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Does treatment collection and observation each day keep the patient away? An analysis of the determinants of adherence among patients with Tuberculosis in South Africa

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Abstract

Directly observed treatment short course (DOTS) has been the recommended strategy for Tuberculosis (TB) control since 1995. Developed as an alternative to inpatient treatment, it involves observation of patients' medication intake to promote adherence. However, the burden of daily clinic visits may affect access to care. Using a mixed methods approach, we consider whether (1) non-adherence differs systematically between patients required to make daily clinic visits and patients cared for under less frequent clinic visits and (2) the association between frequency of required clinic visits and adherence depends on affordability and acceptability of care. Data were collected in facility exit interviews with 1200 TB patients in two rural and two urban sub-districts in South Africa. Additionally, 17 in-depth interviews were completed with TB patients. After controlling for socioeconomic and demographic factors, patient type (new or retreatment) and treatment duration, regression analyses showed that daily attending patients were over twice as likely to report a missed clinic visit ($P < 0.001$) or a missed dose of treatment ($P = 0.002$) compared with patients required to attend clinics for treatment collection less frequently. Missed visits increased with treatment duration ($P = 0.01$). The significant interaction between clinic visit frequency and treatment duration indicated that sustaining daily visits over time may become increasingly difficult over the course of treatment. The qualitative analysis identified treatment cost and duration, patients' physical condition and varying social contexts (family, community and work) as important influences on adherence. These findings suggest that strategies involving daily clinic visits may require reconsideration if resources for TB care are to be used efficiently. The adoption of approaches that place patient interests at the centre of TB treatment delivery would appear to be of high priority, particularly in countries where TB prevalence is high and resources for TB care are highly constrained.

Key words: Access; DOTS; equity; socio-economic status; South Africa; tuberculosis

> **Key Messages**
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> - Daily clinic attendance for tuberculosis (TB) treatment is associated with lower levels of patient adherence than alternative ways of delivering care.
> - The difference in levels of adherence by form of treatment delivery increases with treatment duration.
> - The design of care programmes must be responsive to patient needs given the particular characteristics and contexts of TB patient populations.

Introduction

Tuberculosis (TB) remains a major health problem in many low- and middle-income countries (WHO 2011). Although effective treatments are available, success depends crucially on adherence to a treatment regimen of daily drugs (WHO 2010). Given the infectious nature of the condition, attempts to control the level and spread of the disease depend on achieving high levels of adherence. To promote adherence among TB patients in resource-limited settings, a directly observed treatment short course (DOTS) was developed by the WHO in 1995 as the recommended strategy for TB control (WHO 1997). The strategy was originally developed as an alternative to inpatient treatment for TB and remains a standard form of service delivery in many jurisdictions. In some settings, the implementation of this strategy requires patients to attend the clinic on a daily basis where the provider observes the patient taking the drugs. This strategy simply shifts the adherence issue away from whether patients take the drug, to whether patients attend clinics to be observed taking the drug. Although the drug may be provided free 'at the point of delivery', the way the drug is delivered may impose additional costs on the patient and hence impact on access to care.

WHO has suggested that while direct observation may help ensure patients take the drugs regularly and complete treatment, supervision must be carried out in a context-specific and patient-sensitive manner. Depending on the local conditions, supervision may be undertaken at a health facility, in the workplace, in the community or at home. The WHO further argues that care should be taken to overcome patient access barriers (WHO and Stop TB Partnership 2006). 'The whole purpose of treatment observation would be defeated if it were to limit access to care, turn patients away from treatment, or add to their hardships' (WHO 2010 p. 77).

A systematic review of randomized control trials compared institutional-based DOTS, community-based DOTS and self administration of the drug without any direct observation by a third party (Volmink and Garner 2007). The authors reported that there was no quantitatively important advantage of DOTS, whether administered at an institution or in the community, over patient self administration in terms of either adherence or cure. Although some studies find higher levels of adherence under DOTS than under self administration (Juan *et al.* 2006; Kapella *et al.* 2009), these involve populations with low levels of TB and are based on non-experimental research designs limiting both the validity and applicability of the findings to high prevalence settings. In South African study patients undergoing retreatment for TB fared worse under DOTS than self administration (Zwarenstein *et al.* 1998). In contrast, a systematic review of qualitative studies of patient adherence identified the organization of treatment and care as an important determinant of adherence (Munro *et al.* 2007).

