009, in the process of adding ethambutol to its first-line regimen). In Kenya, data from the region (Tanzania, Uganda) or other sub-Saharan countries (excluding South Africa, which respondents considered as too developed to be analogous to other sub-Saharan African countries) would be acceptable.

At the global level, stakeholders noted a preference for clinical trial data from as many of the six WHO regions as possible.

Data in subpopulations of patients

Evidence of efficacy in subpopulations, especially those excluded from pivotal clinical trials, was described as useful to facilitate adoption, but not essential. The subpopulations mentioned included those with increased risk of contracting TB, needing special care for TB, or suffering more than the usual side effects from TB drugs, such as diabetics,[35] heavy alcohol users,[36] children[37] and pregnant women.[38] Heavy alcohol users were mentioned often because of the perception that they are overrepresented among TB patients and might be at increased risk of liver damage from new drugs.

Global stakeholders and stakeholders in Brazil, Kenya and South Africa noted in particular that data from patients with HIV would be necessary for adoption, including data from patients who may be excluded from earlier trials such as those with low CD4 counts or concurrent ARV treatment. *In vitro*, preclinical and clinical data may be needed to support the lack of drug interactions between new TB regimens and ARV regimens.

WHO recommendation

WHO staff indicated that having clinical trials in multiple countries and regions would greatly assist the process of achieving WHO recommendation of a new regimen. At the country level, global WHO endorsement of a new regimen appears to be necessary but not sufficient for local adoption in all five countries studied, with a local decision-making process also being necessary.

Cost and real-world effectiveness studies

Studies of the costs of providing and delivering a regimen were described as a necessary (Brazil) or desirable (globally and other countries) part of the approval process. These assessments may occur as part of a cost-effectiveness or cost-benefit analysis.

Stakeholders globally and in Brazil, India and Kenya noted that studies on the real-world effectiveness of a new regimen would be necessary as part of a pilot phase of adoption; in South Africa they were described as desirable. Global stakeholders would prefer to see real-world data from several countries before changing their regimen guidelines.

Communications requirements

Stakeholders were asked to specify what information they would need to receive about new TB drug regimens and how they would like to receive such information. Stakeholders desired information on a variety of topics, including current trials underway, progress in enrollment, and progress in addressing some of the concerns expressed above. Preferred methods of receiving this information included list-servs, presentations by clinical trials researchers at regional TB conferences, and local briefings of NTP staff by clinical trials researchers. In addition, some national TB programs noted that the communication of knowledge and technology regarding drug manufacturing would be necessary, based on their strong preference for purchasing drugs from national suppliers, including the national and state laboratories active in countries such as Brazil and South Africa.

Conclusions

To ensure rapid adoption, regimens developed for drug-susceptible disease should be consistent with stakeholder desires, and stakeholders must have the information they need to make informed decisions about a new regimen. This study is an attempt to map those needs as a first step towards ensuring rapid introduction of new and better TB drug regimens once they are available.

A major finding was that there is great variability in perceptions, needs and value propositions among the five countries studied and even among stakeholders within some countries. Some issues that are a central concern in one country appear to be of little interest in others. This emphasizes how much work is needed in the field before introducing new regimens. Even once decision makers are convinced, work will be required to address procurement issues and staff training in the public sector, variable prescribing in the private sector, behavioral change, and acceptance in different patient, caregiver and policymaker populations.[17]

Any new regimen will be introduced in the context of current regimens. Global guidelines for TB treatment[31, 32, 39] allow for various adaptations of standard TB programs and regimens. This leads to differences in first-line regimens such as the choice of the fourth drug, use of rifampicin or ethambutol in the continuation phase, use of FDCs, and variations in doses or dosing schedule. Therefore, introducing a new global regimen may require tailored efforts to address country-specific issues.

The findings reported here are subject to a variety of limitations. This study is qualitative rather than quantitative, and the synthesis of opinions was necessarily subjective, as individuals and organizations in different positions were seen as having more or less influence in different countries. A numerical summing of responses would not accurately reflect the hierarchal decision making involved in adoption of a new regimen. Therefore when stakeholders' responses differed for key adoption issues, the responses of Category A and B stakeholders were given greater weight.

