

## Under- and over-consumption intermittent TB treatment among rural TB patients in south-west China

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### SUMMARY

**OBJECTIVE:** To assess adherence to intermittent directly observed treatment (DOT) during the 2-month intensive phase of tuberculosis (TB) treatment in south-west rural China.

**DESIGN:** A cross-sectional study was conducted in Simao Prefecture, Yunnan Province, China. One hundred and thirty new TB patients registered under DOTS and treated during the 2-month intensive phase and their observers were separately interviewed at their homes using structured questionnaires. Numbers of packs of TB drugs were checked on the spot.

**RESULTS:** Of 130 visits, the same percentage (3.1%) of patients and their observers reported missing  $\geq 2$  consecutive weeks of treatment (prevalence-adjusted  $\kappa = 0.94$ ). The percentages who missed  $\geq 20\%$  of the packs, as re-

ported by patients and observers, were 3.8 and 2.3, respectively (prevalence-adjusted  $\kappa = 0.969$ ). According to the pill count, nine patients (7%) had missed  $\geq 20\%$  of the packs, 10 had over-consumed TB drugs and two had lost respectively five and six packs. Eight of the 10 who had over-consumed had done so due to confusion in the days of the month, and two because they wanted a quicker recovery.

**CONCLUSIONS:** Intermittent regimens in China need to be more carefully monitored to avoid over-consumption of anti-tuberculosis drugs in addition to non-adherence due to under-consumption.

**KEY WORDS:** pulmonary tuberculosis; DOTS; adherence; pill count; China

POOR TREATMENT ADHERENCE has been held responsible for increasing tuberculosis (TB) treatment failure<sup>1–5</sup> and drug resistance.<sup>6,7</sup> To increase adherence, the World Health Organization recommended the DOTS strategy, where patients take each dose of anti-tuberculosis drug under direct observation at least during the intensive phase of treatment (directly observed treatment, DOT).<sup>8,9</sup> All anti-tuberculosis medications are recommended to be taken once daily or on alternate days during short-course regimens. Intermittent treatment was introduced to reduce the costs and burden of direct observation,<sup>10,11</sup> although daily treatment is recommended worldwide.

Several previous studies of non-adherence to TB treatment were based on a review of medical records,<sup>1,12–15</sup> which mainly measured treatment interruption due to missed appointments. Interviews, if conducted, were held mainly at the health service centres, where patients might feel pressured by the provider to claim to be adherent. Intermittent regimens were also less frequently evaluated than daily regi-

mens, as they were less commonly used. China and India are among the exceptions.<sup>11</sup>

China has a high TB prevalence (367 per 100 000 population), and accounts for one-sixth of the world's TB patients (790 000).<sup>16</sup> The country adopted the universal free intermittent DOTS strategy only in 2002, a relatively long time after its participation in a successful multicentre DOTS trial in 1991–1994.<sup>17</sup> While the reported cure rate of TB treatment under DOTS in China was high (95.3% of new positive cases),<sup>18</sup> there have been relatively few evaluations of adherence, which could help validate reports and improve the control programme.

The present study was conducted to document the level of adherence of TB patients by home visit, using different methods for assessment. The study area was Simao Prefecture in Yunnan Province, where most patients reside in remote villages. China is one of the few countries where intermittent treatment is the regimen of first choice.<sup>11</sup> These results may have implications for other countries where intermittent regimens are used.

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## MATERIALS AND METHODS

### *Study design and study setting*

The protocol of the study was approved by the Ethics Committee of the Faculty of Medicine, Prince of Songkla University, and agreed to by the local Centre for Disease Control and Prevention (CDC). Simao Prefecture of Yunnan Province is a mountainous area with a population of 2.5 million.<sup>19</sup> According to national regulations, a TB patient in the study area is always treated at the local county-level CDC. After diagnosis, patients are required to take one pack of anti-tuberculosis drugs every even-numbered day at home in the presence of an observer. If a dose is missed, it should be compensated by taking it the next day, without changing the remaining schedule. In months with 31 days, there are two treatment-free days (on the 31st of that month and the 1st of the next) when no medication is administered. The treatment regimen for new TB patients consists of two phases: a 2-month intensive phase and a 4-month continuous phase (2H<sub>3</sub>R<sub>3</sub>Z<sub>3</sub>E<sub>3</sub>/4H<sub>3</sub>R<sub>3</sub> or 2H<sub>3</sub>R<sub>3</sub>Z<sub>3</sub>/4H<sub>3</sub>R<sub>3</sub>).<sup>\*</sup> The first phase may be extended to up to 90 days, depending on the sputum smear results at the end of the second month of treatment.