In South Africa, TB incidence increased by 400% in the past 15 years (SANAC 2011), although the number of deaths appears to be declining (StatsSA 2014). WHO estimates place South Africa third in the ranking of TB prevalence after India and China (WHO 2011).

Its incidence rate is 1 in 100 and it accounts for 17% of the global MDR-TB burden (WHO 2014). TB services, along with other services in the public health system are based on a decentralized model. The National Department of Health determines overall health policy direction with provincial departments being charged with implementation via the district health system, based on assessments of local populations and contexts. In many cases, implementation challenges on the ground lead to between-community differences in service delivery. In the case of TB, a National Tuberculosis Control Programme (NTCP) was developed in 1995 based on the WHO DOTS strategy and strategic plans were developed with implementation targets for the 2001–2005 (National Department of Health 2000) and 2007–2011 periods (National Department of Health 2007). The most recent treatment guidelines state that DOTS is recommended for all TB clients for the entire period of treatment (National Department of Health 2009). On the ground, this may mean that some communities follow a daily clinic-based DOTS approach, while others follow a more flexible approach with patients being required to attend the clinic either weekly or monthly to collect the supply of drugs. In these instances, community or workplace daily supervision should be provided depending on local implementation practice. This variation in service delivery provides an opportunity to study the impact of differences in programme delivery on overall adherence with drug consumption.

McIntyre *et al.* (2009) presented a conceptual framework in which access to care is represented by the degree of fit between the characteristics and contexts of individuals with health care needs and the way the service is provided. The framework identifies three separate dimensions of access; affordability (the ability to incur the costs of receiving care), availability (provision of care at times and in places that patients can attend) and acceptability (the provision of care in ways that meet the reasonable expectations of patients). Given the infectious nature of TB and increasing levels of drug-resistance (Singh *et al.* 2007), there is public interest in ensuring high levels of adherence. Hence attempts to promote equitable access to care and the efficient use of resources devoted to TB must be based on a broad understanding of barriers to utilization among individuals with needs for TB treatment. Requiring patients to attend clinics on a daily basis restricts the availability of supervision to institutional settings and is likely to reduce affordability by imposing substantial costs on patients in terms of time and transport costs as well as other aspects of opportunity costs (e.g. child care, cover for other normal daily activities). Daily attendance at clinics might therefore do more harm than good if the improvement in adherence in taking the drugs among those patients who can and do attend on a daily basis is more than offset by the number of patients who are unable or unwilling to attend each day.

In this article, we consider whether access to care, as measured by self-reported adherence, differs systematically between communities that differ in availability of supervision as measured by the frequency of clinic-based TB treatment delivery (daily observed treatment at

clinics, vs less frequent clinic visits for treatment collection), after controlling for other determinants of access to care. We then consider whether particular elements of the access framework impact differently on patients coming to the clinic on a daily basis as compared with patients who receive their medication through weekly or monthly clinic visits. In other words—do observed differences in adherence between different service models (i.e. different availability of supervision) correspond with differences in affordability and acceptability?

Materials and methods

In this study, we adopt a mixed method approach. Mixed methods are increasingly utilized as researchers build on the strengths and minimize the weaknesses of quantitative or qualitative research both in a single study and across studies (Johnson and Onwuegbuzie 2004). We used a sequential mixed method design with the quantitative aspects preceding the qualitative in data collection, although the research tools were developed at the same time. The quantitative and qualitative designs permit the collecting of multiple data using different strategies to obtain complementary data (Johnson and Turner 2003) and to ensure comprehensiveness and the triangulation of results (Creswell and Plano Clark 2006). For this to be effective, analytic procedures must be precise and well-articulated with data being reduced in both arms by conventional means (e.g. descriptive statistics, regression analysis, codes, themes) and using narrative to report some quantitative results and counts to report some qualitative ones (Onwuegbuzie and Teddlie 2003). Our results and discussion compare and integrate material from both designs. Such integration is a keystone of mixed methods but it must not be assumed that results are always confirmatory or complementarily (Bryman 2007; O'Cathain *et al.* 2007). In our discussion section, we examine our results for any inconsistencies or incongruities between the two arms (Wagner *et al.* 2012).

