Adherence
in twice weekly therapy
for childhood tuberculosis

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Declaration by Candidate

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1. INTRODUCTION

1.1 AIM

This thesis examines the adherence to therapy as part of a clinical trial to determine the effectiveness of fully intermittent therapy for childhood tuberculosis.

1.2 OBJECTIVES

These were to determine 1) the effectiveness of fully twice weekly therapy in childhood pulmonary tuberculosis, 2) whether adherence rates would be affected by twice weekly dosing and 3) whether certain socio-demographic factors influenced adherence.

1.3 HYPOTHESES

The statistical null hypotheses were:

There were no differences in a) the clinical outcome, b) the adherence rates between the two forms of treatment.

2. LITERATURE REVIEW

The literature review will be set out as follows:

- 2.1 Prologue
- 2.2 Background
- 2.3 The literature on adherence as it relates to tuberculosis therapy
- 2.4 Studies of intermittent chemotherapy for tuberculosis
  - a) for adults
  - b) for children
- 2.5 Studies on adherence in childhood tuberculosis.

2.1 Prologue

The following quotations help to describe the importance of the subject:

"... poor compliance has been, and remains, the principal cause of treatment failure in both developing and developed nations." [38] - Grange in Tubercle and Lung Disease, 1993.

"Patient noncompliance has been identified as the most serious remaining problem in tuberculosis control, and it is a major obstacle in the elimination of the disease." [21] - Cuneo in Clinics in Chest Medicine, 1989.

"The reasons for noncompliant behaviour are not well understood..." [54] - Macharia in JAMA 1992, describing nonadherence in a wide range of diseases.

"Poor patient adherence is a multifaceted problem" [12] - MMWR 1993.

"It will be a long, long war" [9] - Bignall, writing in Tubercle on the occasion of the Robert Koch Centenary.

2.2 Background

Tuberculosis (TB) has been declared a global public health emergency, a heretofore unprecedented step by the World Health Organisation.[100] The province of the Western Cape of South Africa has one of the highest notified or reported tuberculosis incidence rates in the world - 865/100 000 in 1993 - and it is one of few areas with a rising tuberculosis incidence.[37] The rate for the Cape Town metropole in 1993 was 787/100 000. This was in the virtual absence of HIV/AIDS.[24] Stellenbosch as part of that region is one of the most affected districts.[81] It is evident that there is a close relationship between the number of cases of infectious tuberculosis and the tuberculosis morbidity and mortality in children.[49] The Western Cape also has a very high rate of childhood tuberculosis - 901/100 000 in under 4s (1989 figures).[37] The rate for South Africa in the same period was 158/100 000. The ratio of childhood (under 15 years) to adult tuberculosis in the Western Cape in 1993 was 1:3.

The reasons for embarking on a study to determine the effectiveness of fully intermittent therapy of childhood tuberculosis were:

1) The best data published so far have either been too small in number (Kumar[53]) or have had too many dropouts from treatment (Biddulph[8]). In addition, very few studies have well documented adherence rates. 2) There was a need to ease the workload of the staff, and intermittent therapy was considered an appropriate method, but it needed to be researched. There were also considerations of cost reduction and increased convenience for the clients. 3) There was in addition the need to research tuberculosis in a rural setting, as the tuberculosis incidence in nearly all rural areas in the Western Cape was higher than in the urban areas.[37] This dissertation concentrated on adherence in children because of the dearth of scientific knowledge on this very important subject. The World Health Organisation has identified the need for operational research to apply and adapt proven technologies.[98] On the topic of adherence as a whole, there were more than 8000 bibliographic entries for patient compliance by 1991, yet only 37 studies had been conducted in third world countries.[42]

2.3 Adherence as it relates to tuberculosis therapy

Compliance is a term related to many spheres of human activity, eg. compliance with traffic regulations. *Adherence* also is not exclusively medical, and in contrast to compliance, is used in settings where slightly more volition is intended, as in religious adherents.