Anti-tuberculosis drugs for the intensive phase for smear-positive patients who weigh >50 kg consist of two tablets of INH (2 × 300 mg), two capsules of RMP (2 × 300 mg), 4 tablets of PZA (4 × 500 mg) and five tablets of EMB (5 × 250 mg), which are given to the patients for 2 months' consumption (30 packs) at the beginning of treatment. A TB patient treatment card with a calendar is provided to the observer to fill in on the days of drug administration.

### *Selection of subjects and sample size*

All 10 county CDCs were included in the study. New pulmonary TB patients were recruited into the study if they were registered with the DOTS-based programme and had been receiving treatment for 1–2 months during July and September 2006 at the local CDC were aged >14 years, were without any other serious diseases, had no serious mental problems and who gave their consent to data collection. The sample size of the study ( $n = 113$ ) was calculated on the basis of the estimated non-adherence rate of 12% from a previous study in Thailand with 95% confidence limits being  $\pm 6\%$  from the estimate.<sup>20,21</sup>

### *Research tools and data collection*

Patient and observer data collection forms were developed to obtain information on characteristics such

as age, sex, education and knowledge and practice of TB treatment. Date of start of treatment was extracted from the medical records. The number of packs of pills reported as consumed on the TB patient treatment card and from the pill count was also assessed.

The names and addresses of patients and observers were obtained from the local CDC. Local village doctors assisted in making appointments during the second month of treatment. Both the local village doctors and the local CDC staff were trained before working on data collection. Interviews were conducted separately at the patients' homes after verbal consent was obtained (the consent form was read to the patients and the observers). TB patient treatment cards were inspected to reconfirm the date of start of treatment and the number of packs noted as taken by the patients or the observers. Pill counting, about which the family had not been previously informed, was performed on the spot. The number of packs remaining was recorded and was used to evaluate the number of packs consumed in statistical analysis.

### *Definition*

Patients were deemed non-adherent when they had missed  $\geq 2$  consecutive weeks of TB treatment<sup>1,12,21</sup> or  $\geq 20\%$  of the total quantity of TB drugs.<sup>22,23</sup> Drug over-consumption was also identified from the pill count.

### *Statistical analysis*

Descriptive statistics were used to summarise the data. The kappa ( $\kappa$ ) statistic was computed to determine the degree of agreement between patient and observer. If the variables were binary and the prevalence was quite high or low (arbitrarily at 10% and 90%), the value of  $\kappa$  was adjusted for prevalence.<sup>24</sup> For three categories, the weight for cells of full disagreement, partial agreement and full agreement was 0, 0.5 and 1, respectively. The number of packs of pills consumed, calculated as 30 less the number of remaining packs, as calculated from the pill count, was plotted against the number recorded on the TB patient treatment card and against the number of doses expected to have been taken based on the calendar, to determine concordance between the various data sources.

## RESULTS

Of 142 registered adult TB patients, 130 were enrolled in the study. Reasons for non-enrolment were as follows: six returned to the CDC before the date of interview, four worked elsewhere and two could not make an appointment. One hundred and one were smear-positive, and 25 were smear-negative but had cavitations detected from chest radiography. These 126 patients were on 2H<sub>3</sub>R<sub>3</sub>Z<sub>3</sub>E<sub>3</sub>/4H<sub>3</sub>R<sub>3</sub>. The other four were smear-negative but had mild infiltration, and were given 2H<sub>3</sub>R<sub>3</sub>Z<sub>3</sub>/4H<sub>3</sub>R<sub>3</sub>. In this study, the patients and

<sup>\*</sup> H, INH = isoniazid; R, RMP = rifampicin; Z, PZA = pyrazinamide; E, EMB = ethambutol. Numbers before the letters indicate the duration in months of the phase of treatment; numbers in subscript indicate the number of times the drug is taken each week.