Quantitative methods
Sampling
Four health sub-districts in different provinces were selected as sites for this research, two urban (Mitchells Plain, Western Cape and Soweto Region D, Gauteng) and two rural (Bushbuckridge, Mpumalanga and Hlabisa, KwaZulu-Natal), to reflect different geographic locations (rural-urban mix) and to allow for differences in governance contexts. Key officials in the national and provincial health departments were consulted in finalizing the selection of sub-districts.

Two-stage sampling was used in each sub-district, first selecting a representative sample of primary health care facilities, then within these facilities, a representative sample of users. As most public health facilities provide TB services, a minimum of five facilities were selected in each sub-district with probability proportional to size (PPS) methods used to select facilities based on the total number of users in each facility. Within each chosen facility, a random sample of patients was interviewed until the proposed facility sample size was reached. A minimum of 300 patients were interviewed per sub-district; the planned sample size was therefore 1200 respondents. Respondents were included if they were over 18 years of age and had been on TB treatment for at least 8 weeks.

Data collection and capture
Patient questionnaires were developed to collect demographic and socioeconomic data as well as information on health service use, direct costs associated with health care and aspects of access to health care. The questionnaire was administered by trained interviewers in

the language of the respondent's choice on exit from the facility. All interviews were performed under conditions that provided patients with the security to disclose information i.e. a private room at the facility was used for all interviews with only the interviewer and subject present. Interviews were conducted after the completion of care at that visit and the interviewers were not members of the service provision team or otherwise connected to the treatment facility. Completed questionnaires were checked for accuracy by data collection coordinators within each site and double entered into a data entry platform specifically designed for this purpose in Epidata.

Data analysis
Data were analysed using Stata/IC 11.0. In addition to summary statistics, two series of regressions were computed. In all instances, regression models were developed through the inclusion of conceptually relevant variables, and Akaike's information criteria were used to choose the most parsimonious model.

Two separate sets of regressions were run. The first series of logistic regressions focussed on assessing the socioeconomic, demographic and service related characteristics associated with self-reported adherence to TB treatment, measured by self-reported missed clinic visits and self-reported missed treatment doses. Socioeconomic variables included employment, education and a composite asset index that allocated individuals to socioeconomic classes based on household characteristics (including type of house, walls, toilet facility, roof, water supply, electricity for cooking etc), and assets (including fridge, stove, DVD player, television, cellphone, bicycle etc). We constructed the index through a multiple correspondence analysis (MCA). Although the construction of asset indices is commonly achieved using principal components analysis (PCA) (Booysen *et al.* 2008), such a technique is more appropriate for use with continuous, normally distributed data as opposed to the predominantly categorical data often used in asset indices development (Howe *et al.* 2008).

Within a population of TB patients durations of treatment will vary. As a result, patients with longer durations of treatment have been at risk for non-adherence for longer. It is therefore important to control for duration of treatment. However, the impact of duration on adherence may differ systematically between the different forms of service delivery. For example, although patients might be able to accommodate visits to clinics in the short term, over longer periods these daily visits may be more difficult to sustain. However, this sustainability might be particularly problematic for daily patients because the amount of time (and hence other activities) that has to be replaced is much larger for them. Hence, we might expect the impact of duration of treatment on adherence to differ systematically between daily patients and non-daily patients. We therefore include duration of treatment as an independent variable and re-estimate the equation with the addition of an interaction term for frequency and duration of treatment to test for variation in adherence with duration of treatment.

If impact of duration on adherence is greater among daily clinic observed patients, this would suggest that moving away from clinic-based observation has the potential to improve adherence in the TB population in the short term but also in terms of being able to maintain adherence over the duration of the course of treatment.

