INT J TUBERC LUNG DIS 14(12):1538–1547
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Tuberculosis regimen change in high-burden countries

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SUMMARY

BACKGROUND: Experience with past tuberculosis (TB) regimen changes can guide future regimen changes.

METHODS: To explore the process, major players and procedural success factors for recent public sector TB regimen changes, we conducted 166 interviews of country stakeholders in 21 of the 22 TB high-burden countries (HBCs).

RESULTS: Stakeholders described 40 distinct regimen changes for drug-susceptible TB. Once countries committed to considering a change, the average timing was ~1 year for decision-making and ~2 years for rollout. Stakeholders more often cited concerns that were program-based (e.g., logistics and cost) rather than patient-focused (e.g., side effects), and patient representatives were seldom part of decision making. Decision-making bodies in higher-income HBCs had more formalized procedures and fewer international participants. Pilot studies focused on logistics were more common than effectiveness studies, and the evidence base was often felt to be insufficient. Once implementation started, weaknesses in drug management were often exposed, with additional complications if local manufacturing was required. Best practices for regimen change included early engagement of budgeting staff, procurement staff, regulators and manufacturers.

CONCLUSIONS: Future decision makers will benefit from strengthened decision-making bodies, patient input, early and comprehensive planning, and regimens and evidence that address local, practical implementation issues.

KEY WORDS: regimen change; tuberculosis drugs; high-burden countries

THE DEVELOPMENT of new drugs for tuberculosis (TB) is an identified global priority,[1,2] but adoption will undoubtedly bring challenges.[3] For TB regimen change, existing examples can provide guidance for future efforts. In the present study, we examine recent experiences with regimen change in 21 of the 22 high TB burden countries.*

Regimens for drug-susceptible TB have been shortened based on clinical trials[4] and altered due to widespread human immunodeficiency virus (HIV) infection,[5] leaving the two main variants as 2HRZE/6HE and 2HRZE/4RH.†[6] The World Health Organization (WHO) initially recommended both,[5] but then favored the 6-month regimen for high HIV settings (starting in 2003), and then for all settings[7,8] (starting in 2004). The latter change was based on the trial of the International Union Against Tuberculosis and Lung Disease (The Union) demonstrating increased efficacy of 2HRZE/4HR over 2HRZE/6HE.[9]

Some of the resulting changes from 8 to 6 month regimens are documented in this study, as is the adoption of various fixed-dose combinations (FDCs) of TB drugs. FDCs prevent monotherapy,[10] and can simplify regimens for patients, physicians, and procurement and distribution systems, thus potentially helping to reduce medication errors and stock-outs.[11–13] FDC use may increase adherence, although supporting evidence for this is scarce.[14,15] Adoption of FDCs has sometimes been delayed by the lack of access to FDCs with proven bioequivalence to single drug formulations.[16]

Decision making during regimen change requires the balancing of evidence. For future changes, the competition posed by the existing regimen for drug-susceptible disease is considerable. The existing Category I regimen works with ~95% efficacy under trial conditions (so efficacy improvements are impractical and unlikely), and costs US$20–30 for the entire multidrug, multi-month regimen (therefore, drug costs are likely to increase). It can be delivered using only two types of pills (one four-drug FDC and one two-drug FDC; so drug management may be more complex with a new regimen), and uses drugs with few or no other indications (so controlling TB drug use may

*Interviews in Myanmar were not possible due to the intervention of Cyclone Nargis.

†That is, 2 months of isoniazid (H), rifampin (R), pyrazinamide (Z) and ethambutol (E), followed by 6 months of H and E or 4 months of H and R.

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Article submitted 17 February 2010. Final version accepted 1 June 2010.

Revised in online publication, 30 November 2010.

become more challenging). However, shorter regimens for drug-susceptible TB may increase adherence, reduce default, attract more TB patients, and bring higher effective cure rates and fewer new cases of multidrug-resistant TB (MDR-TB). Therefore, the identification of lengthy regimens as a problem and treatment shortening as a global goal have been formalized by the Stop TB Partnership in the Global Plan 2006–2015.[1]

Treatment-shortening research is furthest advanced for 4-month multidrug regimens that include either gatifloxacin or moxifloxacin. Both of these fluoroquinolone antibiotics are in Phase III trials to test the non-inferiority of the fluoroquinolone-containing regimen compared to the standard 2HRZE/4HR regimen.[17]

Regimen change requires active effort[18] by many actors,[3,12] including an agent—often outside the national programs—that is specifically responsible for promoting and facilitating the change.[19,20] Here, we present an analysis of the processes of adoption, introduction and implementation of past TB regimens for drug-susceptible TB. These experiences provide a rationale for prioritizing future actions that will maximize uptake of new TB regimens.

METHODS

Included in this study are the 22 high-burden countries (HBCs) for TB, representing 80% of the worldwide burden of TB. As in our previous study,[21] our primary focus was on public sector decision making, given the importance of the public sector in TB control, and on drug-susceptible TB specifically, as MDR-TB raises very different cost and complexity issues.

Interview topics were based on results from our previous study[21] and the stepwise process of regimen change outlined by the Stop TB Partnership's Retooling Taskforce.[3] A core interview guide about regimen change and the health system, an abbreviated guide for interviewees with experience across TB programs in multiple countries, and a regulatory guide for staff with regulatory expertise were administered during respectively 116, 88 and 46 interviews.

