National Tuberculosis Control Programmes of Nepal and India

Are They Using the Correct Treatment Regimens?

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Abstract: *The paper examines and compares TB drug regimens and the reactions to them in the context of Nepal and India. This is done from the perspective of an attempt to understand the market and other forces driving the sales of TB drugs. The majority of TB patients receive their treatment outside the public sector. The authors argue that while the scientific evidence may be equivocal over the efficacy of the national DOTS regimens, policy decisions should be made in the light of this local context. Secondly, they examine the reaction to the prescribed national regimens from practitioners in the private sector in Nepal and India. Although the regimen decisions were made in part because of cost implications, the very choice of the regimens themselves has hampered efforts to 'integrate' the non-public sector into an overall attempt to control tuberculosis.*

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I
Introduction

With the advent of streptomycin in the 1940s, the management and treatment of tuberculosis has been primarily focused on drug interventions. As therapeutic agents have been developed for TB treatment, the history of research and development into how best to treat the condition has focused primarily on two sets of issues: what combination of drugs taken over what period of time can achieve the best chance of cure, and how can the emergence and prevention of drug resistance be managed [Toman 2004a]. Currently, there is a range of anti-tubercular pharmaceutical agents available on the markets. 'First line drugs' are used for the treatment of non-drug resistant tuberculosis, and 'second line drugs' for the treatment of drug resistant tuberculosis (MDR-TB).[2] Unfortunately the so-called 'short-course regimens' – developed after rifampicin entered the market after the late 1960s - still require at least six months of treatment. Existing understanding and best practice is that therapy is divided into two phases: An initial 'intensive phase'

– lasting usually 2-3 months, and involving combinations of three to four drugs – and a 'continuation phase', in which two drugs are given for a further 4-6 months [Toman 2004b]. Trials have shown that at least two so-called 'bactericidal' drugs are required in the initial phase (either rifampicin and isoniazid, or streptomycin and isoniazid), and that the combination with pyrazinamide in this phase shortens treatment from 9 to 6 months. The intensive phase is said to kill the 'actively growing and semi-dormant bacilli', and 'the continuation phase eliminates most residual bacilli and reduces failures and relapses' [Harries 2004: 124]

Since the 1990s, both India and Nepal have adopted the WHO-advocated TB control strategy, Directly Observed Therapy, short-course (DOTS). This strategy emphasises case-finding activities using smear microscopy of suspects, and then the administration of a short course therapy regimen under 'direct observation' by those responsible to the health system.[3] In the context of Nepal and India, however, the short-course regimen chosen for the DOTS programme differed: India introduced an intermittent regimen (one administered three times per week, rather than daily); and Nepal has a longer continuation phase of treatment but without rifampicin. While these technical decisions were made by small groups of national and international experts, they were controversial. In both cases widespread resistance to the choice of the regimen hindered the uptake of the DOTS programme.

In this paper we examine and compare these regimens and the reactions to them in the context of Nepal and India. We do so from the perspective of an attempt to understand the market and other forces driving the sales of TB drugs, which we address in the first section. The majority of TB patients receive their treatment outside the public sector. We argue that while the scientific evidence may be equivocal over the efficacy of the national DOTS regimens, policy decisions should be made in the light of this local context. Secondly, we examine the reaction to the prescribed national regimens from practitioners in the private sector in Nepal and India. Although the regimen decisions were made in part because of cost implications, the very choice of the regimens themselves has hampered efforts to 'integrate' the non-public sector into an overall attempt to control tuberculosis.

The data for this article comes from the project 'Tracing Pharmaceuticals in South Asia'.[4] In this we mapped patterns of production, distribution, marketing and retail of three key generic drugs (oxytocin, rifampicin and fluoxetine) in three regions of South Asia (Nepal, West Bengal [WB] and Uttar Pradesh [UP]). We drew on qualitative data using semi-structured interviews, in particular with producers, medical representatives, pharmacists (including distributors and retailers), and providers (including qualified and unqualified prescribers). Topics included questions about the everyday working practices of the interviewees, with specific questions about our focus drugs, here rifampicin and

other associated TB drugs. We asked about sub-standard and counterfeit medicines; patterns of supply; prescriptions by certified and non-certified medical practitioners; and over-the-counter sales by pharmacists. Since each of the drugs is inserted in different ways into national and international health programmes, and drug procurement procedures differ widely, we also interviewed donor agencies and health activists about how they saw the problems posed by the supply chains, distribution and consumption patterns of each of the three drugs. Over 80 percent of the interviews were recorded, transcribed and (where necessary) translated into English by the research assistants. In each site we also took whatever opportunities were presented to observe interactions among key members of the field: providers with clients and medical representatives, for example. All unrecorded interviews, and any observation material, were noted down (either at the time or immediately after) and typed up in as much detail as possible as soon as we were able to reach a computer. Because of the roles played by global donors in TB control, we made special studies of the documents on the national TB programmes in India and Nepal in order to investigate linkages between international organisations and donors, and national governments and health systems, as well as how these national programmes interact with the pharmaceutical commodity chains we identified.