Patient-related characteristics include age, sex and whether the patient was a new or re-treatment case. We controlled for rural/urban location given that access barriers, in particular the availability of care, are likely to differ systematically within these settings. Finally, we included a variable that summarized whether the patient was required to collect treatment from the clinic on a daily versus

less frequent (weekly or monthly) basis as an indicator of the availability of supervision.

In the second series of logistic and linear regressions, we further unpacked our findings to understand the affordability and acceptability access barriers associated with different treatment collection frequencies at clinics. In these models, affordability variables included: (1) monthly visit expenditure (including transport costs, and costs incurred while waiting at the clinic); (2) borrowing money to pay for health care costs during the preceding 1-month period; and (3) incurring health care costs in excess of 10% of household expenditure (as a measure of catastrophic expenditure). Acceptability variables included: (1) feeling that the queues in TB facilities were too long; (2) feeling disrespected by TB facility staff; and (3) feeling that the TB facility was dirty. In these regressions, we controlled for age, sex, the asset index, education, employment, urban/rural setting, duration on treatment and whether the patient was a new or retreatment TB case.

Because our interest in these analyses was on the impact of the frequency of tablet collection on adherence and access, we excluded re-treatment patients receiving daily streptomycin injections from our sample.

Qualitative methods
Sampling
The qualitative results draw on 17 in-depth interviews with patients on TB treatment in three out of four of the sites included in the quantitative phase. One of the rural sub-districts was excluded from the qualitative phase owing to research funding constraints. Patients were purposively selected to reflect a range of patient treatment experiences (i.e. patient treatment successful, re-treatment after failure or patient default, patient defaulting), as defined by the World Health Organization (WHO 2009). This required recruiting patients from within the facilities and outside in the community. Providers facilitated the recruitment of patients within the facilities while assistance was sought from non-governmental organizations offering TB services and patient networks for recruiting patients who were considered unsuccessful and defaulters.

Data collection and capture
Interview guides covered a range of issues exploring patient life history (i.e. social support systems, education, income, migration, work), illness trajectories (i.e. from illness onset to diagnosis and treatment, treatment seeking, stigma) and experiences with the health system (i.e. barriers constraining access and engagements with health care providers).The life and illness histories were told as narratives which linked, as the patient saw it, the role of TB and its treatment in everyday life.

Patients were interviewed in their first language by trained field workers. Follow-up interviews were conducted with seven of the patients for either clarification or exploration or both. Interviews were audio-taped, transcribed and translated into English. All patients were assigned pseudonyms to protect confidentiality.

Data analysis
The transcripts were thematically coded in ATLAS ti.6 by two members of the research team working independently. Transcripts were read and re-read with an initial set of codes being identified, from which emerged several major themes such as transport costs and dependency on family members and friends. The researchers then compared the similarities and divergences between their codes and themes to ensure reliability. These codes and themes were then

shared with the larger group who assessed the salience of the codes and quotations given the research questions for this paper. Any suggested modifications were discussed and consensus was reached on themes and quotations. The larger themes were grouped into four central themes; (1) location and distance of facilities, (2) transport costs, (3) dependency on family members and friends and (4) conflict between treatment, work and domestic responsibilities. Presented quotations were selected not only for vividness and descriptions of the illness trajectory but to give voice to as many respondents as possible.

Results

Quantitative findings
Table 1 summarizes the characteristics of TB patients in our sample. Because the sample is based on patients attending primary care facilities, patients with high severity are unlikely to have been included, as they would be treated at secondary care facilities. After excluding patients receiving daily streptomycin injections, the overall sample included 1190 individuals, of whom 13% and 14% reported missing clinic visits and missing treatment doses respectively. In total, 32% of all patients received their treatment through daily clinic observation; but 66% of patients reporting missed visits and 56% of patients reporting missed tablets were from this treatment group. Just over 80% of the sample constituted new (as opposed to retreatment) patients, of whom 64 and 70% reported missing clinic visits and treatment doses. Average duration of treatment was longer among those reporting missing visits and doses. Wealthier respondents had a higher prevalence of non adherence than the poorer group.

