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Implications of the current tuberculosis treatment landscape for future regimen change

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SUMMARY

BACKGROUND: The current tuberculosis (TB) treatment landscape has been studied extensively, but researchers rarely consider how it creates challenges or opportunities for future regimen change.

METHODS: In 166 stakeholder interviews in the TB high-burden countries (HBCs), we investigated areas of first-line TB treatment and control that would affect, and be affected by, a future TB regimen change. Responses were compared with existing standardized data.

RESULTS: Public sector regimens are converging towards a single standard, which facilitates comparison with a single control arm from clinical trials. However, final product design is challenging if the goal is fixed-dose combinations and patient kits, whose current widespread use addresses continuing weaknesses in drug management. Any product must address broad groups, as relatively low levels of drug susceptibility testing (DST) do not allow for individualized therapy. Finally, the protection of new drugs from the development of resistance will be challenging, as the implementation of directly observed therapy and public-private mix programs is incomplete, and substantial private sectors have been identified as early adopters of these drugs.

CONCLUSIONS: Health systems for TB treatment and control must be improved not only to allow better implementation of current treatments but also to set the stage for implementation of new, improved TB regimens.

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

A NEW TUBERCULOSIS (TB) regimen must compete with current regimens[1] based on clinical trial evidence, but it must also fit into the existing health system.[2] Here, we quantify certain parameters of the existing TB treatment landscape and investigate how this landscape would impact the introduction of a new TB regimen.

Within the DOTS approach, a key variable is the choice of regimen by the National TB Program (NTP). These choices have at times been controversial;[3] conservative approaches with the current first-line drugs have been common due to the paucity of alternative drug options. More recently, an increase in the evidence base has helped to fine-tune World Health Organization (WHO) recommendations regarding regimen choice.[4–6] The limited capacity for drug susceptibility testing (DST) in the high-burden countries (HBCs)[7] has not allowed for individualized regimens.

Adherence to the regimen is maximized by delivering TB drugs with directly observed treatment (DOT).[8] Variants of this approach include facility-based or community-based DOT, with observation by health workers, community health workers, or family members.[9] As the optimal strategy depends on context, more recently the emphasis has been on taking a patient-centered approach.[10]

A new regimen would need to fit into TB drug delivery systems that have been simplified over the past two decades. Two leading approaches to minimize problems with weak drug management have been the use of fixed-dose combinations (FDCs)[11] and patient kits. A single patient kit holds an entire 6- or 8-month regimen for a patient; the kits ensure that drugs do not run out mid-regimen, simplify drug quantification, and help patients to understand that the regimen is lengthy, for a fixed term, and requires commitment.

Public-private mix (PPM) programs allow the public sector to monitor and influence the regimens used in the private sector, via activities such as supervision, referral and provision of standardized drugs; they were devised in recognition of the substantial private sector involvement in TB care.[12] Scaled-up PPM interventions are cost-effective,[13] but PPM programs have faced challenges.[14]

The new regimen that may enter this landscape in

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the near future is a 4-month multidrug regimen that includes 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 6-month regimen (2HRZE/4HR, i.e., 2 months of isoniazid [H], rifampicin [R], pyrazinamide [Z] and ethambutol [E], followed by 4 months of HR).[15]

Planning for global regimen change requires greater knowledge about the extent of certain key practices that will affect, and be affected by, regimen change. This article provides such a quantitative overview, and identifies a number of action points that will strengthen delivery of both current and future regimens.

METHODS

While investigating past regimen changes,[11] we surveyed stakeholders about TB health system issues related to regimen change. The countries included in the study are the 22 defined by the WHO as HBCs for TB, and the majority of our questions were on public sector policies, given the importance of the public sector in TB control (although some questions on the private sector were included). The primary focus was on the delivery of treatment for drug-susceptible TB, as treatments for multidrug-resistant TB (MDR-TB) have very different financial and human resource requirements.

From April to August 2008, data were collected by conducting 166 stakeholder interviews in 21 countries, as described[11] (inquires were restricted to e-mail for Myanmar due to Cyclone Nargis). No ethics committee was involved, as the unit of inquiry was held to be institutions (and their behavior) rather than individuals. Informed consent was obtained verbally using a standard script; interviewees agreed that it was 'OK to summarize your comments, without specific attribution to you or your institution, for inclusion in a public report.' Any documents that associated an individual with a response were restricted to the study team, who had signed confidentiality agreements. Before public release of data, responses were combined and anonymized. The substantial number of respondents per country ensured continued anonymity.