To ensure rapid adoption, **regimens should be consistent with stakeholder desires**, and stakeholders must have the information they need to make informed decisions about a new regimen.

It is possible that our sampling did not encompass all of the most relevant opinion leaders in the study countries, or that the study countries are not representative of other countries with high burdens of TB. We believe, however, that the interviews with 222 individuals and mapping of key stakeholders to be interviewed ensured that our survey covered the major decision makers and opinion leaders who currently influence adoption decisions at the global level and in the five countries under study.

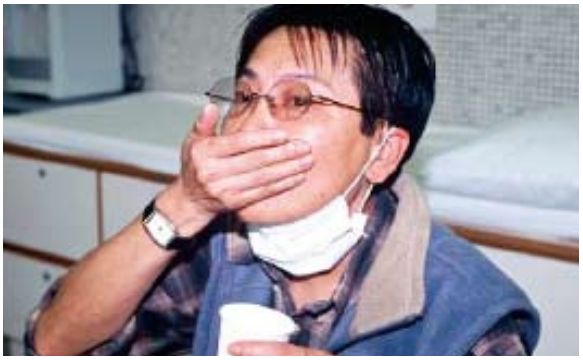
This study is a snapshot of stakeholder opinions at the time of the study (November 2006 to March 2007). In the time between the study and regimen change, opinions can change, new evidence will be brought forth, and the personnel who staff key positions may change. Thus, the findings are more of a guide to the possible variation in stakeholder opinions than a roadmap for future implementation plans in individual countries.

The study methodology was more suited to an investigation of the opinions of key decision makers rather than a representative survey of opinions in broader communities. Therefore, although patients and patient advocates supplied important insights on adherence, side effects, risk-benefit trade-offs and the burden that regimens place on individuals, we interviewed only the few individuals in these countries who would be expected to have influence over regimen change decisions. A larger survey would be needed to adequately assess all patient opinions.

Finally, the opinions stated during this study must be balanced with what is realistically achievable. Individuals who are asked their preferences may readily ask for the most ideal situation, but be willing to settle, for example, for fewer trials and a less onerous burden of proof. For example, stakeholders in India and China requested that clinical trials demonstrate equivalent relapse rates at two years, even though previous publications suggest that trends in relapse rates are clear as early as six months after treatment.[40] Other requests, such as studies in certain subpopulations, were specifically described as desirable but not essential, and might be obtainable in smaller, post-introduction studies conducted after adoption.

Developing regimens that are consistent with stakeholder desires

To be broadly adopted, any new regimen must represent a viable replacement for existing, accepted regimens. The results of this study indicate that stakeholders require a new regimen based on oral delivery, dosing consistent with current, local practices, availability as FDCs in most countries, a high degree of safety, no lasting or serious side effects, lack of significant interactions with ARVs or other essential medicines, and efficacy equal to or greater than the current regimen. These considerations, and the adoption requirements listed on the following page, have influenced portfolio management and drug development decisions at the Global Alliance for TB Drug Development, and we anticipate that they would influence decisions by organizations with similar missions.



There is **great variability** in perceptions, needs and value propositions among the five countries studied.

Data and information needed on products under development

The clinical trials that are minimally required to register a new drug for use against TB may not be sufficient to assure adoption: a drug may be approved by drug regulatory authorities but not included in treatment guidelines or publicly procured and distributed. The major additional categories of data that will aid in adoption are listed in the subsections below. Although some of these categories have been listed before,[17] we believe the following detailed information has not previously been gathered on a global scale.

Requirement for clinical trials in specific countries

Of the five countries studied, it appears critical to conduct clinical trials in four: Brazil, China, India and South Africa. Further study would be required to determine if additional HBCs not included in this study would also require in-country testing; in 2008–9 we have undertaken a study of this and other adoption issues in all 22 HBCs.