Table 2 presents data on the reported frequency of visits by type of programme (DOTS or others). Almost all DOTS patients visited the clinic five times per week. Among every 10 non-DOTS patients, seven visited the clinic once per month with another two visiting once per week (the most frequent among non-DOTS patients). DOTS patients had on average been on treatment slightly longer

Table 1. Characteristics of TB users, in total and by self-reported adherence measures

Variables:	All respondents ($n = 1190$)	Respondents reporting missed visits ($n = 156$; 13%)	Respondents reporting missed oses ($n = -172$; 14%)
Age (median, years)	35.00	32.00	33.00
Male sex	47.23%	48.72%	48.84%
Employed	16.48%	21.79%	19.19%
Asset index (wealthier)	50.34%	61.54%	60.47%
Urban setting	50.76%	82.69%	74.42%
None or basic education	37.51%	33.55%	33.92%
Some secondary education	42.72%	49.68%	47.37%
Completed secondary education	19.76%	16.78%	18.71%
Clinic DOT	32.15%	65.58%	56.40%
New patient (vs re-treatment)	80.07%	64.47%	70.00%
Duration on treatment (median, months)	4.00	5.00	5.00

Clinic DOT, daily observed therapy at clinics.

than non-DOTS patients (5 months when compared with 4.5 months).

Table 3 presents the adjusted odds ratios (AOR) for the dependent variables based on the estimated coefficients in the logistic regressions for missed visits and missed doses. Controlling for socioeconomic and demographic factors, as well as for patient type (new or retreatment) and duration of treatment, frequency of treatment collection is highly significant with daily patients being 2.5 times as likely to report a missed clinic visit ($P < 0.001$) and over twice as likely to report a missed treatment dose ($P = 0.002$) compared with patients with less frequent treatment collection. Re-treatment patients were significantly more likely to have missed visits ($P = 0.003$) and missed doses ($P = 0.031$). Patients in urban settings were significantly more likely to report missing visits and missing doses even after allowing for differences in mode of delivery.

The logistic regressions were re-estimated with interaction terms for frequency and duration of treatment (results not presented here but available from authors). The adjusted odds ratio for the interaction term exceeded 1 for both missed visits and missed doses but was significant only for missed visits ($P = 0.01$). This suggests that the problem of missed visits increases with duration of treatment. Daily treatment observation at clinics might appear to be a successful strategy for ensuring adherence among patients at the start of treatment but less so among patients further along the treatment episode. This is consistent with the hypothesis that daily visits are difficult to sustain over a period of time. That there is not the same level of non-adherence in longer duration for non-daily patients would seem to imply that patients accept the importance of completing the course of treatment but their capacity to do so is compromised by the higher costs to the patient of daily visits.

Table 4 reports summary statistics and adjusted odds ratios (or in the case of mean expenditure on clinic visits, the estimated coefficient) for the three affordability variables and three acceptability variables. Regressions were run controlling for all the factors included in the adherence equations. Each of the factors is found to be greater among daily patients than non-daily patients with all but having to borrow to pay for health care being statistically significant. This suggests that the prevalence of affordability and acceptability barriers to care are significantly greater among daily patients.

Qualitative findings

The qualitative findings were derived from 17 participants with ages from 23 to 53 years; 7 women and 10 men. Six were 'successful' (i.e. cured or completed treatment). All participants were unemployed, except for one who worked part-time in the informal sector. In such circumstances, access to social grants may provide an important source of income. Four participants received a Disability Grant, three received a Child Support Grant and one participant received both grants. Another reported he was intending to apply for a Disability Grant. In the absence of these social grants, most participants depended on their spouses, parents and siblings for assistance.