**Table 1** General characteristics of study TB patients and observers

Items	Patients (n = 130) n (%)	Observers (n = 130) n (%)	P value*
Sex			0.000
Male	92 (70.8)	71 (54.6)	
Female	38 (29.2)	59 (45.4)	
Age, years			0.005
<20	7 (5.4)	3 (2.3)	
20–40	54 (41.5)	77 (59.2)	
40–60	52 (40.0)	45 (34.6)	
>60	17 (13.1)	5 (3.8)	
Education			0.004
Illiterate	36 (27.7)	14 (10.8)	
Primary school	48 (36.9)	51 (39.2)	
Middle school	37 (28.5)	54 (41.5)	
High school or more	9 (6.9)	11 (8.5)	
Family income (yuan/month) <sup>†</sup>			0.362
<500	100 (76.9)	90 (69.2)	
500–1000	19 (14.6)	24 (18.5)	
>1000	11 (8.5)	16 (12.3)	

\*  $\chi^2$ .  
<sup>†</sup> Yuan = 0.13 \$US.

observers were visited during the second month of treatment (mean 53.7, standard deviation [SD] 5.2). Almost all the patients were being observed by close relatives, half of whom were spouses. Over half of the patients resided over 50 km from the local CDC. Patients' and observers' characteristics are presented in Table 1. The male-to-female ratio among the patients was 2.5:1. Most patients were of working age, but with little education and low family income. The characteristics of the observers were similar to those of the patients, except that there was a lesser predominance of males.

Table 2 shows that the levels of TB knowledge among both the patients and the observers were far

**Table 2** Responses of patients and observers to the questions on TB knowledge

Responses	Patients (n = 130) n (%)	Observers (n = 130) n (%)	P value*
TB transmissibility			0.025
Yes	103 (79.2)	117 (90.0)	
Other	27 (20.8)	13 (10.0)	
Mode of transmission			0.045
Correct	65 (50.0)	82 (63.1)	
Incorrect	65 (50.0)	48 (36.9)	
TB curability			0.134
Yes	96 (73.8)	107 (82.3)	
Others	34 (26.2)	23 (17.7)	
Duration of treatment needed			1.000
6–8 months	104 (80.0)	105 (80.8)	
Other	26 (20.0)	25 (19.2)	
Treatment can be stopped when symptoms resolve			0.407
No	84 (64.6)	91 (70.0)	
Unsure	31 (23.8)	30 (23.1)	
Yes	15 (11.5)	9 (6.9)	

\*  $\chi^2$ .

from perfect, especially regarding the mode of TB transmission, curability and when treatment should be stopped. The prevalence of misconceptions ranged from 20% to 50%.

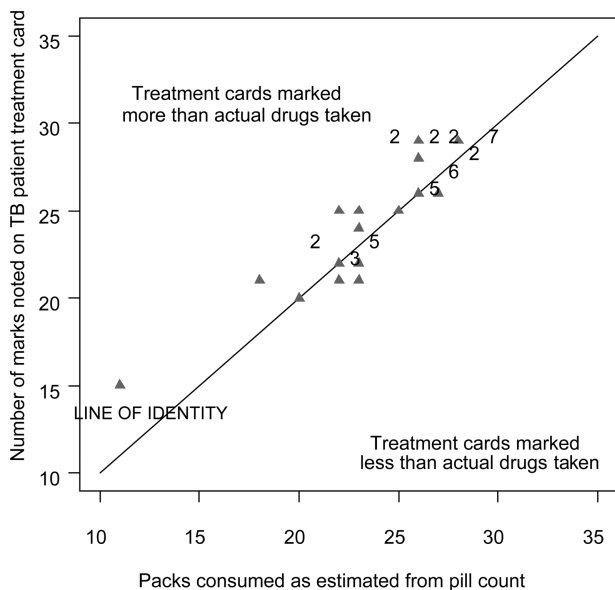
Levels of reported adherence were generally high (Table 3). Serious problems of non-adherence, such as stopping treatment for 2 weeks, were relatively rare. Less serious non-adherence, such as not respecting DOT, was more common. In general, the level of agreement between the patients and the observer, with prevalence adjustment for rare outcome and weighting for ordinal outcome, were moderate to high.

Among 130 TB patient treatment cards, 52 were mainly filled out by the patients and 78 mainly by the observers. Sixteen TB patient treatment cards filled out by the patients showed on average 2.8 more dose marks on the card than the number assessed from the pill count; four cards had the opposite result, with an average of 1.2 doses under-reported (Figure 1). In the case of cards filled out by the observers, the level of over-reporting was similar, but under-reporting was markedly higher (Figure 2).