Understandings of adherence and compliance

Medically speaking, compliance is the technical term for doing as the doctor says, or more formally, "the extent to which a person's behaviour (in terms of taking medications, following diets, or executing life-style changes) coincides with medical or health advice." This is the definition of compliance given by the standard reference work on the subject, "Compliance in Health Care" by Haynes, Taylor and Sackett.[40] This definition is insufficient according to Urquhart,[88] who believes that the time factor should be more explicitly taken into account and thus adherence should be properly defined as "the extent to which the time history of the patient's dosing corresponds to the prescribed regimen".

Chaulet, considering compliance in tuberculosis, adopts a different and wider perspective on the subject. He believes firstly[15] that compliance (in addition to conformity by the patient) also implies conformity between the treatment prescribed by the doctor and that called for by the national tuberculosis programme. He secondly believes[16] that in those countries where the prevalence of infection is intermediate or high, the principal responsibility for compliance resides not with the patient, but with the health providers at all levels. These problems of poor implementation of sound policy have been shown to exist in South Africa.[82, 83, 101] It has been established that in the Western Cape considerable variation exists especially in the treatment of children with TB.[101] Wallace Fox has stated that national surveillance of actual tuberculosis practices was the most important measure in improving national standards in the management of tuberculosis.[33, 34]

Bignall also believes in adopting the wider outlook: "If after careful, sympathetic explanation they still don't want it, then something is wrong with the programme for those particular people in that particular environment".[9]

In accord with these broader views on the subject, the terminology also has come under scrutiny: the term *adherence* has lately come into vogue as being the correct or appropriate term to use. This has occurred because of negative associations of the term compliance: "unworthy submission" as the Oxford Concise Dictionary puts it. It also has the connotation that the patient is merely "docile and subservient".[79] It is notable, however, that the "compliance" terminology is entrenched in the medical literature, along with such intolerant terms as delinquent, defaulter and dropout. Index Medicus lists Patient compliance, Patient cooperation, Patient dropouts and Treatment refusal as the related terms on this subject. Adherence is not a main subject heading, either there or in MEDLINE, the computer-based search modality. Another angle on adherence is that taken by Vander Stichele[90], who says that the measurement thereof is of cardinal importance in clinical trials.

Adherence and compliance are used interchangeably in the literature, and have very similar meanings. However, because of the negative associations of the term

compliance, I have chosen to use the term adherence for this dissertation, and will limit the discussion to adherence by the patient.

Adherence in tuberculosis will thus be further addressed as follows:

2.3.1 Factors associated with adherence.

2.3.2 Scope of the problem.

2.3.3 Measuring adherence.

2.3.4 Improvement strategies/ Management of nonadherence.

2.3.5 Summary

2.3.1 Factors associated with adherence.

Sumartojo[79] has recently reviewed the literature with respect to tuberculosis. She gives the following as conventional characteristics of nonadherents: homelessness, substance abuse, prior history of poor adherence, emotional disturbance, lack of transportation, behavioural problems, dissatisfaction with clinic scheduling, forgetfulness, mental retardation, lack of family or social support, migrant status, illiteracy, unemployment, low income, and minority status. This list would almost seem to contain characteristics generally definitive of tuberculosis sufferers, not only those nonadherent!

Of interest here is that two recent studies in African rural areas have mentioned that male gender is a risk factor for nonadherence.[91, 93]

Sumartojo states that demographic factors[a] are poor predictors of adherence and are in any case a) not inherently causal and b) cannot be altered by the treatment programme. Sumartojo stresses that the above list of those nonadherent is empirical and not analytical. Factors outside the control of the patient like environmental,

[a] Such as age, sex, race, ethnicity, occupation, income, and education.

structural and operational considerations are not taken into account. There is a need to develop accurate predictive models of adherence, that are testable in field trials. She states in addition that it is important to challenge the conventional view that attributes adherence problems solely to the patient. Sumartojo cites studies which have looked specifically at adherence *predictors* in tuberculosis. The pretreatment factors identified were low income, low education, excessive use of alcohol and single status.[17] Again these factors are descriptive of many adult tuberculosis patients.