Each interviewer (one per country, each a professional in the field of TB drug management) 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 decision-making.[1,2] Each interviewer identified, in collaboration with the central study team, an initial set of three key interviewees—one each from the NTP, the WHO country office, and the regulatory authority. These and subsequent interviewees were asked to identify other key individuals and organizations involved in TB health systems and TB regimen decision making.

Interview topics were identified by considering all the regimen change steps outlined by the Stop TB Partnership's Retooling Taskforce[16] and the concerns previously raised by stakeholders regarding new TB regimens.[1] We considered the following as relevant to regimen change: which TB drugs are used (public sector regimens, FDC use, regimen choice in the private sector); how TB drugs are delivered (NTP performance, drug management performance, how DOT is practiced, size of TB private sector, extent of PPM programs); and how the continued efficacy of drugs is ensured (extent of DST, and FDC and DOT issues mentioned above). As there are two fluoroquinolones in Phase III trials for drug-susceptible TB, we asked about the availability of fluoroquinolones and of data on fluoroquinolone resistance.

Interviewees were asked to respond 'to the best of [their] knowledge'. Answers from different interviewees were cross-checked and, where possible, the data collected were compared to WHO data.[17] If stakeholders made a qualitative observation, the observation is noted in the text followed by the names of the stakeholders' countries in parentheses. These observations were elaborations from the questions originally asked, so were only detected in the countries noted.

RESULTS

Public sector regimens

In the public sector, the current regimen provides the baseline against which any new regimen will be judged. Although WHO guidelines have allowed for some variation in treatment regimens for drug-susceptible TB, we found that globally these regimens in HBCs (Table 1) have been moving (Table 2) towards a

Table 1 First-line regimens in the HBCs

Regimen	Dosing	*n*	HBCs
2HRZE/4HR	Daily	13	Bangladesh, Brazil, Cambodia, Democratic Republic of Congo, Indonesia,* Kenya,† Mozambique, Myanmar, Philippines, South Africa, Thailand, United Republic of Tanzania, Zimbabwe
2HRZE/4HR	Intermittent	2	China,‡ India
2HRZE/6HE	Daily	5	Afghanistan, Ethiopia, Nigeria, Pakistan, Uganda§
2HRZS/6HE	Daily	1	Viet Nam§
2HRZE/S/4HR	Daily	1	Russian Federation

*Intermittent in continuation phase.
†Transitioning from 8 months.
‡Daily for those with HIV/AIDS, and daily being phased in for other patients.
§Committed to daily 2HRZE/4HR after our interview period concluded.
HBC = high-burden country; H = isoniazid; R = rifampicin; Z = pyrazinamide; E = ethambutol; S = streptomycin. Numbers before the letters indicate the duration in months of the phase of treatment; HIV = human immunodeficiency virus; AIDS = acquired immune-deficiency syndrome.

Table 2 Movement of HBC regimens towards a single standard

	HBC (year)
Changes bringing regimens closer to 2HRZE/4HR (7 days/week)	
Add E to intensive phase	Brazil (2008)
Continuation phase daily not intermittent	Bangladesh (2008)
From 8- to 6-month regimen	Cambodia (2005); Democratic Republic of Congo (2004); Kenya (2006); Mozambique (2005); Tanzania (2006)
'Daily' increased from 5–6 days to 7 days/week	South Africa (2007); Tanzania (2006)
Changes rejected or indefinitely postponed	
From 8- to 6-month regimen	Afghanistan (2007); Ethiopia (2007); Nigeria (2008)
Dosing frequency	
Intermittent (3 days/week)	China (daily as option), India, Indonesia (continuation phase only), Russian Federation (one option in continuation phase only)*
Daily (7 days/week)	14 HBCs [35% of global burden]
Daily (6 days/week)	2 HBCs [2% of global burden]
Daily (6–7 days/week)	1 HBC [1% of global burden]
Daily (5, 6 or 7 days not determined)	3 HBCs [6% of global burden]

*This accounts for 37% of global burden, based on stakeholder estimates that for public programs 90% of China, 66% of Indonesia (i.e., 100% of continuation phase), 10% of Russian Federation, and 100% of India use intermittent therapy.
HBC = high-burden country; H = isoniazid; R = rifampicin; Z = pyrazinamide; E = ethambutol. Numbers before the letters indicate the duration in months of the phase of treatment.