Each interviewer (one per country) was trained by phone using a standardized information packet and training presentation. Interviewees were identified by a combination of purposive sampling and snowball sampling, as in previous studies of public sector regimen change.[20,21] Each interviewer identified, in collaboration with the central study team, an initial set of three key interviewees—one each from the National TB Program (NTP), the WHO country office, and the regulatory authority. The initial NTP and WHO interviewees were asked to identify other individuals and organizations involved in TB regimen decision making.

From April to August 2008, 166 interviews were conducted in 21 countries (4–12 interviews per country, Table 1). Interviews were conducted in person in all countries but Pakistan, where phone interviews

Table 1 Country stakeholders interviewed

Country	NTP	Regulatory authority	WHO	MoH	NGO/TA provider	TB/chest hospital physician	Researcher/ academic/ associate professor	Donor	Other	Interviews *n**	Respondents *n**
Afghanistan	—	1 (2)	1 (3)		2					4	7
Bangladesh	1	2	2		1	1 (3)	2			9	11
Brazil	1 (3)	1 (2)	1 (2)	1	1		1			6	10
Cambodia	1	2	2		3					8	8
China	1 (2)	2	2			3 (15)				8	21
Democratic Republic of Congo	1	1	1		1		3	1		8	8
Ethiopia	1	1	1		2					5	5
India	1	2	2 (3)	1	1	1 (2)	3 (5)			11	15
Indonesia	1	2 (3)	2 (3)		1		1			7	9
Kenya	1	3	1		5		1	1		12	12
Mozambique	1		2		2			1		6	6
Nigeria	1	1	1		5		1			9	9
Pakistan	1	1	1		1					4	4
Philippines	1	2	1	1	2 (3)		3 (5)			10	13
Russian Federation	NA	1	1	1	1		3		1	8	8
South Africa	1	3			2		4			10	10
Thailand	NA	1	1	2		1	2		1	8	8
Uganda	2	1	1		3	2	2			11	11
United Republic of Tanzania	1	1	1		1		2			6	6
Viet Nam	1 (5)	1 (3)	2	1	2		1		1	9	15
Zimbabwe	1	1	1	1			1		2	7	7
Total										166	203

*Some interviews included multiple respondents. In the columns to the left, the number of distinct interviews is listed, and the number of people interviewed (if different) is listed in parentheses.

NTP = National TB Program; WHO = World Health Organization; MoH = Ministry of Health; NGO = non-governmental organization; TA = technical assistance; TB = tuberculosis.

were used. Informed consent was obtained verbally using a standard script. No ethics committee was involved, as the unit of inquiry was held to be institutions (and their behavior) rather than individuals. Cyclone Nargis prevented interviews in Myanmar; information was therefore gathered from publicly available sources and by e-mail from two expert reviewers.

Responses were collated into country reports, which were reviewed by the interviewers and one or more external reviewers. The reports referenced the source of every response, allowing quantitation of the qualitative responses. Repeated observations by an individual were counted only once. Positive and negative factors for past regimen change were volunteered by stakeholders without the use of any probes (i.e., based on general accounts of past regimen change), thus reducing potential bias. Similarly, expectations about future changes were derived from general questions about the ease and speed of adoption.

RESULTS

Types and lengths of regimen changes

Stakeholders in 21 HBCs were asked about the most recent regimen changes for drug-susceptible TB in their country. They described 40 regimen change events, including 16 FDC adoptions, seven considerations of the change from the 8- to the 6-month Category I regimen, and four deletions of Category III (Table 2). Multiple changes were often introduced at once (Brazil, Cambodia, Indonesia, Mozambique, Uganda, see Table 2). Older adoption events, such as the adoption of the 6-month regimen in many Asian countries, were not mentioned and therefore not included in the analysis.

Timing estimates for decision-making and roll-out were available for 28 of the regimen changes. After excluding four regimen changes that took longer than average due to the size of the country, complexity of the change, or political instability, and three simpler and shorter Category III deletions, the 21 remaining changes took 0.91 ± 0.54 years for decision-making and 1.93 years ± 0.99 years for roll-out (mean ± standard deviation).

In Ethiopia and Nigeria, the change from the 8- to the 6-month regimen was indefinitely postponed after an initial, positive decision, and Afghanistan considered but rejected the same change. Indeed, of the 10 HBCs using the 8-month regimen at the time of the 2003 and 2004 WHO recommendations, only half had changed to the 6-month regimen; these five decisions were reached an average of 2 years after the locally relevant WHO recommendation. Stakeholders reported that the reticence to change regimens was primarily due to a perceived lack of directly observed therapy (DOT) and thus concern about increasing rifampicin (RMP) resistance.