II
Understanding TB drug Mmarkets in India and Nepal

A recent evaluation of the current drug market in India values the Indian TB drug market at USD 94m, with 74 per cent contained within the private sector.[5] The report suggests that this market is mainly for first line drugs, with only 9 per cent for second line, and that the value of this market was driven mainly by the availability of Fixed Dose Combinations (FDCs). For example, a review of CIMS in March 2007 revealed 36 companies in India producing Rifampicin products; 19 in uncombined form and with the range of combined drugs as follows; 34 in combination with isoniazid; 12 with isoniazid and ethambutol; 19 with isoniazid and pyrazinamide; and 19 with the four drugs combined. When we combined the data from CIMS, IDR and MedCLIK the total number of producers marketing a range of single and combined drugs went up to 52 (though in several cases, a single firm – such as Cadila and Wockhardt – markets drugs under two or even three names). The seven companies listed by IMS with the highest sales figures in 2006 were: Lupin Labs. (45.4 per cent) Macleods Pharma (19.7 per cent), Novartis (6.5 per cent), Shreya Lifescience (4.9 per cent), Cadila Pharma (4.7 per cent), Concept Pharma (4.5 per cent), Wockhardt (2.5 per cent). Each produces a different range of FDCs that feed into this intensely competitive local market.[6] Characterized as 'therapeutic anarchy' by one WHO official we interviewed, this wide range of therapeutic combinations from such an array of companies – many of unknown quality – is one of

the major obstacles to controlling TB as a public health problem, and is a major concern for the rise of MDR-TB.

The quality of drugs, and particularly FDCs, is a problem. One survey (including drugs from India) showed that 10 per cent of samples contained less the 85 per cent of their stated content, with more FDCs than single formulations being substandard [Laserson et. al 2001]. It has also been reported in India that only 55 per cent of doctors in one survey prescribed regimens that conformed to the NTP/WHO recommendations (Prasad et. al 2002). In 1998 this had been even fewer at 29.4 per cent, and that 'as many as 102 different drug regimens were being prescribed by 187 PPs' [Singla et al 1998: 387]. Faults in the duration of treatment and drug dosage were also reported (Uplekar et al 1991; Singla et al 1998). In addition, faulty dosages of rifampicin prescribed by practitioners did not take into account weight variations of patients [Prasad et al 2002]. Cost is also important, with patients frequently being over-treated and spending up to five or six times the costs required to achieve cure [Arora et al 2003]. Delays in the recognition of TB also increase costs with delays of referral into the public system (Rajeswari et al 2002). Most of these studies pre-date the WHO recommendation that FDCs should be used routinely in TB treatment, and so this might have shifted in the intervening years. Several RMPs and private doctors interviewed in our project said that they prescribe the brands – AKT (Lupin) and Forecox (MacLeods), for example – and thus it seems not unreasonable to assume that they are less likely to make a mistake with the regimen combination itself.

Almost everyone involved in the provision of DOTS and public TB services we interviewed saw the uncontrolled availability of TB drugs and the 'private sector' as a major, perhaps even the major, difficulty in the control of tuberculosis. A DOTS Programme Officer in Uttar Pradesh assumed that 60-70 per cent of resistance was due to 'barefoot doctors' or quacks, and their misuse of rifampicin, and the giving of incorrect combinations. While he reckoned that some of the bigger companies (like Ranbaxy, Lupin, Macleods, Cadila) behave 'ethically' by visiting only doctors, it is the bare foot doctors that 'know the public pulse'. A local chest physician and RNTCP supervisor also agreed that most treatment of TB patients went on in the private sector and that there were multiple different regimens prescribed, many very poor. Both men linked this directly with the promotion practices of the company Medical Representatives (MRs), feeling strongly that the only way to deal with this was to centralise treatment policies and regimens. In their opinion, the commercial interests of the doctors remain the biggest problem.

In Lucknow, a chest specialist also perceived village doctors and their 'cocktail regimens' that clients stop after a few weeks as an issue. A Lucknow pulmonologist also pointed to the poor quality of rifampicin on the market, arguing that smaller, less well

known companies have bioavailability problems with their combinations. He himself writes the brand names of the bigger companies – Lupin, Macleods, Cadila – to avoid these problems. Similarly the superintendent of a TB Hospital in Delhi, who worked as a State TB Officer in the past, felt that (along with poorly run TB programmes), private physicians and the poor regimens they prescribe were most important cause of the rise of MDR-TB. Third on his list were the patients, as they can be irregular in taking drugs and side effects are an issue as well, he explained. In Kolkata, we were told by the director of a State TB control centre that the private practitioners see the DOTS programme as competition.