**Table 3** Reported practice of TB treatment by patients and observers

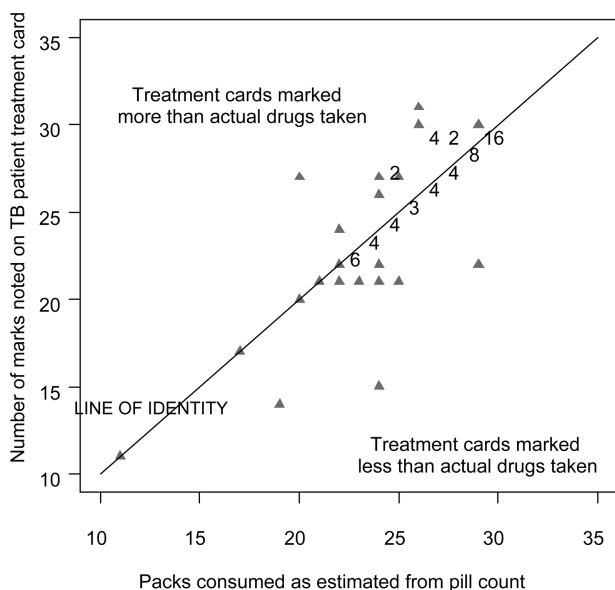
Items	Patients (n = 130) n (%)	Observers (n = 130) n (%)	$\kappa$ table*
Stopped treatment for $\geq 2$ consecutive weeks in			
2 months			a b
No or unsure (a)	126 (96.9)	126 (96.9)	a 124 2
Yes (b)	4 (3.1)	4 (3.1)	b 2 2
			0.484/0.938 <sup>†</sup>
Missed $\geq 20\%$ of packs in 2 months			a b
No (a)	125 (96.2)	127 (97.7)	a 125 0
Yes (b)	5 (3.8)	3 (2.3)	b 2 3
			0.743/0.969 <sup>†</sup>
Compensated next day if forgot to take treatment on time			a b c
Frequently (a)	15 (11.5)	18 (13.8)	a 13 1 1
Rarely (b)	17 (13.1)	14 (10.8)	b 1 8 8
None missed (c)	98 (75.4)	98 (75.4)	c 4 5 89
			0.617
Times under direct observation in 2 months			a b c
>80% (a)	78 (60.0)	80 (61.5)	a 70 8 0
50%~80% (b)	24 (18.5)	28 (21.5)	b 6 16 2
<50% (c)	28 (21.5)	22 (16.9)	c 4 4 20
			0.727 <sup>†</sup>
Followed all medical instructions in the			a b c
1st month			a b c
Good (a)	105 (80.8)	112 (86.2)	a 98 4 3
Normal (b)	21 (16.2)	13 (10.0)	b 13 8 0
Poor (c)	4 (3.1)	5 (3.8)	c 1 1 2
			0.419 <sup>†</sup>
Followed all medical instructions in the			a b c
2nd month			a b c
Good (a)	111 (85.4)	118 (90.8)	a 108 2 1
Normal (b)	14 (10.8)	8 (6.2)	b 8 6 0
Poor (c)	5 (3.8)	4 (3.1)	c 2 0 3
			0.558 <sup>†</sup>

\* For  $\kappa$  table, the row gives patient data; the column gives observer data.  
<sup>†</sup> Prevalence-adjusted  $\kappa$ .  
<sup>‡</sup> Weighted  $\kappa$ .

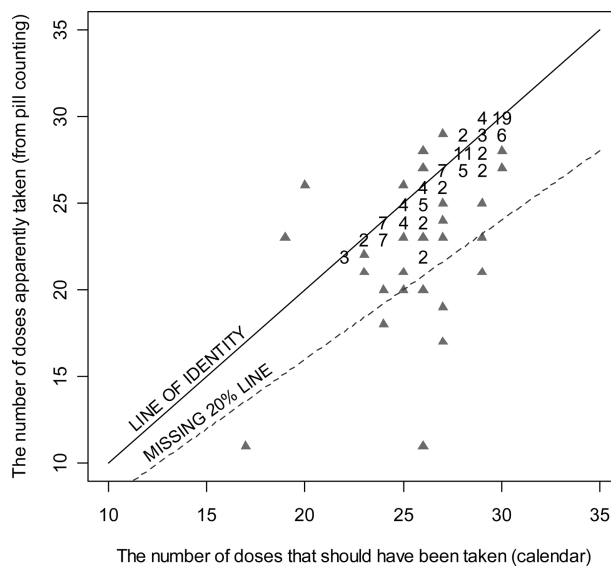


**Figure 1** Number of packs noted on TB treatment card by patient as having been taken vs. number of packs estimated by pill count. Diagonal line = line of identity. Subjects are represented by triangles or number. TB = tuberculosis.