However, the strongest predictor of adherence over 6 months was operational, namely adherence over the first month.[28] It is also noteworthy that a Montreal study found that adherence was improved in those who came for a follow-up within the first 4 weeks of therapy.[56]

Factors that produce good adherence

Five general categories of factors studied have been identified - these have been reworked by Stone:[78]

1) Situational factors.

These are economic, cultural, family and physical environment factors. The effects of these vary with circumstances, and are not amenable to easy change. Reviewing cultural factors specifically, Sumartojo found little common ground between cultures in terms of influences on adherence. She concludes with the assertion that the quality of services might well override any cultural influence on treatment outcome.

2) Nature of the illness.

Acute, painful and serious illnesses elicit the highest rates of adherence, and long duration chronic illnesses, like tuberculosis, elicit the lowest rates.

3) Treatment regimen.

As the complexity increases, adherence drops, worsening with the number of drugs and the frequency and complexity of administration. Once or twice daily therapy is clearly superior to thrice or four times daily.[88] It is not clear whether daily or intermittent therapy - twice or thrice weekly - is the easier for the patient. In terms of how the treatment is administered, it is well established that supervised therapy clearly improves adherence

in patients with tuberculosis.[79] This needs no elaboration. Sumartojo states that directly observed therapy (DOT) has been shown to improve adherence in both research and day-to-day service situations. The effects of DOT, however, do not persist after supervision stops.[79] In the Phillippines, blister packs have been used successfully where DOT was not possible.[89] It is noteworthy that side-effects of treatment do not appear to have a negative impact on adherence - where side-effects are mentioned in a study, most often no parallel mention is made of related adherence effects.[47] In fact, one Hong Kong study states that "adverse effects of treatment are an uncommon cause of poor compliance".[46] The same Hong Kong group found in a subsequent study that only 5% of patients required treatment modification as a result of significant adverse effects of the drugs - again no mention was made of nonadherence.[14] A Brazilian study of twice weekly versus daily therapy found that permanent discontinuation of therapy due to adverse effects occurred in less than 1% of patients on each regimen.[10] Westaway and Wessie report on care-givers' perceptions of problems in giving TB treatment to children, but none were related to side-effects of medication.[94]

4) Demographic characteristics.

As already seen (Sumartojo[79]), little can be altered here. It seems that these factors have more of an impact on utilisation of health services in the first place, rather than on adherence to treatment.[b]

5) The physician-patient interaction.

In terms of how tuberculosis services are structured worldwide and for the purposes of this discussion, read this as: The *service*-patient interaction. This has been found to be consistently positively associated with adherence, and is highly responsive to intervention. Two aspects of the interaction carry importance: effectiveness of communication and the emotional impact.

a) Effectiveness of communication:

Good recall of information about the illness, accurate recollection of the physician's expectations and increased knowledge of the prescribed regimen all increase

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[b] Adherence viewed in its broadest sense - why people choose certain services like traditional healers in preference to others, or choose not to utilise any service, or choose to come only at a late stage - was beyond the scope of this thesis.

adherence. In addition, a long established relationship with a specific physician also gives "unusually" high adherence rates. Sbarbaro underlines this: "I am deeply convinced that only through a relationship with a health professional truly concerned with the patient's entire health ... can we hope to influence a patient's health behaviour".[68] Sumartojo states that outreach workers also independently improve adherence.[79] Comprehensive services and thorough case management have been shown by Werhane et al in 1989 and by Curry in 1969 to have a potent positive effect on adherence.[79] All these contribute to effective overall communication. A recent study conducted by Dick in Cape Town has shown that where tuberculosis nurses were trained in communication skills, the risk of nonadherence in their clients was significantly reduced.[26] This intervention also led to increased motivation and enthusiasm in the staff, factors which are associated with improved treatment outcomes.

b) Emotional impact:

When patients feel satisfied with the interaction, when *their* expectations have been met, when they feel accepted, appreciated and respected, then they adhere better to treatment. In contrast, excessive waiting time - indicative of low respect - is associated with poor adherence and high dropout. In adult settings, friendliness and a relaxed atmosphere are not necessarily conducive to adherence. But antagonism, tension and confrontation are predictive of nonadherence. In paediatric settings, when mothers believed they were viewed as "good mothers", their adherence in giving their childrens' medication was enhanced.[40] It was lessened if they sensed unfriendliness, hostility, tension or punitiveness.