Table 2 Past regimen changes described by stakeholders

Country	Regimen changes	Date of decision
Afghanistan	Introduce Category III regimen (including HRZ 3-drug FDC)	2003
Bangladesh	Intermittent to daily dosing in continuation phase	2008
	Adoption of FDCs	2002
Brazil	12 to 6 months (4RHZ/2HR); addition of RH FDC	1979–1980
	Add E to intensive phase; alter H and Z doses, new RH FDC (plus new MDR-TB regimens)	2008
Cambodia	8 to 6 months; introduce (RHZ) and (RH) FDCs	2005
	Introduction of 4-FDC	2008
	Adoption of WHO's pediatric TB guidelines	2008
China	FDC adoption	Ongoing
	Delete Category III regimen	2007
	Option of daily treatment	2007–8
Democratic Republic of Congo	4-FDC adoption	2001
	8 to 6 months; change from intermittent to daily continuation phase	2004
Ethiopia	4-drug FDCs for Category I and II, replacing (RHZ)S	2004–2005
	4-drug FDCs for Category III regimen	2007
	8 to 6 months (stalled for fear of poor adherence)	2007
India	Daily to intermittent regimen	1997
	Combipack and pediatric formulations	2005–2006
Indonesia	FDC adoption (included dosage and frequency changes)	2002 (partial); 2005
	Deletion of Category III	2006
Kenya	8 to 6 months	2006
Mozambique	8 to 6 months, including new FDC	2005
Myanmar	FDCs daily (replaced intermittent loose drugs)	2004
Nigeria	Introduced 4-FDC for Category I and II	2007
	8 to 6 months (not completed)	2008
Pakistan	Adoption of FDCs	2000
	Deletion of Category III	End 2002
Philippines	Single agents to FDCs	2002
Russian Federation	Introduction of Categories I, II, III	2003
	Introduction of Regimen IIb	
South Africa	Change from 5 to 7 days per week dosing	2007
	FDC adoption	1996
Thailand	Deletion of Category III (plus change in MDR-TB regimens)	2008
	FDC adoption	2005–2006
	Change to short-course regimen	1983
Uganda	10 to 8 months, and introduction of FDCs	1995–1996
United Republic of Tanzania	8 to 6 months	2006
Viet Nam	FDC adoption (3-drug and 2-drug)	1997
	9 to 8 months	1999
Zimbabwe	FDC adoption	2007

H = isoniazid; R = rifampin; Z = pyrazinamide; FDC = fixed-dose combination; E = ethambutol; MDR-TB = multidrug-resistant tuberculosis; WHO = World Health Organization; S = streptomycin.

Role of decision-making procedures and bodies at country level

Capacity to consider TB regimen change varies among the 21 HBCs. Nine of the HBCs have specific bodies and clear procedures to consider regimen changes; six have specific bodies but somewhat unclear procedures; two have bodies that could potentially fulfill such a function; and four do not have such bodies.

Membership of decision-making bodies was exclusively or almost exclusively national in 10 HBCs, a mixture of nationals and internationals in six HBCs, and led by the NTP but with large numbers of international organizations represented in four HBCs. Higher-income countries had more predominantly national representation in these decision-making structures.

The decision to adopt was most often reached by consensus-driven committees, but decisions in at least three HBCs were reportedly made by a single individual. Although the latter approach led to rapid decision making, in one HBC this decision was later overturned.

The TB decision-making bodies were described as having a public health orientation, with the notable exception of Bangladesh, whose committee included more physicians and was reported to take a more medically oriented view. Patient input was rarely mentioned in accounts of past regimen changes (Kenya only) and descriptions of future regimen change procedures (Brazil, Kenya and Nigeria only), and patient advocates were listed as members in few of the decision-making bodies (Bangladesh, Brazil and Indonesia only).

Types of evidence used to justify past regimen changes

Factors cited most commonly as supporting past regimen changes (Table 3) were WHO recommendations (both globally and from local country offices), and results from in-country studies (clinical trials, effectiveness studies or pilots—see below).

The supply of free drugs from the Global Drug Facility (GDF, available only as FDCs) was cited as a major reason for regimen change in 8 of the 16 FDC adoptions described. FDCs were also adopted based on the potential for improved adherence and easier logistics (four and five of the FDC adoptions, respectively).

There was a noticeable predominance of programmatic considerations in decision making, with less mention of issues that would directly affect individual patient acceptability. For example, major stakeholders in countries such as China and the Philippines stated that FDCs were adopted due to ease of drug management, but they did not mention patient benefits such as reduced pill burden. Across all HBCs, certain concerns closer to patient care (side effects from thioacetazone, and lower pill burden) were mentioned only once.

In general, awareness of WHO recommendations (Table 3) penetrated to the country level more successfully than did the global evidence base (e.g., peer reviewed, clinical trial results). Improved efficacy was noted as a reason for changing from 8 to 6 months only in the Democratic Republic of Congo and Kenya (and for making other changes in three other HBCs). One stakeholder in each of these two HBCs cited the evidence from the Union trial that demonstrated the clinical superiority of the 6-month regimen.[9]

There was a perception of insufficient evidence to support decision-making, contributing to a difficulty reaching consensus (13 stakeholders each, Table 4). Exacerbating these conditions, local studies were started but were either not completed or not sufficient to inform decision-making (five HBCs), and there was a lack of effectiveness data and lack of local studies (two to three HBCs each). Some stakeholders noted that some past regimen changes were based less on direct evidence and more on a push (from global technical organizations) for global standardization.