The forces that drive this growth in the market in its current form – the increased use of numerous and varied combinations – is linked to several factors from the international, national and more local arenas. Interviews conducted with marketers working with Lupin and other TB drug producing companies allowed us to begin to paint a picture of the forces at work in the production of this 'anarchy'. It is to this we turn to next.

Firstly, the WHO and the International Union Against Tuberculosis and Lung Disease (IUATLD) currently promote the use of FDCs as a means of reducing monotherapy and decreasing the risks of developing drug resistance. This they have been doing since 1994, and with renewed vigour since 1998 (WHO 2002b). The 4-dose FDC was added to the WHO essential drug list in 2002 (WHO 2002c). WHO suggests that their use also decreases the risk of mal-prescribing and means that fewer tablets have to be taken at one time by the patients. This advocating for the use of FDCs has accompanied the increasing use of the Global Drug Facility (GDF) for many countries procuring their DOTS programme drugs. Companies such as Lupin and Macleods strive for these lucrative GDF contracts, and this has had an effect on the promotion of FDCs over and above single dose drugs.[8]

Secondly, a more local explanation for the rise of FDCs is that rifampicin and the single first line drugs are price-controlled by the Government of India. Changing the various drug combinations is a mechanism for avoiding this.

Thirdly, companies also respond to pragmatic prescriber forces. One Medical Representative (MR) working for Lupin explained that the range of TB products they produce was a direct response to the changing patterns of how medical practitioners prescribe. He went on to explain the different dosages in tablets and how these are prescribed as per the weight of the patient. Further, he explained how different combinations of single tablets are prescribed for differing 'sets of patients' based on their capacity to understand the importance of the length of treatment, and their awareness of the issues and thus to prevent the growth of MDR. Part of the MR's job is to survey the prescribing habits of the doctors. The availability of a range of combinations and dosages is rationalized as a factor of the difference between individual patients, and the doctors needs to respond to these:

> "'Suppose, a person comes from the village, he will not have the awareness as to how he is supposed to take all the four medicines. For him, the doctor will write in fixed dose combination. It will be easier, just two tablets daily he has to take. If a patient goes who is well aware and informed, he will be given AKT4. So it differs from patient to patient. So every doctor writes all the drugs. So a big doctor of chest TB will write all the drugs, individual drugs, fixed dose, AKT4."'

An MR can meet up to 200 doctors per month, and the prescribing habits of these doctors are fed up the Lupin chain of command, to the area managers, and then to the product management team who has oversight of the trends across the whole country and abroad. The MR explained that Lupin must be reactive. Promotion of these products responds to what the doctors do, and this is monitored through the chemists' surveys.

The larger companies also have a concern for patient convenience, linked to a concern for the vexed question of patient adherence to treatment. Thus a marketing manager from West Bengal told us why AKT4 is in strips, and how these are created so the patient *has* to buy all the drugs necessary for treatment and not just single drugs that they can afford. He emphasised the importance of the strip: it is cheap, and the patient can carry all the drugs 'in his pocket'. Another MR suggested that their marketing is always conducted within the parameters set by the WHO. They encourage this in the doctors he meets, he said, but within this the product promotion depends on the individual prescribing behaviour of that doctor, and the company decides what gifts can be presented. From a pragmatic perspective, then, the wider the range of products and combinations that you have then the more likely that you are able to dominate the market.

In Nepal, too, interviews indicated how markets were conceived of in this way. So an employee of Concept in Nepal explained that their Rifa-i-6 product is unique because it has pyridoxine (vitamin B 6) added to the rifampicin and isoniazid, unlike other companies' products. A Lupin MR in Kathmandu will try to talk the doctors out of using Macleods' FDC products. As AKT4 comes in a combi-pack, and each tablet can be removed separately, then this allows the rifampicin to be taken before breakfast. He claimed that the bioavailability of the Macleods' rifampicin is reduced in their FDCs.

An ex-State TB officer in Delhi explained that FDCs are good for compliance, and different combinations are made to reflect the different weights and needs of patients. Companies, he suggested, are concerned with patient management issues and responsive to these, and to the question of compliance, but just the sheer numbers make it so complicated. A WHO advisor in India also reckoned that the number of FDCs on the market was an issue of different dosages for different weights of patients, although he too was confused about the reasons for the huge numbers available on the market. For him, the remaining problem was one of quality assurance and this is why the RNTCP needs to procure drugs centrally. A private doctor in Kolkata said that the problem with 50 or so companies pushing their combinations in the private market place is that it is very difficult to know if the information that the companies give is valid or not. His advice was to stick with the well-known brands, those of Novartis, Lupin and Macleods.