In summary then, the best predictor of adherence is the client's own history of adherence. The best interventions for ensuring adherence are a) supervision of therapy, and b) quality services which satisfy both the medical and emotional expectations of the clients. A surprising finding was that medication side-effects play little part in nonadherence.

2.3.2 The scope of the problem:

Tuberculosis aside for a moment, there are a few notable studies which depict the magnitude of adherence difficulties across the board of medical diseases: 1) Marston in 1970 surveyed 33 carefully conducted studies, covering a wide range of medical problems, and found a median of 43% of patients nonadherent.[55] 2) Macharia in 1992, using meta-analysis of randomised trials, showed an average appointment-keeping rate of merely 58%.[54] Nonadherence is thus not disease-specific for tuberculosis.

For tuberculosis, the picture is discouraging. In developing countries, the proportion of patients with active disease who complete therapy under standard conditions is as little as 20 - 40%.[56] In the USA, the CDC reports that only 75% of patients with active tuberculosis actually complete the usual 6 month therapy inside *12 months*.[13] Among those who are homeless and alcoholic, nonadherence approaches 90%.[79]

The South African situation

No figures on adherence to tuberculosis therapy are specifically and routinely published by the Department of Health in South Africa. The 1992 Tuberculosis Control Programme is credited with a 78% cure rate.[23] This is based on the "old South Africa" boundaries - the so-called homelands were excluded. The abscondment rate was 17% and the death rate 5%.

Three studies are cited by Strebel and Seager in "A Century of Tuberculosis: South African perspectives" edited by Coovadia and Benatar.[19] These will be used to illustrate some of the points made below in how adherence is measured:

1) Soweto figures from 1978 show that only 28% had received 80% or more of the required therapy by one year.[66]

2) In the Ciskei region, a Hewu study showed that 75% of patients placed on daily supervised therapy completed 80% of their doses.[20]

3) A cross-sectional study in the Western Cape found that 82.5% of patients had completed more than 75% of their treatment by the survey date.[2]

A recent study from Kwazulu/Natal - Hlabisa Health Ward - showed a very high rate of adherence, measured by completion rates, where 83% completed therapy.[95] This was

achieved using twice weekly ambulatory therapy, and success was attributed to many different modalities of treatment sites and supervisors used, as well as regular audit and feedback to the team involved.

The report of the Western Cape's Strategic Management Team: Task Force on Tuberculosis of December 1994 showed that 19% of the patients fail to complete 80% of their treatment.[37] But the report also states that the data are not accurate. More accurate data for Cape Town by Dick show that only about 60% (56.4%, 62% and 58.3% in 3 different studies) of patients complete 75% - 80% or more of their prescribed tuberculosis medication.[26] The Western Cape Regional Services Council (now the Cape Metropolitan Council), which carries the single largest annual caseload of tuberculosis of any local authority in South Africa, reports that in 1993 the rate of patients completing treatment was 63%, whereas the treatment interruption rate was 21%.[81] These data were collected longitudinally for each patient.

2.3.3 Measuring adherence

There is no gold standard for measuring adherence, either in tuberculosis or generally[79, 88, 90]. There are two broad ways of quantifying the phenomenon of adherence in tuberculosis, the first being categoric and the second numeric:

Rate	**Definition**
Completion or dropout rate	(No. so categorised/ No. enrolled) x 100%
Adherence rate	(Doses taken/ Doses prescribed) x 100%

Note: The completion or dropout rate can also be found expressed as adherer, complier, intermediate adherer, nonadherer, defaulter, absconder or delinquent rates as the case may be. Adherence can be studied as a continuous variable without categorising patients, but in most practical settings and research studies categorical classification is utilised.