The most frequently cited factor hindering a decision to change was cost (Table 4). In China, it was a

Table 3 Positive factors affecting decision-making during past regimen changes

Decision factor during regimen change	Total respondents *n*	Countries *n*
WHO recommendation (global)	52	19
Results from in-country study (randomized controlled trial, effectiveness or pilot study)	20	10
WHO recommendation (country office)	17	13
Free drugs from GDF	9	8
Increased efficacy	7	5
Improved adherence	7	6
Easier logistics (delivery, procurement, distribution)	7	5
Lower cost (of delivery, etc)	4	2
Union recommendation	4	4
Public sector following private sector example	4	3
Adoption by neighboring countries as positive influence	3	3
Results from Union trial	2	2
Introduction of other systemic changes	2	1
Reduction in side effects	2	2
Pressure from civil society	1	1
Lower pill burden	1	1
KNCV recommendation	1	1
Stop TB Partnership recommendation	1	1
ISTC as guidance	1	1
Cost-effectiveness data	1	1
Physicians outside NTP led the way	1	1
Treatment alignment with private sector	1	1
Manufacturers promoted the change to NTP	1	1
Easier to do DOT 3×/week	1	1
Change easier due to pattern of previous changes	1	1
Total responses	151	
Total respondents in this section	100	

WHO = World Health Organization; GDF = Global Drug Facility; Union = International Union Against Tuberculosis and Lung Disease; TB = tuberculosis; ISTC = International Standards of Tuberculosis Care; NTP = National TB Program; DOT = directly observed therapy.

Table 4 Negative factors during past regimen changes

Delay or difficulty during decision making or roll-out	Total respondents *n*	Countries *n*
Cost as significant determinant	20	8
Insufficient evidence	13	10
Lack of consensus slowed decision making	13	8
Problems with drug logistics after change	12	10
Local study started but not completed or insufficient for decision making	6	5
Better DOT needed in continuation phase/ fear loss of R to resistance	5	4
Lack of acceptance by physicians	4	2
For 6 months: must delay HIV/AIDS drugs by 6 months or use efavirenz	3	1
New drugs failed QA tests	3	1
Lack of local study slowed decision	3	3
Delay due to phase-out of old drugs	3	2
Insufficient effectiveness data	2	2
Delay due to raising new budget	1	2
Adherence benefit less important	1	1
Changed who had power in system	1	1
Concern about side effects	1	1
Concern about stability of drugs	1	1
No written procedures for regimen change	1	1
Resistance from local WHO officer	1	1
Regimen change was slowed because it was packaged with other interventions	1	1
Delay due to resistance from local manufacturers	1	1
Total responses	95	

DOT = directly observed therapy; R = rifampin; HIV = human immunodeficiency virus; AIDS = acquired immune-deficiency syndrome; QA = quality assurance; WHO = World Health Organization.

Table 5 Evidence required for future regimen change

Requirement*	Total respondents *n*	Countries *n*
Safety and efficacy		All
Price information/depends on price	37	15
Assessment of logistics prior to implementing	28	10
Cost-effectiveness data	20	9
Implementation evidence from other countries	13	6
Drug resistance data	11	7
Funding for training	10	7
Greater efficacy	7	4
Reduction in relapse rate	5	3
Proof of improved adherence	4	3
Intermittent regimen	4	1
Evidence of patient acceptance	4	2
Second-line regimen that has an alternative to fluoroquinolones	3	2
Sputum conversion rate	3	1
Evidence of provider acceptance	3	2
List of adverse effects	3	3
Fewer side effects	3	2
Adoption in high-income countries	2	1
Better DOT as prerequisite	2	2
Pill burden that is the same or less	2	2
New mechanism of action	2	2
Delay for drug manufacturer's contract to expire or for the disposal of current stocks	2	2
Education that shortening of the regimen is not due to corruption	2	2
Equal or lower cost for program	1	1
Local manufacturing	1	1
Improved drug management as prerequisite	1	1
WHO African Region recommendation	1	1
Data from TB-HIV co-infected individuals	1	1
Involvement of HIV program and no ARV interactions	1	1
Involvement of drug manufacturers	1	1
Safeguards against non-TB use of new drugs	1	1
Total	178	

*A question in this section asked about 'data required from local clinical trials', so mentions of 'local trials' were not scored here (but see Table 6).
DOT = directly observed therapy; WHO = World Health Organization; TB = tuberculosis; HIV = human immunodeficiency virus; ARV = antiretroviral.

'primary determinant' slowing FDC adoption; in Thailand, cost alone delayed FDC adoption, and then resulted in a 2-year hiatus in the roll-out. The need to raise additional funds in TB budgets also delayed regimen changes in Afghanistan and Kenya.

Evidence needed to support future regimen changes

Price was the evidence that most stakeholders would request for future changes (Table 5). Cost-effectiveness data were also requested (20 respondents, Table 5), although only one stakeholder had mentioned it as playing a part in past regimen change (Table 3), and several stakeholders mentioned that absolute cost was more influential than more formal cost-effectiveness analyses.

Cost was also the main reason why a 4-month regimen might not be favored (17 respondents in five HBCs). The most cited reason for favoring a 4-month regimen—improved adherence (22 respondents in 11 HBCs)—was volunteered over 5-fold more often than the main patient-centered reason (reduction of side effects, four respondents in two HBCs).