The pill count revealed that half of the patients took fewer packs than recommended. This was because most of the missing days were rarely compensated. Nine patients (7%) had missed  $\geq 20\%$  of their medication, while 10 (8%) had taken more medication than instructed (Figure 3). Two patients had lost respectively five and six packs, making the pill count lower than expected; five had over-consumed their medications during the change of the months ending on the 31st, due to confusion; three patients first took



**Figure 2** Number of packs noted on TB treatment card by observer as having been taken vs. number of packs estimated by pill count. Diagonal line = line of identity; subjects are represented by triangles or number. TB = tuberculosis.



**Figure 3** Number of packs estimated as having been taken (pill count technique) vs. expected values based on calendar. Solid line = line of identity; dashed line = missed 20% of treatment; subjects are represented by triangles or number.

their medication on the date of diagnosis, which was an odd day and again on the following (even) day and on every subsequent even day; and two patients over-consumed their medications intentionally at the turn of the month, as they felt that the symptoms were serious and they wanted to improve quickly.

Subsequent follow-up from the TB treatment records revealed that 10 of these 130 patients were sputum smear-negative at the end of the second month of treatment. The odds ratio between missing 20% of pills and sputum conversion at the second month was 1.56 (95% CI 0.17–13.86).

## DISCUSSION

From these 130 home visits, the majority of the patients were male, of working age, had a low level of education and low family income and lived far from the treatment centre. They and their observers, who were close relatives, had a poor understanding of the nature and transmission of the disease. Both groups reported high levels of adherence with high consistency, but adherence to DOT was not strict. From the pill count,  $\geq 20\%$  of total packs were missing in 7% and over-consumption of drugs at the turn of the month had occurred in around 8% of patients.

The DOTS strategy was introduced in Yunnan Province, China, in 2003 and ambulatory care for TB patients was moved from the hospital to the CDC respiratory offices. With the prevailing poverty among TB patients and the need to travel for long distances for treatment, financial and geographic barriers may have been a problem.<sup>12</sup> With these common barriers

the reported relatively low incidence of TB in Yunnan, China (101/100 000), compared to other neighbouring countries such as Thailand (142/100 000), Vietnam (176/100 000) and Laos (156/100 000), should be taken with caution.<sup>16</sup>

In our study, the patients and the observers had a limited knowledge of TB, but the level of knowledge was somewhat higher than that reported in previous studies.<sup>12,13,25</sup> The most serious fault was to stop treatment once the symptoms had improved. Despite these misunderstandings, the TB cure rate in the study area was consistently reported to be high (85.9–93.3% from 2004 to 2005).<sup>26</sup> It is possible that the misunderstandings were corrected during subsequent visits to the health service centre after the intensive phase of treatment.

According to the patients and the observers in this study, 3.1% consecutively missed  $\geq 2$  weeks of treatment, which was low compared with figures from Thailand (11.5%),<sup>21</sup> Malaysia (10%)<sup>12</sup> and the United States (11%).<sup>1</sup> The lower rate of non-adherence may be expected, given that patients in the early phase of treatment were included in our study whereas the different phases of treatment were mixed in others. Motivation to take treatment in the initial phase, when the symptoms are still serious, may lessen in the extended phase.<sup>27</sup>

The methods of data collection may also explain the differences in the results obtained. Two of the above-mentioned three studies were based on medical record reviews. Pill counting, which had been used in the early phase of adherence studies,<sup>23,28–31</sup> was less commonly employed, and was not used at all in those three studies cited. Had this method not been used in our study, the proportion of under-treated patients would have been underestimated and over-consumption would not have been detected.

DOT observers in China are mainly family members, and strict adherence to DOT is not respected, at least in this study area. In many other countries, the same trend has been observed. While China can still maintain its high cure rate without strict DOT, failure to strictly follow DOT was a significant reason for low cure rates in many countries such as Thailand,<sup>32,33</sup> India<sup>34</sup> and Pakistan.<sup>35</sup> In the early phase of DOT trials, China used 'barefoot doctors' as DOT observers,<sup>17</sup> but this was considered unfeasible due to financial constraints. Thailand has tried to use village health volunteers as a choice of observers. Despite the reported success in using these volunteers in many health programmes, their role as DOT observers was not effective.<sup>32</sup> Use of alternative DOT observers in China still needs further research.