Table 3 Weight bands used for adult Category I regimens

	Rifampicin dosages in treatment guidelines?				Weight bands
Country	300 mg	450 mg	600 mg	750 mg	*n*
Brazil	Yes	Yes	Yes	No	3
China (daily)	No	Yes	Yes	No	2
China (intermittent)	No	No	Yes	No	1
Democratic Republic of Congo	Yes	Yes	Yes	Yes	4
Ethiopia	Yes	Yes	Yes	Yes	4
India (intermittent)	No	Yes	Yes	No	2
Indonesia	Yes	Yes	Yes	Yes	4
Kenya	Yes	Yes	Yes	No	3
Nigeria	Yes	Yes	Yes	No	3
Pakistan	Yes	Yes	Yes	Yes	4
South Africa (IP)	Yes	Yes	Yes	Yes	4
Tanzania	No	Yes	Yes	No	2
Uganda	Yes	Yes	Yes	Yes	4
Total	9	12	12	6	

Light gray denotes weight bands that are not present in a country, and countries with only 3 weight bands. Dark grey denotes countries with only 1–2 weight bands
IP = intensive phase.

single standard of daily 2HRZE/4HR (true for 13/22 HBCs). These data are in agreement with WHO data,[17] with the exception of a recent regimen change by Bangladesh. After our interviews were completed, Uganda and Viet Nam also committed to the 6-month regimen.

Weight band information for adult (>30 kg) Category I patients (i.e., new smear-positive or serious smear-negative cases) was available for 12 HBCs (Table 3). Exact cut-offs for weight bands differ between countries but, more importantly, so do the number of weight bands. Of the 12 HBCs, only half used four weight bands. Thus, some HBCs do not dose entirely within the recommended range of 8–12 mg/kg of rifampicin.

Variants on the standard regimen

Stakeholders were asked if there were any variants on the standard Category I regimens. The two main categories of regimen variants mentioned were 'overtreatment' (the addition of extra drugs to 'ensure a cure') and the beginning of a regimen change (see private sector section below). Overtreatment reportedly arises because physicians are faced with rising drug resistance and inadequate DST capacity; distrust in drug quality was also mentioned by one stakeholder. Their solution is often the addition of a single drug, usually a fluoroquinolone, even though this may be the only new, active drug in an otherwise failing TB regimen (Indonesia, Philippines, and Thailand for Category I; China and Russian Federation for Category II).

Use of fixed-dose combinations

A critical component of the TB treatment landscape is the use of quality-assured FDCs. Current use of FDCs by NTPs was reported (Figure) as being more widespread than indicated by WHO data.[17] Stakeholders reported that NTPs in 20/22 HBCs use a two-drug FDC, usually for the continuation phase. The remaining two countries are China, which is piloting both two- and four-drug FDCs, and India, which is the only HBC NTP with no use or plans for use of FDCs. Both China and India use co-blistered drugs as an alternative to FDCs.

Stakeholders also stated that 18 of the 20 HBC NTPs that were using a two-drug FDC were also currently using a four-drug FDC. The two that were not were Brazil, which had firm plans to adopt a four-drug FDC in 2009, and Viet Nam, which reportedly

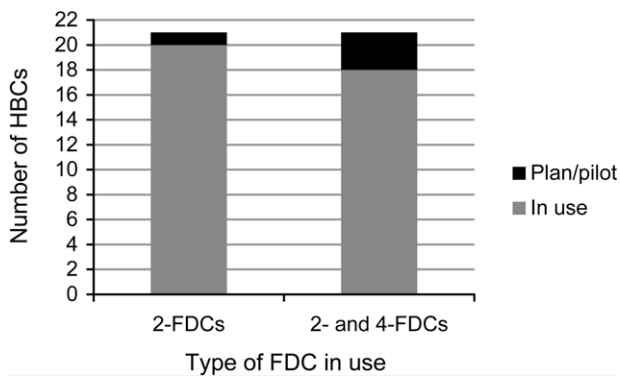

Figure Number of HBCs using 2- and 4-FDCs. HBC = high-burden country; FDC = fixed-dose combination.

remained open to a four-drug FDC if and when it drops streptomycin from its Category I regimen. Finally, three-drug FDCs were reportedly in use in the public sector in 15 HBCs, primarily for Category II (retreatment). We did not assess quality assurance mechanisms, such as tests of bioavailability, although these are a vital component of any FDC strategy.