Now we can begin to understand why there are so many FDCs on the market, as companies respond to the prescribing habits of the doctors, keep an eye on the WHO recommendations, and advertise their differences. But the national programmes and the

regimen prescribed through the DOTS programmes in India and in Nepal also have their effects. We begin with the case of India.

The Indian Scenario: Intermittent vs Daily Rregimens and the Iissue of Direct Observation

India launched its Revised National TB Control Programme (RNTCP) from 1997. The DOTS programme was rolled out between 1997 and 2005; latterly the expanded STOP TB programme was adopted. The regimen for the national programme is currently divided into three categories, each one intermittent.

1216:0:.1. Category One, for those with smear positive disease, and serious patients, involves Isoniazid (H), Rifampicin (R), Ethambutol (E), Pyrazinamide (Z) three times a week for two months, followed by Isoniazid (H) & Rifampicin (R) three times a week for a further four months.

1432:0:.2. Category Two, for treatment 'failures', 'relapse' and treatment after 'default', has Streptomycin (S) added for the first two months, then the 4 drugs for a month followed by HRE for a further five months.

1648:0:.3. Category Three (less serious non-infectious disease), has HRZ for two months and then HR for four months.

These are provided in 'patient-wise boxes', not as FDCs. These sturdy boxes are marked with the patient's name, and have bags in them (coloured differently for each category of treatment), which contain the blister packs for an entire course for one patient, the intensive phase and the continuation phase separately. For both phases pyridoxine has been added as 'filler' for the days when the TB drugs are not taken. Direct observation has also been decreased to once per week for the continuation phase rather than daily when the TB drugs have to be taken in the IP.

The rationale for intermittent therapy is linked to the presupposition that direct observation is mandatory, and that it is easier to be observed three times a week than on a daily basis. In the Q & A section on the RNTCP website we find:

> 'What is the basis for supervised, intermittent therapy?
> Various studies have shown that during domiciliary treatment, when patients have to take drugs for a prolonged period, there are a large amount of concealed irregularities. Regular clinic attendance does not translate into regular treatment. Non adherence to treatment is a universal human trait and can only be overcome by establishing a human bond between the patient and provider. Daily supervision of treatment is not logistically feasible in India. In vitro experiments have demonstrated that after a culture of mycobacterium tuberculosis is exposed to anti tuberculosis drugs for a period of time, it takes several days (the LAG PERIOD) before renewed growth of bacteria occurs. Other than thiacetazone, all other drugs exhibit this lag phenomenon and can be used for intermittent therapy'. [11]

One WHO advisor argued that the Indian TB programme had attained 86 per cent success using intermittent therapy. The Indian programme had been against the idea

of FDCs, he said, and anyway they have as good treatment success as those that use FDCs. He saw the reasons with 'defaulters' as much more complex than problems with ensuring patient compliance – these problems might include cultural issues or operational issues, he argued, rather than the regimen itself. In other words, the failure levels in the intermittent regimen were not worse than in the daily regimen. He remained unconvinced by the trials that suggest that intermittent therapy has worse outcomes. Similarly an ex-State TB Officer for Delhi argued that the outcomes are good for the IR, although it is even more important to observe the patient directly. Although FDCs are not used in the programme, he stated that their packs are dose-related, and have a longer shelf life. As they are singly swallowed, there is less of a problem about the absorption of rifampicin. The director of the state TB control centre and a WHO advisor in Kolkata assured us that the IR is based on 'science' and that it is very important to persuade others of this fact. The problem lies with default, but surely, they rationalized, it is better to be directly observed three times per week rather than daily? Another government doctor agreed, and said that the choice of the IR was a local Indian concern, and based on the direct observation issue. They added pyridoxine, he said, so that patients can say 'I am taking TB drugs every day of the week', and this is what they think. He feels that supervisors who give patients their medicines for a month at a time should be punished.

What evidence is there for this use of IR as the national regimen? In a review of the existing evidence Tom Freiden, the WHO TB officer in India when it was introduced, and a passionate defender of DOTS, justifies its use scientifically (Freiden 2004). He suggests that experiments in animal models even show an increase in efficacy using intermittent HRZ, and – speculatively – that it is 'perhaps slightly more effective than the daily regimen' (ibid. 132). A 2005 Cochrane review is more circumspect, arguing that there is no evidence to support assertions that intermittent regimens are better than daily ones, and calling for more research. A recent review of the evidence suggests that the relapse rate for IR in India is not known, as the data are not systematically followed up (Bhargava & Jain 2008). These authors argue that further evidence, since the publication of the Cochrane review, points to a significant advantage to daily therapy over IR. Our point here, however, is not to argue over the evidence base for its use – which remains equivocal - but to point to broader, local and pragmatic issues which may be more important than the 'science'.