Location and distance from facilities

The affordability of travelling daily to the facility is a challenge in a context of widespread unemployment. For many patients, this means walking to the facility. People with TB often suffer severe weight loss and physical malaise and they often speak of how physically demanding travelling by foot to receive their treatment is:

> I won't be able to make it to the clinic every day. But I don't have a choice I must come ... That is about forty five minutes ... Like today if I feel it is not near, it is a distance. And at first they told me she [DOTS supporter] will be there at three o' clock and I went there three o' clock and they told me no after six. And I came back to the clinic because I did not get my pills. I had to wait for strength ... they [clinic staff] said ... she will be there at seven o' clock in the evening because she is working. I can't make it, it is dark that time and it is far and there is no way I can go there .... <u>I walk more than an hour where normally it took me an half an hour to get here in the past. Every time I have to sit on the pavement to catch my breath and the pain in the chest.</u>

Table 2. Frequency of attendance and duration of treatment by patient type

	DOTS ($n = 382$)	Other ($n = 806$)
Frequency of clinic attendance		
Five times per week	380 (99.5%)	
Three times per week	2 (0.5%)	
Once per week		166 (20.6%)
Every second week		54 (6.7%)
Monthly		585 (72.6%)
Every 2 months		1 (0.1%)
Mean (IQR) duration on treatment in months	4.45 (3.00–5.00)	5.09 (3.00–6.00)

Table 3. Regression results for determinants of missed visits and missed doses

	Missed visits			Missed doses		
	AOR	95% CI	*P*-value	AOR	95% CI	*P*-value
Variables:						
Age	0.97	(0.95–0.99)	0.006	0.97	(0.96–0.99)	0.005
Male sex (versus female)	1.12	(0.76–1.65)	0.560	1.10	(0.77–1.58)	0.597
Employed (versus unemployed)	1.32	(0.82–2.10)	0.257	1.10	(0.70–1.72)	0.677
Asset index (wealthier versus poorer)	1.00	(0.65–1.56)	0.991	1.14	(0.76–1.71)	0.533
Urban (vs rural) setting	3.85	(1.99–7.44)	0.000	2.00	(1.16–3.45)	0.012
Education:						
Some secondary (vs basic or none)	0.98	(0.61–1.56)	0.930	0.94	(0.61–1.44)	0.760
Completed secondary (vs basic or none)	0.65	(0.35–1.22)	0.183	0.71	(0.41–1.25)	0.238
Clinic DOT vs other	2.54	(1.57–4.12)	0.000	2.08	(1.32–3.26)	0.002
New (vs re-treatment) patient	0.53	(0.35–0.81)	0.003	0.64	(0.43–0.96)	0.031
Duration on treatment	1.05	(1.01–1.09)	0.008	1.03	(1.00–1.07)	0.086

AOR, adjusted odds ratio; CI, confidence interval; Clinic DOT, daily observed therapy at clinics.

Table 4. Access barriers by treatment collection frequency, and regression results for access associations

Outcome variables:	Descriptive statistics			Regression	
	All respondents	Respondents on clinic DOT	Other	AOR[a]	*P*-value
Monthly direct visit expenditure (mean ZAR)	39.16	71.50	23.83	0.78	<0.001
Borrowing to pay for health care (%)	18.77	10.99	22.46	1.82	0.057
Incurring health care expenditure > 10% household expenditure (%)	32.85	32.47	33.04	5.02	<0.001
Feel that queues are too long (%)	28.14	34.91	24.94	3.32	<0.001
Feel disrespected by facility staff (%)	18.89	17.28	19.65	2.44	0.001
Feel that facilities are dirty (%)	11.97	12.07	11.93	2.68	0.002

Regressions are run controlling for age, sex, asset index, education, employment, urban/rural setting, duration on treatment, and whether a new or re-treatment TB case; given the skewed nature of cost data, monthly direct visit expenditure was logged prior to running the linear regression.

Clinic DOT, daily observed therapy at clinics.

[a]Adjusted odds ratio except for monthly direct visit expenditure for which it is the estimated regression coefficient.