In 12 HBCs it was clear that loose drugs were only available in very limited amounts (e.g., for side-effect management), suggesting that FDCs were the primary dosing formulation used by NTPs in these countries. Of the remaining countries, two (India and China) use few or no FDCs, and seven yielded responses that were unclear. Only in Thailand was it stated that providers could choose whether they used loose drugs or FDCs.

The Global Drug Facility (GDF) supplies eight different adult and pediatric FDCs. Five additional FDCs were available in at least one HBC other than the Russian Federation; the latter country had 14 additional, unique formulations.

Patient kits and drug management

Although we did not ask about packaging, the use or adoption of patient kits in the country was mentioned by stakeholders in Kenya, Myanmar, Nigeria (adoption initiated) and Viet Nam (adoption desired but not yet initiated). The GDF reported that, in at least one of the last 3 years, they have supplied patient kits to 23 countries (including 6 HBCs, namely Afghanistan, Indonesia, Kenya, Myanmar, Nigeria and the Philippines; T Moore, GDF, personal communication based on GDF database). In addition, India and South Africa supply their own kits. These 8 HBCs represent 42% of the worldwide burden of smear-positive TB.[17]

When asked about strengths and weaknesses of drug management, stakeholders mentioned significant issues with TB drug stock-outs in 7 HBCs (Cambodia, China, Democratic Republic [DR] of Congo, Kenya, Pakistan, South Africa and Uganda), TB drug expiries in 2 HBCs (Ethiopia and Tanzania) and both stock-outs and expiries in 4 HBCs (Indonesia, Mozambique, Nigeria and Zimbabwe). Seven of these HBCs figure amongst the 11 HBCs previously reporting stock-outs of first-line drugs at either central or peripheral locations.[17]

Extent of drug susceptibility testing

Stakeholders stated that eight HBCs conduct no testing for fluoroquinolone resistance in the public sector outside of a clinical trial setting. Another 8 HBCs test some MDR-TB patients and/or retreatment patients for fluoroquinolone resistance, but often at one or very few treatment centers. Widespread testing for fluoroquinolone resistance was claimed only in the Russian Federation and was planned for the future in Brazil (DST capacity not determined in four HBCs). The WHO reports that 9 HBCs have access to second-line DST either within or outside the country.[17]

This lack of fluoroquinolone DST contrasts with the widespread availability of fluoroquinolones, which are used for a number of non-TB indications. Stakeholders stated that fluoroquinolones require a prescription in 18 HBCs (none required in 2 HBCs; status unknown in 2 HBCs), and yet they are available over the counter in 15 HBCs (mixed opinion or unclear in 5 HBCs; not available over the counter in 2 HBCs). Many respondents made it clear that fluoroquinolones were freely and widely available in their country. Fluoroquinolones were believed to be used for first-line TB treatment in the public and private sectors in the Russian Federation and in the private sector in 5 HBCs in Asia; opinions on this topic for China were mixed.

Extent of directly observed treatment

Stakeholders were asked to describe the frequency of DOT in both treatment phases and to identify the personnel conducting DOT. Due to the variability of DOT within most HBCs, answers were not always simple to interpret. However, stakeholders did mention that encounters with health care centers are often restricted to weekly, biweekly or monthly visits (Table 4). In many HBCs, stakeholders noted that direct observation is primarily conducted by family (Indonesia, Kenya, Mozambique, Zimbabwe), self (Ethiopia, Nigeria, Russian Federation) or either family or self (China). The concept of self-DOT seems contradictory and was not an option in the interview guide; the answer is nevertheless reported because it was provided.