Firstly, the use of intermittent therapy has increased the anxiety over direct observation of treatment. As a Lupin representative we interviewed argued, effectiveness is not at stake should every dose be taken, but if a dose is missed with the intermittent regimen you are in effect missing three doses. This fact of the intermittent dosage schedule explains why the government regimen needs to be observed, contra to the daily regimen for which observation is not necessary, he said. For this reason he – as did others –

saw the regimen as less effective. In his opinion, the rationale for the choice of the intermittent regimen was cost, decided by certain 'agencies'. The problem lies solely in the programme itself and its rigid structures of observation. How is it possible, he said, to have volunteers across India observing all these TB patients take their drugs? Not unreasonably, he asks:

> 'Because you are not getting your entire medicine in one go, you will have to go to the DOT centre, take your medicine, take your medicine there and come back... And you cannot get DOT treatment other than your centre. Suppose I am going for a marriage in some other city, I will not get the medicine and you are not giving medicine for those periods to carry on with this. What will happen then?

He also sees it as a problem of the psychology of the patient, who would rather be taking daily doses of the drug. Intermittent therapy is 'not tuned in their mind,' he said. However, he also explained that he has talked to many doctors who are not prepared to get involved in the DOTS programme, because of staffing and resource issues and that it increases their administration loads through the stringent recording and reporting formalities.

Perceptions of the local understandings and meanings attributed to intermittent therapy and the DOTS programme are thus a particular problem for the Indian Revised National Tuberculosis Control Programme. Several chest physicians noted that by recommending the addition of streptomycin to a regimen that is failing, as in the case of category two, the WHO is contradicting one of its cardinal rules: that you never add a single drug to a failing regimen, as to do so could well be the equivalent of monotherapy (cf Bhargava & Jain 2008). Those in the RNTCP acknowledged this, but asked what else they could do (given the lack of laboratory ability to diagnose MDR and such limited resources).
Further interviews with chest physicians revealed these perceptions and difficulties with the current DOTS programme and its regime. A chest physician in UP, and a visiting RNTCP supervisor, highlighted that in their experience, private doctors exploit the perception that DOTS is intermittent therapy, as most patients would rather have the daily therapy. Again, they argued this meant that direct observation was even more essential. In Lucknow, the doctor in one DOTS centre acknowledged that many private doctors say that the government medicines are no good, and that they write prescriptions for their own benefit. Another senior chest specialist in Kolkata said that the DOTS programme will not work: that DOT is not implemented strictly enough; that Category 2 and 3 are both wrong; that the programme doesn't take the issue of side effects seriously enough; that they haven't worked out what to do with migrants;[12] that there is far too much MDR-TB that they have no idea about because of the lack of laboratory backup. There is no way that they will 'contain' the TB issue by 2015, he claimed. He was also disappointed that the WHO recommendations are not 'evidence based'.

A Kolkata pulmonologist also stated that middle class patients would avoid the

government clinics because they are dirty, crowded, and they don't trust the free medicines. Another senior and influential senior chest physician in Kolkata quoted the book *Timebomb,* and a recent piece of research suggesting that in a survey of 100 doctors, 85 different regimens were prescribed! However he was highly critical of the DOTS programme for several reasons: the criteria were too rigid, people had to wait too long to get their medicines, and the whole programme was too 'cumbersome'; it failed migrants; he regularly sees patients under the DOTS programme who are not having their issues addressed, and most people are suspicious of, and don't like, the government services. Yet another Kolkata private physician explained that he doesn't like the DOTS regimen because it is too short, and that he only refers the poor to the DOTS clinic, stating that 'if a patient can afford the medicine I don't send them'. Many find the direct observation too inconvenient and lose too much potential income. Another Kolkata chest physician, himself responsible for supervising a DOTS clinic, admitted that he doesn't send TB patients there if they would like to see him privately. The government programme is overly bureaucratic and the drug supply often poor, he said. The patients don't understand why they take drugs on alternate days. For him, the question of trust is primary, but in the government clinics they 'force compliance'. The times are inconvenient, and whereas he gives his private cell number to patients to call should they want to, patients just don't feel close to the clinic staff. He admitted that the issue with his private patients is keeping track of them. Again, another private practitioner who does not refer anyone to the DOTS programme sees the issue with lack of flexibility of direct observation and patients losing work; and that no-one takes the free drugs seriously. Yet another private practitioner, after complaining about the irrationality of category two, focused on the question of trust, in this case trust in companies, and so she prescribes Lupin's products. She likes the idea and theory of the government service, but in practice it is different, and the profile of the government services needs to improve. The most high profile and vocal anti-DOTS advocate, and secretary of the Bengal Tuberculosis Association, is mainly concerned that the drugs are given on alternate days, whereas it should be daily: It looks to him as if 'ours is a poor country, we cannot afford it'. He also has a problem with the lack of flexibility with weight schedules, and that therefore too many patients get the wrong dosages.