Adoption of regimens by key countries (including high-income countries) may encourage others to adopt. However, local evidence may be influential for public programs where, as for TB, drugs are often purchased with local finances rather than donor funds,[41] and regimen choice (between existing, accepted regimens and new regimens) lies with local public sector programs. This emphasis on local decision making is an important factor to consider when devising clinical trial and country introduction strategies for a new TB regimen.

Resistance data

Concerns about resistance were identified as a potential stumbling block for adoption specifically of a moxifloxacin-containing regimen. There are two major concerns associated with fluoroquinolone resistance in a first-line regimen: one is the possibility of higher than anticipated baseline resistance due to broad use in other indications, often in patients who may have undiagnosed TB; the other is the possibility of increasing resistance resulting from usage in first-line therapy, leading to the loss of fluoroquinolones as part of an effective regimen for treating MDR-TB. To address these concerns, there is a need to better understand and, where the data exist, communicate the extent of baseline resistance to fluoroquinolones in TB. Current knowledge of fluoroquinolone resistance is limited,[42] suggesting that substantial effort is needed to understand fluoroquinolone resistance not just in MDR-TB patients but in treatment-naïve patients. The eventual adoption decision for a moxifloxacin-containing regimen will depend not only on clinical trial results but also on an assessment of resistance levels at the time of decision making. It will be important to survey the resistance situation with regard to both first- and second-line drugs (in both treatment-naïve and MDR-TB patients), and to take into account the possible availability of improved diagnostics and new, alternative drugs for the treatment of MDR-TB. By the time of an adoption decision, new diagnostics may be capable of excluding those first-line patients with fluoroquinolone resistance, and new drugs may allow for alternative treatments for MDR-TB.

Other desired data

In addition to operational research and post-introduction studies in subpopulations, cost studies were described as necessary or desirable. Such studies should review the direct and indirect costs of the regimen to the patient and to the public program. These costs may change if implementation of a shorter regimen leads to improved adherence, fewer defaults, fewer retreatment cases, and fewer drug-resistant cases. It may be possible to insert new scenarios into previously developed models for TB epidemics,[43] development of drug resistance,[44] and cost and cost-effectiveness.[45–55]

The effectiveness or pilot studies required by most stakeholders may be conducted or commissioned by NTPs as part of a phased roll-out program, by the WHO to inform guideline changes, or by a drug sponsor to facilitate adoption. These studies lack many of the controls inherent in pivotal trials (e.g., blinding, stratification and randomization), and thus are more appropriate for measuring patient and provider acceptance rather than efficacy.

Communicating with stakeholders

This study has identified a variety of data that stakeholders desire to make informed decisions about adoption. Decision making will be facilitated by actions in three main categories: ongoing consideration of the needs and opinions in the field; generation of new data that address those needs; and communication to inform those in high-burden countries. Information is needed at all levels of TB control to ensure not only treatment guideline change by key decision makers, but also full implementation by TB control programs and acceptance by providers and patients. Early communication with local stakeholders is needed for both eventual adoption and design of an appropriate clinical trial strategy.

On many issues, this study found that there was little uniformity of opinion among, and even within, countries on what was needed. This diversity highlights the challenge of implementing rapid global uptake of new regimens. Satisfying everyone might take enormous, and perhaps unavailable, resources. Indeed, one role of communication will be to convey what is and is not possible and to emphasize which data are useful for evidence-based decision making. Development of a product that addresses stakeholders' needs and concerns as much as possible—via a continuous process of investigation and two-way communication—will provide the most efficient pathway to timely adoption and implementation of regimen change.

Early communication with local stakeholders is needed for both eventual adoption and design of an appropriate clinical trial strategy.

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Annex 1: Interview Guide

Current perceptions of first-line TB treatment

1. Of the following, which do you perceive as the top two major unmet needs/key areas for improvement in first-line TB treatment? Bottom two? Interviewer, please probe to understand respondent's reasoning and how respondent defines the unmet need.

   a) Safety of current agents?
   b) Tolerability of current agents?
   c) Implementation issues?
   d) Compliance issues? (please elaborate)
   e) Length of treatment?
   f) Mode of administration?
   g) Compatibility with HIV drugs?
   h) Resistance susceptibility?
   i) Other?