Private sector size and PPM coverage

The importance of the private sector in TB regimen change depends on how many TB patients access

Table 4 Frequency of patient contact with health care system in the HBCs

Phase	Frequency of encounters with health care system*	HBCs
Intensive	Weekly	Indonesia, Pakistan, South Africa, Zimbabwe
	Biweekly	Brazil, Kenya
	Monthly	China,† Mozambique
Continuation	Weekly	India
	Biweekly	Brazil
	Monthly	China,† Ethiopia, Indonesia, Kenya, Mozambique, Nigeria, Pakistan, Russian Federation, South Africa, Zimbabwe

* Listed only when responses were clear; may not be uniform through a given country.
† This is for collecting drugs from the county doctor. Some patients then do family DOT; others see the village doctor every other day.
HBC = high-burden country; DOT = directly observed treatment.

private treatment. Based on the mean of stakeholder estimates (and a recent prevalence survey in Viet Nam[18]), the private sector treats ~30–53% of the TB cases in 8 HBCs; ~8–17% in 5 HBCs; and ~4% or less in the rest (Table 5).

TB treatment in the private sector was reported as being prohibited in Brazil and the Russian Federation, prohibited but without enforcement in Cambodia and Zimbabwe, and not prohibited in the remaining 18 HBCs. Stakeholders added that TB drug sales in the private sector are prohibited at least in Brazil, DR Congo, Ethiopia, the Russian Federation, and Zimbabwe, and TB drugs in Tanzania are restricted to the public sector via importation controls.

The influence of PPM programs depends on their size. Stakeholders were asked about the number of patients and physicians in PPM programs. Up to 9 HBCs reported having minimal or no PPM programs (Table 5). For the remaining HBCs, the percentage of incident cases covered by PPM programs is often unclear.[17] Based on WHO and stakeholder estimates, we calculated that PPM programs involve over 500 physicians in only Cambodia, India, Indonesia, Pakistan and the Philippines, detect 22% or less of the private sector in all but Kenya, Myanmar, and the Philippines, and leave 29% or more of a country's total incident TB cases being treated in the private sector without the benefit of PPM in 6 or more HBCs (Table 5).

Early adoption by the private sector

Stakeholders noted that practices in the private sector, although much less uniform, have often preceded the process of public regimen change, especially if the NTP resists regimen change for a long time. (Non-recommended practices may also be adopted by the private sector, but this study focused on WHO and NTP guidelines.) Past examples mentioned by stakeholders included: adoption of FDCs in the Philippines

Table 5 Estimated size of private sector and PPM programs

Country	A Percentage of patients getting TB treatment from private sector, mean of estimates*	B Percentage of private sector covered by PPM (estimate)†	C Percentage of incident patients in the unregulated private sector, i.e., in private sector but NOT in PPM, C = A − (A × B)
Afghanistan	50%	0%	50%
Bangladesh	13%	14%	11%
Brazil	0%	No PPM	0%
Cambodia	40%	4%	38%
China	15% (non CDC hospitals)	Extensive PPM	Low
Democratic Republic of Congo	0%	Unknown	0%
Ethiopia	1%	13%	0.9%
India	45%	⩽13% (13% of the Indian population lives in districts with at least some PPM activity‡)	⩾39%
Indonesia	53%	5%‡ or 20%§ of private physicians are enrolled in PPM	43–50%
Kenya	3.5%	67%	1.2%
Mozambique	2.5%	No‡ or minimal (5 physicians§) PPM	2.5%
Myanmar	44%	34% (15% of all incident cases are covered by PPM‡)	29%
Nigeria	30%	Probably incomplete, as there are only 410 PPM physicians§ and ~65 000 private patients	Unknown
Pakistan	45%	5% of private physicians§ or 20% of notified cases.[19] (One third of districts have at least some PPM‡)	32–43%
Philippines	40%	68% (~27% of all incident cases are in PPM‡)	13–19%
Russian Federation	0%	No PPM	0%
South Africa	4%	Unknown	Unknown
Thailand	12%	22% of private physicians§	9.4%
Uganda	0%	No PPM	0%
United Republic of Tanzania	17%	Minimal PPM (12 physicians§)	~17%
Viet Nam	8%¶	No PPM	8%
Zimbabwe	0%	No PPM	0%

*Estimated percentages are coded as high (dark grey), medium (light grey) or low (white). Some cases may later transfer to public sector (e.g., Cambodia and Myanmar). The figures include hospitals in China that are government-funded but not aligned with the national TB program, but they exclude large faith-based organizations and NGO sectors in Cambodia, DR Congo and Nigeria.