Completion or dropout rates:

Treatment completion rates: This measure can be used in the case of tuberculosis because there is an endpoint definable at the start of therapy. In the case of a number of chronic diseases (adult asthma, diabetes, epilepsy or hypertension) treatment could be lifelong, and this measure would not be applicable. The definition is the number of patients completing treatment or discharged-as-cured over the number of patients starting. This measure could however be time bound, eg. measuring the percentage completing a required therapy by 6 months, or 12 months as in the Soweto study above.[66] Adherer rates: This is the number of patients adherent (eg. 75% or better adherence) over the total on treatment. The results from Hewu above are an example of this measure.[20] It is similar to the completion rate, but differs from the *adherence* rate, below. Delinquent/ defaulter/ dropout rates are also reported in trials as an indication of the adherence to therapy. This is the number of patients who at one or other time during their treatment were nonadherent (various definitions are operative here, eg. missed 14 or more consecutive days on treatment, or whose monthly rate was <80%, were defaulting (missed >2 months of treatment) or who dropped out altogether. This must be seen as invaluable extra information because it alters the power of the conclusions or recommendations of any particular work.

Adherence rates: (doses taken/prescribed x 100%)

This should be measured longitudinally, not cross-sectionally, and the intention-to-treat (or inception cohort) method should be used.[102] If cross-sectional methodology is used, results could be skewed to reflect spuriously greater adherence rates. The intention-to-treat method uses as denominator all those who were initially enrolled, not only the treatment completers. It analyses the cohort by intention to treat. The systematic loss to analysis of nonadherents cannot otherwise be overcome by statistical manoevres.[40] The method entails monitoring the adherence of each patient longitudinally from the commencement of therapy until the point of discontinuation.

The adherence rate which ensures cure has never been scientifically determined, and so the definitions of nonadherence that are used differ. Few authors actually give their definitions of nonadherence, and if they do it is often just *en passant*. Because "count-compliance" is often used, and because dose-timing information is not available, it is scientifically impossible to correlate therapeutic outcome with adherence.[88] Thus definitions which use a cut-off point are at this stage still arbitrary, but there are no objective data to recommend one cut-point above another. Possible ways of addressing this lack are:[40]

Biologically, where nonadherence is defined as falling short of the point where the desired therapeutic outcome is unlikely to occur.[26]

Epidemiologically, where nonadherence is defined in terms of Tuberculosis Control Programme objectives.[15]

Statistically, where nonadherence is related to a measure of central tendency, eg. the median.[26]

Chaulet states that the failure rate of regimens increases when over 25% of doses are omitted.[15] This is probably the origin for the 75% cut-off which is often used.

The two adjacent large local authorities in Cape Town have thusfar used different definitions. The Cape Town City Council Health Service has used a level of 80% doses taken/doses prescribed as the categorical cut-off, whereas the Western Cape Regional Services Council (now the Cape Metropolitan Council) has used 75%. The new South African National Tuberculosis Register system surprisingly uses 67% as the cut-off for treatment interruption - 2 months off treatment over the 6 month period is considered a "treatment interruption".

Of the numerator and denominator in the above equation, the prescribed doses (denominator) is the easier to obtain: from the patient's notes, study protocol or standard treatment regimen of the Tuberculosis Control Programme. The doses actually taken (numerator) is more difficult. Haynes, Taylor and Sackett[40] divide the measures used to monitor or estimate the actual doses - and thus adherence rates -

into 4 categories of decreasing credibility:

a) Objective direct and longitudinal measures

b) Immediate direct measures

c) Objective indirect measures

d) Subjective indirect measures.

a) Objective direct and longitudinal measures

This category is the only one viewed by Vander Stichele[90] as suitable for measuring compliance in clinical trials. Such measures are 1) *devices* and 2) *markers* or tracer substances.