(emphasis added)...I only get my three pills then I have to walk back home. Mark, urban site

I took the small taxi, like when I was serious [too ill to walk]... and when I was walking, there must be someone standing next to me because I did not have balance to stand alone (emphasis added). Mathew, urban site

Transport costs

For those unable to walk to the facilities for reasons of poor physical health, access to affordable transport was essential. In the absence of it, patients spoke of being unable to seek daily treatment from the health facility with implications for treatment adherence:

It was difficult for me because when coming to the clinic, I have to use the little amount that I have and it costs me R26.00 to come and return... sometimes I don't have money to come to the clinic. Mdiduzi, rural site

Me, I stayed away too many days... because I can't make it every day... if I had taxi fare, then I would have come here to the clinic... some of them [other patients] live around the corner and I live far. I can't walk every day. Mark, urban site

Dependency on family and friends

The location of the clinics in relation to where patients live might not only limit physical access for TB patients but also indirectly require access to transport. In a context of poverty, high unemployment and dependency on social grants, patients often speak of having to depend on family members and friends to either transport them to the facilities or provide them with the means to pay for it:

My wife gave the money because some of her customers paid her. [Without her money]. . . I would not come because [it] is too far from my place up to here. Mdiduzi, rural site

I borrowed money [for taxi fare]... I asked him R30.00 to buy me something to eat as well because you get hungry there because you sit long. Cintle, urban site

Conflict between treatment, work and domestic responsibilities

Besides the implications for transport costs, daily visits to the facility also carry significant opportunity costs of time, particularly for those who are working. Patients face a dilemma between work and treatment and this is often in the context of patients who are the head of households:

I must work because there at home, there is nothing [food]. I can't come here every day. What is my child going to eat and she is going to school? Mathew, urban site

Yes, I didn't have money. There was no food in the house because those tablets, you can't take them without food in the stomach. I tried to borrow some money from someone to sell some cheap stuff at home, so that I can eat because even my children were not working. They were looking to me to bring food on the table. That is why I look like someone who is taking treatment wrongly [defaulting treatment]. Then, after I sold those things, then I saw the profit; there was food in the house. Then I always came in here... always. So when I started having some money, I always came to the clinic always. Jama, urban site

Jama's reference to '*taking treatment wrongly*' also speaks to her concern that she is being judged and unfairly labelled as a defaulter when in fact there are factors beyond her control which constrain her ability to adhere to the recommended treatment.

Having to wait at the clinic also entails opportunity costs for patients:

Say we went to the clinic eight o'clock and we sat there till one o'clock and still waiting for this sister... they are negligent. They let you sit long. Funeka, urban site

Discussion

The development of the DOTS approach to TB treatment was based on avoiding unnecessary hospitalization of TB patients. Treating patients in their communities can reduce system costs, release hospital beds for other uses and allow individuals to return to normal activities. However, the requirement for daily observation clinics imposes substantial costs on individuals which reduce adherence. Daily observation need not require clinic visits, with South African treatment guidelines allowing community health workers, workplace supervisors or family members to be observers (National Department of Health 2009). In this study, particular locations retained drug supplies at the clinic and required patients to attend the clinic for daily doses to be received and observed. Hence our study population could be divided between those on programmes that required daily clinic visits to receive the dose and those that did not.

Expanding on Volmink and Garner's (2007) review and adding to Zwarenstein's (1998) findings, we identify a clear association between mode of delivery (or availability of supervision) and levels of self-reported adherence. This association appeared to correspond to the distribution of affordability and acceptability factors in the study

population. Adherence does not appear to suffer in patients that are not required to make daily clinic visits but the burden of treatment on these patients is lower. Daily visits impose substantial burdens on the patients and their families as well as on the health care system in terms of human resource requirements. Our mixed method design allowed for the explicit emergence of these burdens, especially on patients, highlighting not only cost and duration of treatment but also the importance of the physical condition of the patient and the role of varying contexts (family, community and work). The qualitative phase thus largely confirms the quantitative one but also enhances its explanatory strength with respect to the nature of the contexts affecting adherence.

It is worth noting that in most cases the 'daily' patients were provided with sufficient drugs to last for a weekend and hence daily directly observed treatment became 'working day' observed treatment. Providers trusted patients to adhere to treatment over the weekend (when providers may not have the time or inclination to observe treatment), but not during the normal work week. Redesign of the service in this way may have more to do with satisfying the demands of providers than improving adherence among patients.