These practitioners involved in treating TB patients raise many criticisms of the programme. These range from broader perceptions of the quality of government services, to questions of trust and accountability. But central, too, were the criticisms – some reflecting on the evidence debates, others perhaps from personal prejudice – on the use of IT in the DOTS regimen. No one we spoke to used it in their private practices. At the least this adds fuel to their criticism of the government services, and makes the flexibility that many patients require more difficult. How do these issues play out in Nepal, where the technical issues are somewhat different?

III
DOTS and the Rregimen in Nepal

The regimen chosen for the DOTS programme in Nepal is administered daily, has to be supervised institutionally as DOT in the intensive phase and was until late in 2008 as follows:[13]

Category One: 2HRZE/6HE

Category Two: 2SHRZE/1HRZE/5HRE

Category Three: 2HRZ/6HE

This eight month regimen, administered daily, lacks rifampicin in the continuation phase. One senior advisor to the TB programme in Nepal acknowledged that the WHO does not like using rifampicin through the whole regimen. This would mean that DOT is necessary for the whole six months rather than just in the intensive phase he argued. He also suggested that it was too expensive for Nepal. As in the Indian situation, the decision or at least justification for the regime came from the absolute need to observe directly any combination of drugs administered to patients that contains rifampicin.

The criticisms and issues related to this regimen in Nepal differed from those in India. Here there was widespread criticism of the continuation phase drugs, rather than the dosage schedule. For example, a senior and well known TB specialist in Nepal explained that he uses a six month regimen, as he prefers the continuation phase with rifampicin in it. For this reason, he said, he only referred those who could not afford it into the DOTS programme. He was concerned with the 'slightly higher' relapse rates when the CP contained INH instead of rifampicin. He had talked the issue of rifampicin in the CP over with many of his colleagues and that they shared his concern, although the patients themselves are not aware of these issues. Another senior Kathmandu chest physician stated that he was somewhat suspicious of the cure rates claimed by the DOTS programme. He also gives rifampicin to all his patients throughout the full regimen, and as he was responsible for the treatment of army personnel with tuberculosis he had not adopted the DOTS regimen for this reason. He saw the DOTS regimen in Nepal as an inferior regimen, and was surprised that the patients themselves were not shouting for the better regimen. He is unable to accept that they have 90 per cent cure rates with the ethambutol-based regimens. He also treats patients privately because many have difficulties and 'hassles' going to the DOTS clinic every day, and taking the time off work can be expensive.

Outside Kathmandu, the concerns were the same. A senior physician in Lumbini, in the Western Region, also complained that the Category 1 regimen was not good, and that he did not like HE in the regimen at all. Since the combination of HE was 'bacteristatic' he explained, they should have HR in the continuation phase as this is 'bactericidal'. As

he said: 'From my experience, by giving HE in the continuation phase there is a high chance of relapse.' So he does not refer to the DOTS programme, but prescribes the HR regimen. He also had a problem with the quality of the government drugs, and with the lack of accountability in the DOTS system: 'one person does the check up, another person does the test and then another person gives the medicine', so no one cares. At the nearby DOTS clinic, the young man working there said there were some problems with several doctors in the local government hospital: they ignore DOTS and treat all their patients privately. They complain that the regimen is no good, he told us, and they asked him why they should give poor quality drugs when they have their own. He was sceptical of this claim, and thought it more likely related to their business interests: they own or had shares in private clinics. Many patients who arrive late to the clinic have not even heard that the TB medications are free, he said.

However, despite these claims of not liking the current regimen the market for rifampicin and TB drugs has changed since the DOTS programme started, certainly in Kathmandu. It was widely represented during our interviews in Kathmandu that sales in the private sector for TB drugs had decreased after the success of the DOTS programme. A Macleods' MR explained that the market had fallen out of their TB sales, including second line drugs since the implementation of the country wide DOTS-plus programme (for cycloserine, ethionamide, and PAS). He said that prior to this in Nepal they had no competitors for these three drugs. He reckoned that the numbers of patients not availing themselves to free TB drugs was small, and limited to a few with 'high social status' and those who wanted to keep their disease secret. This marketer said that he had not been able to break into the market of the few high profile TB specialists who remain loyal to certain other companies. He also highlighted how the products launched in the country are dependent on existing trends and sales of other companies.

The Sales Manager for a Nepali company explained that a combination of the emergence of the government DOTS programme and companies like Lupin diversifying into combination strips had reduced their own sales. He argued that while they would produce rifampicin for the government, this market is too vulnerable for them: there is no guarantee that the government would purchase from them. Although he did not mention this, now that the DOTS programme in Nepal procures all their drugs from the GDF there is no opportunity at all for local Nepali companies to sell to the government.