Contribution of and requirements for local research

The distinction between clinical studies, effectiveness studies and pilots was not clear to all respondents. However, descriptions of past regimen changes included the following accounts of local research: four HBCs did no local studies; nine HBCs did only pilot studies; Bangladesh, China, Indonesia and the Russian Federation did effectiveness studies; and Brazil, India, South Africa and Uganda did randomized controlled trials (RCTs) plus pilot studies (Table 6). Of the nine HBCs that did only pilot studies, only two indicated that these pilot studies were part of the decision-making process. The remaining seven were described as part of a phased roll-out, with the adoption decision already having been made, and the pilot contributing only to the refinement of operational aspects before full implementation.

For adoption of a future regimen by the NTP, stakeholders stated that local clinical research would be: required in-country by Brazil, China, and possibly India; required only at a regional level by 11–12 HBCs; and not required by seven HBCs. They believed that local effectiveness studies would be required in-country by 12 HBCs (although in half of these the

Table 6 Requirement for local effectiveness studies*

Country	May require local effectiveness studies for future NTP adoption	Did research by a local institution contribute to any past regimen change?	Were in-country trials mentioned in the specific accounts of regimen change in this study?	Were the resulting data (from previous column) used in decision making?
Afghanistan	No	No	None	No
Bangladesh	Yes, limited	Yes	Effectiveness studies and pilot studies	Yes
Brazil	Yes	Yes	RCTs and pilot studies	Yes
Cambodia	Yes, limited	No (pilot by donors)	Pilot studies	Yes
China	Yes	Yes	Effectiveness studies	Yes
Democratic Republic of Congo	No	No	None	No
Ethiopia	No	No	None	No
India	Yes	Yes	RCTs and pilot studies	Yes
Indonesia	Yes, limited	No (trial conducted by KNCV)	Effectiveness studies and pilot studies	Yes
Kenya	Regional	Yes	Pilot studies	No†
Mozambique	No	No	Pilot studies	No
Myanmar	Unknown	NA	NA	NA
Nigeria	Yes, limited	No	Pilot studies	No
Pakistan	Yes, limited	No	None	No
Philippines	Yes, limited	Yes	Pilot studies	No‡
Russian Federation	Yes	Yes	Effectiveness studies and pilot studies	Yes
South Africa	Yes, but regional OK	Yes	Yes, non-specifically. RCTs and pilot studies mentioned elsewhere in report	Yes
Thailand	Yes	No	Pilot studies	No
Uganda	Mixed opinion	Yes	RCTs and pilot studies	Yes
United Republic of Tanzania	Mixed opinion	Yes	Pilot studies	No§
Viet Nam	Yes	Yes	Pilot studies	Yes
Zimbabwe	Mixed opinion	Yes	Pilot studies	No

*Responses are color coded, with unknown responses in white, negative responses in red, partially positive responses in yellow, and positive responses in green. Thus, countries with multiple green entries have been and will be strongly reliant on local evidence for change.
†The Kenya Medical Research Institute (KEMRI) provided data for other regimen changes not described in detail in this study.
‡Local evidence showed that compliance was low, but not that FDCs would improve this.
§The National Institute of Medical Research (NIMR) may have contributed evidence for other regimen changes not described in detail in this study.
NTP = National TB Program; RCT = randomized controlled trial; NA = not available; FDC = fixed-dose combination.

studies should be limited in scope to operational issues and/or pilot studies).

Stakeholders stated that studies by local researchers could serve multiple functions, including bridging the gap between clinical trial and field conditions, empowering local advocates to support a change, and speeding adoption.

Local manufacturing and quality assurance

Some governments favor locally manufactured drugs (to support nascent industries), whereas donors may insist on internationally sourced drugs (if local drugs are not proven to meet international standards of quality assurance). During a regimen change, uncertainties about funding source may lead to uncertainties in new drug procurement. For example, during an FDC regimen change in Indonesia, the funding source for the new drug was reportedly changed from government to the Global Fund to Fight AIDS, TB and Malaria (Global Fund), thus requiring a switch from local manufacturers to Global Drug Facility (GDF) drugs. This left local manufacturers with excess supply, and was a disincentive to their future participation in the TB drug market. This problem is more likely for HBCs that are developed enough to have local manufacturing, but still reliant on outside

funding for a substantial portion of their TB drug procurement.

First-line anti-tuberculosis drugs were reported as being produced by local (in-country) manufacturers in significant quantities in 13 of the 22 HBCs.* Procurement from local manufacturers was described as being absolutely required only in Brazil, but encouraged (sometimes strongly, if government funds are being used, e.g., in Indonesia) in 12 additional HBCs.

Procedural delays, difficulties and best practices

Prior to roll-out, several procedures were mentioned as potentially causing major, local adoption delays—up to a year or more for each. These include getting sufficient funds into long-range budget plans (for training and drug costs for a new regimen); addition of a drug to the National Essential Medicines List (NEML); negotiating and doing technology transfer between global and local manufacturers; procurement processes; and using up old drug stocks before rolling out (as countries stockpile 12 months or more of current drugs).