†Where noted, this figure comes directly from stated survey information‡ or WHO data.§ In all other cases, this was calculated as (number of patients treated by PPM) / [(incident cases, all forms) × (% patients in private sector)]. The first and third terms in this equation were stakeholder estimates.

¶Based on the recent prevalence survey results.[18]

PPM = public-private mix; TB = tuberculosis; CDC = Centers for Disease Control and Prevention; NGO = non-governmental organization; WHO = World Health Organization.

and Viet Nam; the daily continuation phase in Bangladesh; and the changes from an 8- to a 6-month regimen in Kenya and Uganda. Certain private sector practices may also predict future changes, as they mimic the global consensus more than the current national guidelines (e.g., the RHZE intensive phase in Viet Nam, 6-month regimen in Pakistan and Viet Nam, and daily dosing in India, estimated by one stakeholder to be practiced by ~40% of private practitioners in India).

Stakeholders believed that regimen change 'should' occur first in the public sector (54/59 responses) due to the public sector's greater adherence to standard regimens. But they acknowledged that change may be more likely to occur first in the private sector. Private physicians reportedly want to offer new treatments to attract patients; this may lead them to seek out change (Indonesia, Philippines, and Viet Nam) and sometimes oppose a public sector regimen change so that the private sector retains its edge (China, Kenya). Early adoption in the private sector may be even more likely with a new, relatively expensive TB drug, as at least some private patients can pay (China, Indonesia, Philippines, and Viet Nam). Stakeholders in Indonesia and Pakistan noted that the private sector may also be a major audience for any new MDR-TB drugs as, according to them, currently the private sector bears most of the burden of this treatment.

Within the 17 HBCs responding to the relevant question, regimen choice in the private sector is most strongly influenced by medical associations (mentioned in 11 HBCs), drug companies and their representatives (10 HBCs), specialists (4 HBCs), and social marketing programs (2 HBCs). NTPs and PPM programs were often mentioned as playing a minor role.

DISCUSSION

Any new TB regimen will enter a complex treatment environment that includes various first-line regimens, retreatment regimens, MDR-TB regimens, pediatric regimens, extra-pulmonary regimens, fixed-dose combinations, patient kits, weight bands, and diagnostic and DST protocols. The potential impacts of a new regimen across all of these factors must be considered. To form a basis for this analysis, we outline here the current treatment landscape and the implications for future TB regimen change. Some of these data were verifiable (e.g., current regimens in guidelines), other questions elicited consistent answers (e.g., extent of DST), while private sector size was, in the absence of new data collection mechanisms, an estimate. In sum, however, we believe these data provide a valuable overview of the current treatment landscape.

Regimens and their use

The most basic component of the current treatment landscape is the first-line regimen. Convergence of HBC Category I regimens towards a single standard (2HRZE/4RH, with dosing 7 days a week) will make the assimilation of Phase III clinical trial results easier, as this regimen matches the control arm used in these trials. This convergence is consistent with movement in WHO guidelines from a list of equal options[20] to a clear preference for a single Category I regimen[5,6] based on an improved evidence base.[4] Where known, 'daily treatment' usually means 7 days a week. Thus, TB drug developers will probably not need to provide evidence of the efficacy of 5-day dosing to accommodate NTP demands.

Under WHO guidelines, all current first-line TB drugs are weight banded. This is thought to be necessary for at least some of the drugs to keep them within acceptable limits of efficacy and toxicity, and its uniform application eases the design of FDCs. We found, however, that the implementation of weight banding is variable. Of note, weight banding is not necessary for many of the new TB drugs currently being tested (i.e., the same dose can be given to all adult patients). Building on previous analyses,[21] stakeholders could ideally reach a consensus on how many adult weight bands are necessary for new regimens. Initially, new regimens may be a more complex mix of weight banded and non-weight banded drugs, but truly novel regimens may not require weight banding.