1) Devices rely on mechanical events to register a pill taking event. The original (all-disease) prototype was developed by Moulding in 1962 for the very purpose of monitoring compliance in tuberculosis. However, such gadgets have been largely ignored by the tuberculosis experts since.[67] The most exciting modern devices are electronic recording systems: microelectronic circuits contained in the cap of a classical drug container to record the time of opening and closing of the container, thus storing data on times and dates. Data can be fed into a microcomputer by plugging a cable into a tiny female jack on the cap, and then processed for analysis.[90] This gives unprecedented feedback to the health care providers, both for the individual patient and for programme evaluation.

2) Markers are "substances, which are co-formulated with study drug and placebo to measure patient compliance with drug therapy".[90] These include radioactive substances, inert molecules, stable isotopes (notably deuterium oxide - heavy water) and pharmacological substances like low dose phenobarbital or digoxin.[88,90] They work on much the same principle as HbA1c (in diabetes, albeit inversely), in that the level of adherence to therapy is related to the blood level of the identified marker. Some markers can also theoretically measure the chronology of dosing.

b) Immediate direct measures, eg. blood levels of the drug, or urine tracer tests. In tuberculosis, this would usually be an INH urine test, a commercially available paper strip test. The colorimetric Potts-Cozart test for INH has been used by the State of Arkansas, USA, in preference to the commoner INH urine tests.[69] The problem with this

method is that it often measures "white coat compliance", or the adherence in the immediate pre-appointment period. This difficulty can be circumvented by random visits to the patient to obtain specimens.

c) Objective indirect measures, eg. Directly observed therapy, count compliance, pill count or attendance for prescription refill. The last two can unfortunately easily be distorted by the patient discarding leftover tablets. This is the commonest method used operationally by the tuberculosis services. Also included in this category by Haynes, Taylor and Sackett is *therapeutic outcome* - a biological measure of compliance.

d) Subjective measures, eg. interview of the patient, the patient's family or of the clinician. That clinicians cannot subjectively accurately identify those nonadherent has been emphasized by a number of authors.[40, 78, 79] This measure is usually the least reliable. Some of the early writers on the subject believe, however, that a well conducted interview is a better means of obtaining the adherence rate than pill count.[88] This art was termed *clinimetrics*.

Research quoted by Sumartojo agrees with the above weighting. Stone[78] states that estimates of the degree of adherence seem to be negatively correlated with the objectivity of the method!

Sumartojo suggests that probably the best approach to measure and express adherence would be to use multiple measures. Vander Stichele has suggested the development of an adherence index to reflect the vagaries of complex patient behaviour.[90] Expressing adherence as continuous longitudinal data and a statistical reporting format might also become the standard.

Summarising adherence rate measurement then, one can conclude that no single adherence measure is sufficient to tell the full story of a complex interaction, and that accurate adherence data are not easily obtained.

Methods used locally

Dick [26] in her PhD thesis "Adherence to antituberculosis therapy in Cape Town" utilised count compliance with the categorical cut-off as 75% doses taken/doses prescribed, employing the inception cohort or intention-to-treat method. Dick categorised the patients as adherents, defaulters and erratic. Periods of no treatment in weeks were reported, as well as average dose units per week.

2.3.4 Improvement strategies/ Management of nonadherence.

In general, the literature on nonadherence is not well described in this regard. Reichman outlines a number of methods for improving adherence and at the same time intimates a need for international collaboration on programmes to enhance adherence.[63] The methods were directly observed therapy, incentives and enablers, fixed-dose combination pills, patient education, appointment reminders, and comprehensive services. I could find no easy step-by-step measures or "recipes" to manage nonadherence as it occurs in the clinics. There were a few guidelines, however in the following reports:

1) The American Lung Association of South Carolina has outlined a number of methods used to improve adherence with therapy, called "Enablers and Incentives"[27]. Enablers are indirect measures that help the patient to more readily complete the therapy. Incentives are large or small, and can be food, goods or services. (The distinction between enablers and incentives was not clear.) They are aimed at getting the client to take medicine and keep appointments. Some examples of enablers and incentives are food, clothing, automotive accessories (eg. motor oil), fishing supplies, household cooking utensils, general services (eg. laundry), transportation, specials for holidays (eg. Thanksgiving hams), help with children, personal care and flowers for the garden.