The biggest problems identified during roll-outs were related to drug logistics. Regimen changes put additional stress on drug procurement and distribution systems. Phase-out plans were reportedly lacking in Cambodia and Pakistan; large-scale expiries and drug destruction occurred during regimen changes in Cambodia, Democratic Republic of Congo, Kenya and Zimbabwe; there were overlapping orders of new and old drugs and substandard drugs in Indonesia; and a regimen change led to a drug shortage in Nigeria. Finally, the quantity of drugs in stock drove the speed of roll-out in Kenya (first delay, then acceleration) and the Philippines (immediate roll-out prior to completing a pilot).

Training was mentioned frequently. One stakeholder in the Philippines noted that training costs would delay the implementation of serial regimen changes, and a stakeholder in Mozambique noted that community-based DOTS is becoming more widespread, and that this may make retraining for a new regimen more challenging. Finally, a stakeholder in Nigeria noted that, during a treatment-shortening regimen change, patients received insufficient information and believed they were being shortchanged by government staff.

Successful practices in past regimen changes included early identification of sufficient funding (Philippines), redistributing old drug regimens from early adopting districts to late adopting districts (Tanzania), timing a change to coincide with a drug tender, and early engagement of regulators on regulatory requirements and manufacturers on product specifications (South Africa).

* Bangladesh, Brazil, China, India, Indonesia, Kenya, Myanmar, Pakistan, Philippines, Russian Federation, South Africa, Thailand and Viet Nam.

DISCUSSION

The first step required for regimen change is the identification of a problem that is felt to need a solution.[20] Attainment of WHO targets for case detection and treatment success may lead NTPs to become complacent, and indeed a number of stakeholders stated that they would be unlikely to approve a future regimen change because the current program is working well. The recent adoption of universal treatment targets[22] should refocus programs on how innovations, including a new TB regimen, could improve program outcomes.

Factors promoting TB regimen change, as noted by stakeholders in this study, included WHO recommendation, evidence from local pilot projects, free drugs supplied by the GDF, increased efficacy (for the 6-month regimen) and simplified logistics (for FDC adoption). Barriers to regimen change included cost, lack of sufficient evidence and lack of capacity for changes in drug logistics. Best practices included early identification of funding sources and early engagement of procurement staff, manufacturers and regulators.

Regimen change involves both a global and a local consideration of evidence. The interviewers and some respondents in this study were international technical assistants, which may have introduced some bias toward international viewpoints, but in general we examined the characteristics of regimen change from a local perspective. This revealed the importance of issues that most directly confront national-level stakeholders, such as cost and logistics, with less frequent mentions of patient-related issues and benefits.

Even with the restriction of the study to recent events, the description of those events may have included inaccuracies due to recall error or personal bias. We tried to minimize such problems by collecting accounts from multiple sources, and assuring those sources that their opinions would remain confidential. Notably, the large number of countries covered, and the relative concentration of decision-making power among a small number of individuals per country, did not allow for significant cross-country analysis.

Planning for regimen change

As all HBCs have been through at least one regimen change in recent memory, the idea of a regimen change in the future will not be entirely unfamiliar. However, introduction of novel TB drugs (rather than a reassortment of the current drugs, as in many past TB regimen changes) may present additional challenges, so sufficient preparation will be particularly important.

Structures and processes for TB regimen change vary (Figure). For public sector regimen changes, there is a gradient of country capacity—in the decision-making apparatus, manufacturing ability, piloting capability and expectations of in-country trials—and these factors often track together (i.e., if one factor is high in a given country, so are the remaining factors).

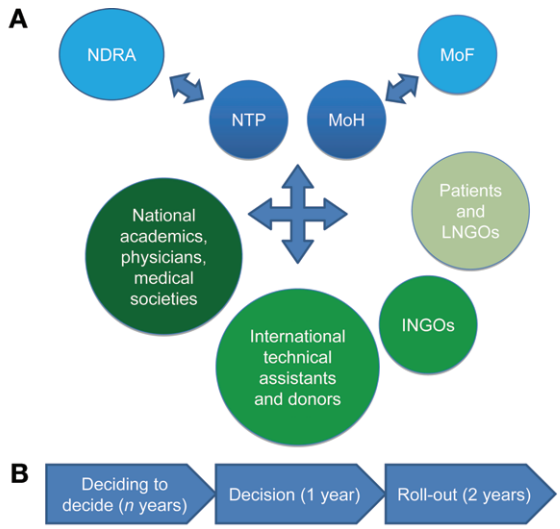

Figure Influence diagram for regimen decision making. **A.** The NTP and MoH are central to decision making, with the NTP providing guidance on priorities to the NDRA, and the MoF requiring a cost justification from the NTP and MoH. In an advisory capacity, national academics, physicians and medical societies are dominant in richer countries, whereas donors, international technical assistants and INGOs can be more influential in lower-income countries. In most countries studied, patients and LNGOs have little or no influence. **B.** Together, this group must decide to discuss a topic, then reach a decision, leading finally to implementation. NDRA = National Drug Regulatory Authority; NTP = National TB Program; MoH = Ministry of Health; MoF = Ministry of Finance; INGOs = international non-governmental organizations; LNGOs = local NGOs. This image can be viewed online in color at http://www.ingentaconnect.com/content/iuatld/ijtld/2010/00000014/00000012/art00010

Introduction plans for the two extremes of this gradient may look quite different: from coordination of multiple national stakeholders and technical partners driven by global consensus (e.g., Cambodia) to working with a perhaps more integrated and research-focused government sector (e.g., Brazil).