These analyses will have important implications for the development of new FDCs. With FDCs now widely adopted (in excess of previous reports[17]), their presence in new regimens is expected.[1] Development of new FDCs takes time and resources. Thus, the introduction of a completely novel first-line TB drug may result, at least initially, in the replacement of four- or even two-drug FDCs with loose pills, thus increasing the number of commodities to be handled and the chances that at least one will be subject to a stock-out.

Many countries in Asia have large private sectors for TB treatment. Based on Table 5, private sectors in the HBCs may treat ~21% of the global TB burden, but only ~5% of the global burden is covered by PPM. In a more recent analysis, drug usage data in 10 HBCs yielded a relative ranking of private market size similar to that estimated by stakeholders.[22] However, for the more significant private markets, their absolute size appears to be substantially greater than the stakeholder estimates, likely due to repeated treatments in the private and public sectors.

Stakeholders indicated that the private sector can act as an early adopter, although with the risk that providers will use treatment regimens of variable length and with low adherence,[23] resulting in a risk of increased drug resistance and poor treatment outcomes. The modest size of most PPM programs (documented previously[24] and in this study) suggests that, in most countries, the current PPM programs are unlikely to reduce this risk substantially. As new TB

drugs move through development, expansion of PPM efforts and increasing implementation of the International Standards for Tuberculosis Care (ISTC)[25] via professional associations will be essential.

The costs and benefits of DOT and adherence

The WHO has recommended DOT for any intensive phase and for continuation phases that include rifampicin.[5] In many settings, however, and especially in the continuation phase, DOT goes no further than family supervision and may require only one visit to a health care center per month, as noted in this study. Thus, a 4-month regimen may save just two visits and only modestly reduce the burden on the health care system.

However, a 4-month regimen would result in other epidemiological[26,27] and programmatic savings. It would reduce by one third the size of the caseload that must be monitored, followed for side-effects management, and traced for defaulters. Furthermore, many health care systems maintain other, more frequent forms of DOT (e.g., community-based DOT) and other adherence interventions (provider training, patient health education, reimbursement, peer support, defaulter tracing, attendance prompts, contracts, and removal of barriers at community and family levels). The expenses of providing these interventions in the final 2 months of treatment warrant further investigation. This is not, however, an area where it is possible to generalize. Adherence approaches, and the partner organizations who implement them, vary widely even within a single country.

DST coverage and prospects for its expansion

The possible emergence of drug resistance has been a prominent concern during past regimen changes, resulting in significant adoption delays.[11] This is of particular concern for a future fluoroquinolone-containing first-line TB drug regimen. Fluoroquinolones are a mainstay of second-line drug treatment; they are used for major non-TB indications, and are widely available over the counter. This would greatly increase the challenges of managing their rational use.

Ensuring sufficient use of DST for future determination of drug resistance, even for the existing first-line drugs, will not be easy. The baseline levels of DST use are low—only 4.7% of retreatment cases and 2% of new cases.[17] The current study confirmed that existing fluoroquinolone DST capacity is extremely limited and its use almost always restricted to cases of treatment failure or MDR-TB. Furthermore, insufficient DST in a background of rising MDR-TB was reportedly increasing the pressure for ad hoc addition of more drugs during first-line treatment.

DST has been recommended and used primarily as a tool for surveillance[28] and regimen design[29] rather than treatment; it has therefore been targeted only at retreatment cases, as this is where trends in resistance development are first seen.[30,31] However, the availability of line-probe assays and GeneXpert®, the formation of the Global Laboratory Initiative (GLI), the expanded populations being targeted for DST in new treatment guidelines,[6] and the aggressive plans for expansion of MDR-TB treatment have raised the prospect of a greatly increased level of DST for first-line drugs. Indeed, DST capacity is already expanding.[19]

Prior to introducing a fluoroquinolone-containing first-line regimen, decision makers would benefit from an assessment of fluoroquinolone resistance rates in treatment-naïve TB patients (which may require a dedicated initiative) and a realistic assessment of likely future DST coverage (for both first-line drugs and fluoroquinolones). To limit concerns about resistance, efforts to implement a fluoroquinolone-containing regimen and build DST capacity should be linked geographically. Quality assurance efforts,[32] which are not considered in depth here, will also remain crucial. In fact, for the introduction of new TB drugs in general, a broad consideration of measures to protect the drugs from resistance development (DST, DOT, FDCs, and strict controls over drug quality and distribution) will be an important part of the decision process.