In a brief survey of TB drugs' sales outside a major public hospital in Kathmandu, six retailers each said that their sales of TB drugs had decreased, and that the available drugs were now mainly combined drugs from the major Indian producers. All stocked Lupin's products, but Macleods, Concept and Cadila were also represented. Outside another large teaching hospital with a well-functioning DOTS clinic run by a very enthusiastic community physician, not one of five retailers admitted to stocking any

TB drugs. One paediatric Kathmandu physician complained that it was very hard to get any uncombined rifampicin since the DOTS programme had gained momentum. Another physician suggested that companies like Lupin now barely needed to market their drugs, as the brand names are now so well known: 'everyone knows AKT4, you ask any layman, he will know about AKT4'.

However, despite this a technical subcommittee of the National Tuberculosis Centre decided on the six month regimen and the main issue was really only the cost of the rifampicin. A senior representative at this meeting acknowledged this regimen had lower 'relapse rates' and less 'treatment failure', and it is more acceptable because of the decreased time it has to be taken. Adherence should increase, despite the need for increased observation. In autumn 2008 the new regimen was rolled out across Nepal.

In Nepal, several issues emerge from these research observations. Firstly, in the wake of a well run DOTS programme, sales of certain single and combination drugs can decrease. Nepal is dependent on TB drug imports from India, and the evidence points to the possibility that more FDCs from reputable Indian companies are on the market now as a consequence. From a public health perspective, this is surely better than the Indian situation: The chances of mal-prescribing and consumption ought to decrease as a consequence. Secondly, the decision to change the national regimen from an eight-month to a six-month one will also allow even greater harmony between the national regimen and those prescribed in the private sector.

IV
Discussion

Critiques of the DOTS policy are wide ranging and suggest, for example, that it doesn't address poverty, with which TB is ultimately associated, and that prevention campaigns based on case management have never eliminated a disease (Enarson D & N Billo 2007); or that the DOTS strategy is unlikely to overcome the massive social, cultural and economic barriers that feed tuberculosis (Gandy & Zumla 2002); or that the uncritical application of DOTS regimens in areas where TB, as a complex bio-social issue where levels of MDR-TB are not known, may deny patients the drugs they really require for MDR-TB (Farmer 2003). This latter point is also true in India, and is a particular problem for the category 2 treatment protocol (Bhargava & Jain 2008). However, much of the debate around DOTS has focused on direct observation. WHO pushed the direct observation angle very hard, to the bewilderment of many involved in and researching TB control issues. For example, in the WHO publication *Toman's Tuberculosis,* amongst the operational requirements in the key to cure is that treatment should be directly observed, by a 'trained, accountable individual' and that this is particularly important when rifampicin is included in the regimen (Toman 2004c). Ultimately, the argument

goes, 'the only means of ensuring that treatment is taken as prescribed is by direct observation' (Bock 2004: 265). Ian Smith, the first WHO MO for Tuberculosis Control in Nepal, and a pioneering DOTS advocate, phrased it thus:

> There are several ways by which we protect Rifampicin. The most effective and important is to observe every dose taken by the patient. Other ways include combining tablets of Rifampicin with Isoniazid to prevent monotherapy in fixed dose combination tablets (but quality and bioavailability must be ensured), use of blister packs, training health workers, using 'balanced' regimens, restricting use of Rifampicin to mycobacterial diseases only, and preventing misuse of medicines by ordering supplies on the basis of reported cases (Smith 2004)

By insisting that this observer of treatment is accountable to the health service the WHO and other DOT advocates have stimulated heated debates that have ranged across the sciences and social sciences, and been the focus of many editorials, perspectives and opinion pieces in major medical journals and elsewhere.[15] This focus on 'observation' has tended to be at the expense of other aspects of the overall policy. However, baffling to many of us researching and commenting on this direct observation component of DOTS has been the ideology underlying the policy, that of the lack of trust towards either the patient (Bakhish 2006) or to the patient's family members (Nichter 2008). A Cochrane review of direct observation studies for randomised and quasi-randomised controlled trials comparing health worker, family member and community member observation with self administration at home found no evidence of difference for DOT compared with self-administered treatment (Volmink & Garner 2007). When more qualitative studies were also reviewed, more richness was added to the critique including: the importance of socio-economic circumstances and individual agency; the importance of stigma; differing explanatory models of TB; that punitive sanctions are a barrier to the uptake of services; and that services need to fit more easily into the patterns of patients lives rather than vice versa (Noyes and Popay 2007). Only recently has the WHO released its insistence on DOT publicly – partly in response to these criticisms – as a component of TB control, but this may take a long time to filter down in practice across the diverse locales where DOTS programmes come to ground.