Costs, risks and benefits

Based on the evidence from past regimen changes documented here, stakeholders evaluate possible TB regimen changes on both negative (cost and risk) and positive (benefit) grounds.

Cost concerns focused on the direct costs of retraining, adjusting drug management, and recurring drug procurement, rather than on formal cost-effectiveness analyses. Changes in health outcomes are generally considered not in cost terms but as 'risks' and 'benefits' at the level of epidemiology. As past examples made it clear that regimen change decisions may be based on budget alone, financing solutions need to be in place at the same time that medical evidence is presented. Compared to current regimens, some future regimens (e.g., including gatifloxacin) may have similar direct drug costs; others (e.g., including moxifloxacin), although shorter and provided at cost, may be significantly more expensive.

The adopter's perception of risk has been described as 'the fundamental obstacle to the spread of change'.[18] A perception of risk arises because evidence on regimen change is almost always equivocal —there is inevitably some opposing evidence or lack of critical positive evidence. For the introduction of FDCs, the specific risk was that providers might struggle with side-effect management, resulting in poorer adherence and greater relapse;[23] there was also a concern that substandard manufacturing would be more likely for the more complex FDCs.[16]

For introduction of the 6-month regimen, the most prominent risk was an increase in resistance to RMP —seen as the most valuable sterilizing drug—due to the use of RMP for the entire regimen.[24] Thus, the initial recommendation was to implement the 6-month regimen only where DOT could be ensured during the entire regimen.[6]

Benefits of new regimens may also be incompletely defined. For FDCs, prior to introduction there was no calculation of predicted epidemiological benefits, and little evidence was provided to decision makers regarding potential changes in adherence or effectiveness.[11,14] However, the theoretical benefits of FDCs included simplification of drug logistics.[11] Such simplification is, as this study found, central to the practical concerns of local stakeholders. In addition, the promise of reduced resistance development, even if not fully documented, was appealing given the public health orientation of global stakeholders. Although the introduction of FDCs also reduced pill burden, this was rarely noted as having influenced decision makers.

The pressure for adoption of the 6-month regimen increased once it was shown to be clinically superior to the 8-month regimen.[9] However, with the efficacy of the first-line regimen now at 95% or above in a clinical trial setting, the adoption of future, shorter regimen changes must rely on benefits other than increased efficacy. Treatment shortening is expected to increase adherence and thus increase effective cure rates and reduce the emergence of MDR-TB (a possible benefit not promoted widely for the 8- to 6-month change). Furthermore, shorter regimens will increase patient tolerance (and thus potentially increase patient recruitment), reduce the time of exposure to potential side effects, and be consistent with the historical, global trend in the TB field of treatment shortening.

Highlighting any patient benefits during future decision making about regimen change will not be easy. The current study revealed that patient perspectives were not incorporated in most previous TB regimen change decisions. Rather, the emphasis has been on system-based incentives (e.g., free drugs and simplification of procedures for providers, such as through use of FDCs). Given the increased role of advocates and civil society, future decision making may also

need to highlight issues, such as side effects, that are of interest to patients.

Local data requirements

The current Phase III trials are designed to show that the efficacy of 4-month regimens is 'non-inferior' to that of 6-month regimens. Many stakeholders in the current study stated, however, that treatment shortening will likely improve adherence and thus regimen effectiveness in real-world settings. A large effectiveness trial or demonstration project, which was requested by many stakeholders, could potentially prove that this logic holds.

The conduct of such a project would be consistent with the need for effectiveness data in other therapeutic areas, such as malaria,[20] although, due to the longer treatment duration for TB, such a project could add several years to the timelines for regimen change. A demonstration project could provide the three key inputs requested by stakeholders: data on adherence (Table 3); logistics assessment; and implementation evidence from other countries (Table 5). It would overcome past misgivings that local data were insufficient and that regimen change was driven by standardization rather than evidence.

CONCLUSION

The focus of many stakeholder comments was on practical considerations for regimen change. This is a reminder that any new TB regimen must be adapted to local practice and delivery systems. Furthermore, the evidence base for new regimens should address not only the public health and patient considerations but also practical issues. With this comprehensive approach, and continued strengthening of local decision-making structures, the impact of new TB regimens can be maximized.

Acknowledgements

The study team thanks all the stakeholders who generously donated their time and insights. This study would not have been possible without the determined data collection efforts of Management Sciences for Health (MSH) staff and consultants R Mohammed (Afghanistan), A Chowdhury (Bangladesh), J Keravec (Brazil), V Chambard (Cambodia), S Hollist (USA, China), G Bukasa (DR Congo), E Ejigu (Ethiopia), N Gurbani (India), S Suryawati (Indonesia), S Kinyanjui (Kenya), G Kahenya (Zambia, Mozambique), A Marsden (France, Nigeria), J Wong (Philippines), S Borisov (Russian Federation), S Banoo (South Africa), S Ratanawijitrasin (Thailand), S Taychakhoonavudh (Thailand), K Abaasi (Uganda), S Kimatta (Tanzania), R Mbwasi (Tanzania), N T P Cham (Viet Nam) and J Chirenda (Zimbabwe), and the review of one or more country reports by A Barraclough, G Daniel, V Dias, N Heltzer, T Moore, F Smithuis, G Steel, P Suarez, H Vrakking and A Zagorski. The authors are very grateful to R Shretta for early guidance and to J Broekmans, M Espinal, A Ginsberg, C Hennig, M Kimerling, T Moore, P-Y Norval, M Spigelman and S N Wiweko for their comments on the draft publication.