Improving adherence might therefore benefit from a more patient-focused approach to TB treatment. For example, Macq *et al.* (2003) argue that DOTS use should be part of a complex set of interventions for TB treatment that is responsive to patient contexts. Orr (2011) studied adherence to TB treatment in Canadian aboriginal populations and concluded that the design of care programmes must be responsive to patient needs given the particular characteristics of these populations. In many aboriginal communities, adults may be absent from their normal community for substantial periods of time, undermining any attempt to improve compliance through a DOTS approach.

Our analysis is limited to a dichotomous measure of adherence—the prevalence of any missed clinic visits (or missed treatment doses). Hence we are not able to address questions of different levels of non-adherence (the number of missed visits or treatment doses). However that reflects the policy concern with achieving full (as opposed to improve) adherence. Moreover, adherence is measured using self reports of missed clinic visits and treatment doses which will be subject to reporting, recall and interviewer bias that may have underestimated the level of non-adherence. However, there is no reason to believe that such biases would be systematically associated with the treatment modality.

A second limitation is the cross-sectional design and the implications that has for the interpretation of the results. In particular, it limits the study to observations of differences between populations without allowing us to make any statements about the impact of changing the organization of care on adherence within communities. Moreover we cannot rule out the possibility of reverse causality, i.e. that those less likely to adhere to treatment and more likely to be required to make daily visits, as would be the case if providers had some a priori knowledge of patients' expected adherence. Such conclusions would require longitudinal data collection over a period in which care delivery changed. Moreover given the limited range of data collected, the cause of differences in adherence may not be limited to the availability of supervision. For example the analysis did not control for substance abuse or alcohol consumption. Nor did we have information on reasons for treatment failure among individuals being retreated. Clearly the availability of supervision under different models of care is just one, albeit important, potential cause of adherence problems. We do not suggest that decreasing clinic visit frequency would eliminate all adherence problems.

A further limitation involves the absence of information on health status, meaning we cannot determine whether differences in adherence are associated with different outcomes. However, the systematic review does suggest that differences in adherence between treatment modalities are reflected in differences in outcomes (Volmink and Garner 2007). Moreover our study was based on subjects attending for care at primary health care facilities that met our inclusion criteria. As a result, patients with severe and drug resistant forms of TB are unlikely to have been part of our study population, although for some subjects their condition may have become more severe, and require care at secondary care facilities after their interviews. Our findings are therefore limited to patient populations attending primary care facilities.

Finally, there may be selection bias in the choice of visit frequency. Providers may use their assessment of patient adherence to taking the medication in deciding visit frequency with the less adherent being required to visit facilities on a daily basis. If this is the case, our analysis would overestimate the association between treatment modality and non-adherence because of the non random distribution of patients between modalities. However the association with treatment modality is even greater for self reported missed visits indicating that irrespective of any patient selection based on provider assessment of patient adherence, the use of daily visits is not associated with a higher level of adherence. But further research should account for these possible provider preferences.

Notwithstanding these limitations, our findings suggest that consideration be given to whether daily clinic visits represent an efficient use of resources for TB patient care. If observation of drug taking is needed, it does not require clinical expertise and would be manageable through means that do not involve daily clinic visits. Furthermore a recent meta-analysis showed that DOTS did no better than self-administration in reducing adverse clinical outcomes (see Pasipanodya and Gumbo 2013). Hence the importance of adopting a more patient focussed approach to TB care would appear to be of high priority, which would include discussing options for monitoring adherence with patients in the context of the patients own characteristics and circumstances (see Fried *et al.* 2015), particularly in countries where TB prevalence is high and resources for TB care are highly constrained.

Ethical issues

Ethical approval for the study was granted by committees at the University of Cape Town, the University of the Witwatersrand and the University of KwaZulu-Natal. Permission from health department officials and individual facility managers was obtained to conduct the study in the selected facilities. Written informed consent to participate in the study was obtained from each participant; participants were only interviewed if they were over 18 years of age.

Conflicts of Interest: None declared.

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