CONCLUSION

By considering the current health systems used for TB treatment, TB drug developers can prioritize products that are more likely to meet the needs of TB programs, physicians, and patients. The same analysis can also highlight areas of health systems strengthening that can be undertaken now to facilitate future regimen changes. Improvement of drug management, and expansion of PPM, DOT (and other adherence mechanisms), FDC use, and DST are all initiatives that have been highlighted as benefiting the delivery of current treatment regimens.[19,33] The case for these actions is only strengthened by considering their impact on the introduction of new TB regimens.

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RÉSUMÉ

CONTEXTE : Le paysage actuel du traitement de la tuberculose (TB) a été largement étudié, mais les chercheurs ne considèrent que rarement la façon dont il crée des défis ou des occasions de modifications futures des régimes.

MÉTHODES : Lors de 166 interviews de responsables dans les pays à fardeau élevé de TB (HBC), nous avons examiné les zones du traitement de première ligne et de la lutte qui pourraient affecter ou être affectés par une modification ultérieure du régime antituberculeux. Les réponses ont été comparées avec des données standardisées existantes.

RÉSULTATS : Les régimes du secteur public convergent vers un seul régime standard, ce qui facilite la comparaison avec un seul bras contrôle provenant d'essais cliniques. Toutefois, le schéma du produit final représente un défi si le but visé est constitué de combinaisons à dose fixe et des kits pour les patients, dont l'utilisation répandue actuellement répond aux faiblesses persistantes de la prise en charge des médicaments. Tout produit doit s'appliquer à de larges groupes, puisque les niveaux relativement faibles des tests de sensibilité aux médicaments (DST) ne permettent pas un traitement individualisé. Finalement, la protection à l'égard du développement de la résistance pour de nouveaux médicaments constituera un défi puisque la mise en œuvre du traitement directement observé (DOT) et les programmes mixtes publics-privés (PPM) sont incomplets et que des secteurs privés substantiels ont été identifiés comme adoptant précocement les nouveaux médicaments.

CONCLUSIONS : Les systèmes de santé doivent s'améliorer pour le traitement et la lutte contre la TB, non seulement pour permettre une meilleure mise en œuvre des traitements actuels mais aussi pour se mettre en état de mettre en œuvre de nouveaux régimes antituberculeux améliorés.

RESUMEN

MARCO DE REFERENCIA: El panorama actual del tratamiento de la tuberculosis (TB) ha sido el centro de numerosos estudios, pero en pocas ocasiones los investigadores han examinado las dificultades y las oportunidades que esta situación ofrece a las futuras modificaciones del protocolo terapéutico.

MÉTODOS: Mediante entrevistas a 166 interesados directos se investigaron los aspectos del tratamiento antituberculoso de primera línea y del control de la enfermedad que serían pertinentes en una futura modificación de la pauta terapéutica y que se verían afectados por la misma. Las respuestas se compararon con los datos normalizados existentes en la Organización Mundial de la Salud.

RESULTADOS: Los tratamientos suministrados por los sectores públicos convergen hacia una pauta única, lo cual facilitaría la comparación con un solo grupo de referencia en los estudios clínicos. Sin embargo, el diseño del producto final es problemático cuando las metas son las asociaciones de dosis fijas o los estuches para pacientes, cuyo uso generalizado revela en la actualidad continuas deficiencias en materia de gestión de los medicamentos. Todo nuevo producto se debe dirigir a amplios grupos de personas, pues la baja cobertura con las pruebas de sensibilidad a los medicamentos no permite los tratamientos individualizados. Por último, un aspecto difícil será la protección contra la aparición de resistencia a los nuevos medicamentos, pues la ejecución del tratamiento directamente observado es incompleta, la instauración de programas sanitarios mixtos del sector público y privado no está generalizada y además, se observó que una proporción importante del sector privado adopta en forma temprana las nuevas pautas.

CONCLUSIÓN: Es importante perfeccionar los sistemas sanitarios dedicados al tratamiento y el control de la TB, no solo con el fin de optimizar la ejecución de los tratamientos actuales, sino con el objeto de preparar el terreno para la introducción de nuevas pautas mejoradas de tratamiento antituberculoso.