Financial support for this study came from The Netherlands Ministry of Foreign Affairs' Department of Development Cooperation (DGIS) and the Bill & Melinda Gates Foundation.

Conflict of interest statement: WAW, CC, HRI, EG and NRS were or are employed by the Global Alliance for TB Drug Development, whose activities are aimed at developing and making available new therapies for TB. NK and DL are employed by Management Sciences for Health, which provides technical assistance with drug management in many of the high-burden countries.

Role of the funding source: the sponsors of the study, other than those directly employing the authors, had no role in study design, data collection, data analysis, data interpretation, or writing of this report. The corresponding author had access to all data in the study and had final responsibility for the decision to submit for publication.

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RÉSUMÉ

CONTEXTE : Les expériences concernant les modifications antérieures de régime pour la tuberculose (TB) peuvent servir de guide pour les modifications futures de ces régimes.

MÉTHODES : Nous avons mené 166 interviews de responsables nationaux dans 21 des 22 pays à haut fardeau de TB afin d'explorer le processus, les acteurs principaux et les facteurs de succès des procédures des modifications récentes du régime TB dans le secteur public.

RÉSULTATS : Les responsables ont décrit 40 modifications distinctes de régime pour la TB à germes sensibles aux médicaments. Une fois que les pays sont soucieux d'envisager une modification, la durée moyenne est d'environ 1 an avant la prise de décision et d'environ 2 ans avant l'exécution. Les responsables ont cité plus souvent des préoccupations basées sur le programme (par exemple la logistique et le coût) plutôt que focalisées sur le patient (par exemple, les effets collatéraux) ; les représentants des patients ont rarement pris part à la décision. Les organes de prise de décisions dans les pays à haute prévalence et à revenus plus élevés disposent de procédures plus formalisées et d'un plus petit nombre de participants internationaux. Les études-pilote orientées sur la logistique ont été plus courantes que les études d'efficience, et les résultats sont souvent perçus comme insuffisantes. Une fois la mise en route démarrée, les déficiences dans la prise en charge des médicaments sont fréquemment avancées, avec des complications supplémentaires lorsqu'une fabrication locale est nécessaire. Les meilleures pratiques pour une modification de régime ont compris un engagement précoce du personnel pour la budgétisation, du personnel pour l'achat, des décideurs et des fabricants.

CONCLUSION : A l'avenir, les preneurs de décisions pourront bénéficier d'organes renforcés de prise de décision, de l'apport des patients, d'un planning précoce et complet et de régimes et de preuves permettant de faire face aux problèmes de mise en œuvre pratique au niveau local.

RESUMEN

MARCO DE REFERENCIAS: La experiencia previa con las modificaciones del régimen antituberculoso puede orientar los cambios en el futuro.

MÉTODOS: Con el propósito de investigar el mecanismo, los principales actores y los factores de éxito del procedimiento en las recientes modificaciones de las pautas del tratamiento antituberculoso en el sector público, se llevaron a cabo 166 entrevistas a interesados directos del país en 21 de los 22 países con alta carga de morbilidad por tuberculosis (TB).

RESULTADOS: Los interesados directos describieron 40 modificaciones precisas de las pautas del tratamiento de la TB sensible a los medicamentos. Una vez que los países se habían comprometido a considerar la introducción de un cambio, el tiempo promedio hasta tomar la decisión fue de 1 año y el lapso hasta la introducción de las modificaciones fue 2 años. Los interesados citaron con mayor frecuencia cuestiones relacionadas con el programa (como los aspectos organizativos y los costos) y no centradas en los pacientes (como las reacciones adversas) y los representantes de los pacientes rara vez participaron en la toma de decisiones. Los organismos decisorios en los países con mayores ingresos y alta morbilidad contaban con procedimientos más formalizados y menos participantes internacionales. Los estudios preliminares que se centraban en los aspectos organizativos fueron más frecuentes que los estudios de eficacia y en muchas ocasiones se consideró que la base científica era insuficiente. Una vez comenzada la ejecución, se expusieron con frecuencia fallas en la gestión de los medicamentos y las complicaciones fueron mayores cuando se precisaba fabricarlos localmente. Entre las prácticas óptimas de modificación del régimen se encontraron un compromiso temprano el personal encargado del financiamiento, del personal de servicios de adquisiciones, las instancias normativas y los fabricantes.

CONCLUSIÓN: Las personas encargadas de tomar las decisiones en el futuro encontrarán muy útil la existencia de organismos decisorios fortalecidos, las sugerencias de los pacientes, el planeamiento precoz y exhaustivo y el régimen terapéutico que hayan dado prueba de responder a las necesidades prácticas de ejecución local.