2. If a new regimen were approved for first-line treatment of tuberculosis and required four months of treatment vs. six months of treatment, what would be your initial reaction to incorporating this regimen into the NTP guidelines? (Probe: receptive, hesitant or resistant.)

3. What additional data would facilitate adoption into the guidelines?

   a) What clinical endpoints would be required? (Probe: efficacy, safety, tolerability, non-inferiority/ superiority, relapse rate, follow up period, sputum/culture conversion)
   b) What type of trials would you need to see? (Probe: investigator-sponsored trials, country-specific research, real-world evidence, observational studies, specific patient types, specific trial lengths)
   c) What outcomes data, if any, would be useful? (Probe: incidence of resistance, speed to symptomatic relief, mortality)
      i) How would this data be used in support of your decision to include/exclude a drug into guidelines?
   d) What health economic data would be useful? (Probe: cost-effectiveness, impact on total health costs, daily adjusted life years, values, etc.) Please explain further.
   e) What level of resources would be required to change the treatment regimen?
   f) Would you need any other data or information?
   g) Would you need to be aware of what the retreatment regimen is before accepting a shortened regimen?

4. Based on this treatment regimen, what trade-offs do you feel would be acceptable to make for the shortened treatment regimen? Interviewer, please probe all of the following trade-offs and note which would be acceptable to forgo if presented with a four-month regimen. Also note exactly what endpoints would be acceptable.

   a) Increased side effects? (Probe: skin pigmentation, nausea, other)
   b) Safety issues? (Probe: QT intervals, liver toxicity, etc.)
      i) Requiring additional monitoring?
   c) Requiring ingestion with food?
   d) Increased cost? By what percentage more than the existing regimen?
   e) Negative impact on resistance?
   f) Increased drug-drug interactions (Probe: importance of ability to use in patients with HIV [on and off ARVs], impact on concomitant TB drugs)?
   g) Number of pills required per day? (Probe: How many is considered unacceptable?)
   h) What if the new regimen was only available as single agents and not as an FDC?
   i) Frequency of dosing each day? (once vs. twice a day)
   j) Daily treatment (i.e. five days per week) vs. three times per week?

5. What if this regimen was now shortened from four months of treatment to two months, how would your previous responses change? What additional trade-offs, if any, do you feel would be acceptable to make for this two-month regimen that weren't acceptable for the four-month regimen?

6. If the price of a new agent increases overall first-line regimen costs, how will that impact your decision to adopt into the guidelines?

7. Up to what premium would you support the replacement of the current regimen with a four-month regimen?

8. Up to what premium would you support the replacement of the current regimen with a two-month regimen?

Perception of a regimen substituting moxifloxacin for isoniazid

9. What do you see as the top two most attractive attributes of such a regimen?

   a) Probe: four-month treatment vs. six months, compliance, low drug-drug interactions, excellent safety profile, resource-sparing due to shorter regimen

10. What are the top two drawbacks, if any?

Wrap-up

11. Before we wrap up our discussion, are there any questions that you feel that we should have asked but did not?

12. Closure

    a) Ask if there are any questions or concerns about the project.
    b) Thank for participation.

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About the Global Alliance for TB Drug Development

The TB Alliance is a not-for-profit, product development partnership accelerating the discovery and development of new TB drugs that will shorten treatment, be effective against susceptible and resistant strains, be compatible with antiretroviral therapies for those HIV/TB patients currently on such therapies, and improve treatment of latent infection.

Working with public and private partners worldwide, the TB Alliance is leading the development of the most comprehensive portfolio of TB drug candidates in history. It is committed to ensuring that approved new regimens are affordable, adopted and available to those who need them.

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For more information on TB drug development and the TB Alliance, please visit **www.tballiance.org**.

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