However, few of these studies have taken into account the specifics of the regimens themselves, as we have here. In short, we argue that it is important to take the local context of drug availability and practitioners' understandings and perceptions into account when planning services. The absolute insistence on DOT, in that it remains the rationale for the intermittent therapy in India, is a serious policy error. Intermittent therapy may well have higher relapse rates than daily therapy, although there may not be enough supportive evidence to support this claim. More importantly, however, in a context where most of the TB treatment services still lie in the private sector, and given such widespread resistance, why add to excuses that private practitioners may provide for not referring into the system? It is hard enough to implement public services

as it is. The same issue applied in Nepal, but for a different technical reason: Here, and despite the apparent success of the DOTS programme, a major problem was that rifampicin was not used in the continuation phase. Given that market forces, and the success of the DOTS programme, has resulted in the wider availability of a few well-known and trusted companies' FDCs being available on the market, it seems to make sense that policy should further this thrust, rather than struggle against it. In short, while the science is important, so too are the local market conditions and local practitioner perceptions when considering national policy. National programmes should be more pragmatic when considering regimen choice.

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Note :

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[2] The 'First line drugs' are as follows: Isoniazid (H), Rifampicin (R), Ethambutol (E), Pyrazinamide (Z), and Streptomycin (S). 'Second line drugs' include Kanamycin (KM), Amikacin (AMK), Capreomycin (CM), the Quinolones (FQ) – Cipro, Ofx, Gfz, Mfx - the thiamides (Ethionamide or Prothionamid), Cycloserine (CS), and Para-aminosalicylic Acid (PAS))

[3] The DOTS policy includes five core elements; political commitment to increasing resources and including TB as an activity integral to national health systems; sputum microscopy services so that the disease can be correctly identified; short-course chemotherapy, including the direct observation of treatment; uninterrupted supply of drugs and finally, recording and reporting systems (WHO 2002).

[4] A full description of the project and its methods was presented at an Edinburgh dissemination workshop in June 2009. Roger Jeffery, 2009. Tracing Pharmaceuticals in South Asia. Draft background paper: 'Project Design and Basic Data'.

[5] TB Alliance, November 2006. Analysis of the Global TB Drug Market and Country-Specific Case Studies of TB Drug Distribution Channels. India Case Study.

[6] Lupin's full list of products available on the market, for example, includes first line drugs and those for the treatment of MDR-TB. In short, the first line drugs are available as single tablets, in strips as single tablets and in Fixed Dose Combinations (FDCs), all with branded names. The branded AKT range – AKT2, 3 & 4 – are 'kits', or strips, of rifampicin and isoniazid; rifampicin, isoniazid, and ethambutol; and rifampicin, isoniazid, ethambutol and pyrazinamide respectively. Akukit is the two dose combination, and Akurit 3 and 4 the 3 and 4 dose FDC, all combined in the one tablet. There are also different dose tablets for the individual drugs, including a paediatric range and combinations. Lupin's are the most popular brands on the market in India and Nepal.

[7] This paragraph of the paper is taken from a review of the existing data prepared by Ricks: 'The Role of Private Practitioners and Pharmacists in Tuberculosis Control in India'. August 2008. Dissertation prepared for the Centre for International Public Health Policy.

[8] On the rationale for FDCs see Blomberg et. al 2001, who highlight that the bioavailability of rifampicin in FDCs is a particular issue, one that is easily compromised if manufacturing norms are not strictly adhered to.

[9] The GDF is run by a group from the Stop TB partnership secretariat and housed in the WHO. Announced in 1998, a business model for it was developed through 2000, and it was launched in 2001. It acts as a mechanism whereby countries running DOTS programmes can procure their drugs (see http://www.stoptb.org/gdf/).

[10] RNTCP 2005. Technical and Operational Guidelines for Tuberculosis Control. http://www.tbcindia.org/pdfs/Technical%20&%20Operational%20guidelines%20for%20TB%20Control.pdf (accessed June 2009).

[11] http://www.tbcindia.org/replies.asp (Accessed March 2009)

[12] Currently policy in India states that all patients have to register an address and prove it before they can enter into the programme. For many migrants this is a real problem. One private doctor in Delhi we spoke too, and who had signed up to act as a private DOTS provider, had been struck off the programme because recognizing this as an issue she had falsified some of the addresses, then promptly lost them to follow-up.

[13] In the Autumn of 2008, after the data collection for the research finished, the Nepal NTP started the process of changing its regimen to a six month one. However, an in-depth review of the programme in 2007 advised that one of the disadvantages of this shift was that – as in India – DOT for any rifampicin based product would result in greater demands on patient time, increasing the direct observation from 2 to 6 months.

[14] In a review of the Nepal TB programme in which Ian Harper participated in Autumn 2007, this issue was a key concern raised with the team in an open discussion about the regimen with respiratory physicians.

[15] For a summary of the 2003 BMJ debates see Harper (2006). Here the issues were framed as the questions of 'science' and evidence, contra the WHO's dependence on 'faith'.