TB patient treatment cards are supposed to improve adherence to treatment. While the WHO recommends that observers fill out the treatment cards,<sup>8,9</sup> 40% of our patients did so themselves and with greater accuracy. Records from both groups were, however,

unreliable and the effect of card filling on adherence will need further study.

Missing doses and over-consumption of medications, if they occur, may be more serious in the case of intermittent regimens than with the daily regimen. Missing a day without immediate compensation the day after leads to 3 consecutive days being missed, which may be important for drugs that have a relatively short plasma half-life such as INH (half life 1–5 h), RMP (half life 2–3 h) and EMB (half life 3–4 h).<sup>11</sup> On the other hand, the bulk of tablet administration, which in intermittent regimen increases from 300 mg to 600 mg for INH, from 1500 mg to 2000 mg for PZA and from 1000 mg to 1250 mg for EMB, may increase the likelihood of toxicity when over-consumption occurs. China has as many as 2 890 000 TB patients who require the intermittent treatment.<sup>16</sup> If the findings of 8% over-consumption of medications can be generalised from this study, this kind of problem should not be ignored. To monitor the problem more closely, pill counting should be more widely used, especially in countries where intermittent medication is chosen.

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## R É S U M É

**OBJECTIF :** Evaluer en Chine rurale du sud-ouest l'adhésion aux premiers 2 mois du traitement antituberculeux sous DOT au cours d'un traitement intermittent.

**SCHÉMA :** On a mené une étude transversale dans la Préfecture de Simao, Province de Yunnan, Chine. On a enregistré 130 nouveaux patients tuberculeux pour DOTS qu'on a traités au cours de la phase intensive de 2 mois ; on a également interrogé séparément à leur domicile les observateurs du traitement, chacun au moyen de questionnaires structurés. On a contrôlé le nombre de paquets de médicaments antituberculeux sans informer préalablement les intéressés.

**RÉSULTATS :** Sur les 130 visites, un pourcentage égal (3,1%) parmi les patients et leurs observateurs a signalé un abandon de  $\geq 2$  semaines consécutives ( $\kappa$  ajusté de

prévalence = 0,969). Les pourcentages d'abandon de plus de 20% des paquets signalé par les patients et les observateurs ont été respectivement de 3,8 et 2,3 ( $\kappa$  ajusté de prévalence = 0,969). Si l'on se fie au décompte des comprimés, chez neuf patients (7%) l'utilisation des paquets a été inférieure de  $\geq 20\%$ , chez 10 patients il y a eu une surconsommation des médicaments antituberculeux et deux patients ont manqué respectivement cinq et six paquets. Chez huit des 10 patients, l'excès de consommation a été dû à une confusion à la fin du mois et chez deux à leur souhait de guérir plus rapidement.

**CONCLUSIONS :** Le régime thérapeutique intermittent appliqué en Chine doit être suivi avec plus d'attention pour éviter une surconsommation de médicaments en plus d'une non-adhésion sous forme de sous-consommation.

## RESUMEN

**OBJETIVOS:** Evaluar el cumplimiento terapéutico durante los 2 primeros meses de tratamiento antituberculoso con la DOTS en pauta de días alternos, en el suroeste rural de la China.

**MÉTODOS:** Se llevó a cabo un estudio transversal en la prefectura de Simao de la provincia de Yunnan, en China. Se entrevistaron separadamente 130 casos nuevos de tuberculosis registrados en la estrategia DOTS que habían recibido 2 meses de tratamiento de fase intensiva y sus observadores, mediante cuestionarios estructurados en entrevistas domiciliarias. Se verificó inopinadamente la cantidad de paquetes de medicamentos antituberculosos.

**RESULTADOS:** El mismo porcentaje (3,1%) de pacientes y observadores informó ausencias durante  $\geq 2$  semanas

consecutivas (índice  $\kappa$  ajustado por la prevalencia = 0,94). El porcentaje de pacientes que comunicó haber omitido más del 20% de paquetes fue 3,8% y el de observadores fue 2,3% (índice  $\kappa$  ajustado por la prevalencia = 0,969). Según el recuento de comprimidos, a 9 pacientes (7%) faltaron  $\geq 20\%$  de los paquetes, dos pacientes perdieron cinco y seis paquetes y 10 pacientes consumieron medicamentos antituberculosos en exceso, ocho de ellos por confusión hacia el final del mes y dos debido a su deseo de recuperarse más pronto.

**CONCLUSIÓN:** La pauta de días alternos en China precisa más cuidado, a fin de evitar un consumo excesivo de medicamentos además del incumplimiento por consumo insuficiente.