2) The South Carolina Department of Health and Environmental Control and the New York City Department of Health have attempted to improve adherence using many strategies, often combined.[11] They are a mixture of "carrot" and "stick": apart from enablers and incentives mentioned above, they also use directly observed therapy (DOT), court-ordered DOT and even commitment for in-patient management for recalcitrant nonadherers.

However, in light of the review by Stone summarised above on page 9, a more perspicacious and rational approach should be that of Rouillon,[64] who sees a default as "an omission on the part of the patient or the services, an omission which necessitates a corrective intervention, in the interests of the patient and/or in those of the community", again de-emphasising a convergence on the patient. The primary focus of action following nonadherence is then not solely on the patient but includes the services and the community. She makes the point that *preventive* management of adherence is the most important, and that all 5 levels of those involved need to be proactively motivated: Politicians, legislators and leaders; planners; doctors and staff of the public health services; the community; and lastly, patients. The most important group to be motivated, she states, are the staff who carry out the Tuberculosis Control Programmes, because their efficiency and attitudes have a direct effect on the quality of the services, on their delivery and on the patients themselves. The problem with this approach is that these staff are often reluctant to change their ways. In the words of Rubel and Garro: "Because delivery of health care is governed by time-honored traditions learned during professional training and supported by programmatic norms, however, efforts to modify attitudes and behavior of clinical staff often meet with resistance." [65]

2.3.5 Summary

In Cape Town, an area with very high incidence rates of both adult and childhood tuberculosis, the extent of nonadherence to tuberculosis multi-drug therapy is high - about 40%. Accurate data on adherence rates are not easily obtained, and objective indirect methods have thusfar been employed. The best predictor of adherence is the patient's own treatment record, and the best methods for improving adherence are supervision of therapy and satisfying the patients' emotional and medical needs. More emphasis should be placed on preventive management of nonadherence by training and motivating the staff in the clinics, difficult as this may be.

2.4 Literature on intermittent chemotherapy for tuberculosis

The first consideration should be to theoretical models. Mitchison and Dickinson did experimental laboratory work on this subject in the 1960's on guinea pigs.[58] The work was then summarised again by Mitchison, and the verdicts for the various drugs were as follows:[57]

Isoniazid	Effective in dose intervals up to 4 days; 8 days too long.
Rifampicin	More effective when given intermittently.
Pyrazinamide	Similar duration of sterilising activity from 1 and 4 day exposure.
Ethambutol	More effective when given intermittently.
Streptomycin	Little change in activity as doses became more intermittent.
Ethionamide	Little change in activity as doses became more intermittent.
Thiacetazone	Much less effective if given intermittently.

Intermittent therapy for the main drugs clearly works in vitro. With isoniazid (INH), no regrowth occurs between doses if spaced over 4 days, but 8 days seems too long a period. This is borne out by clinical studies described in the following section, which proved that once weekly therapy was ineffective. Rifampicin is more effective intermittently because the mycobacterium is much more susceptible during the growth phase than it is during the preceding lag phase. The mechanisms for pyrazinamide and ethambutol are unclear. Pyrazinamide may inhibit the organism to then be killed by host defences.

2.4.1 Intermittent chemotherapy for tuberculosis - adults

Case study research using intermittent therapy for tuberculosis started in 1953, just a few years after the introduction of isoniazid. In summary, the history of the advances in intermittent therapy mirror the advances in the usual daily therapy. The main advances (simplified) were[3]

a) the move away from monotherapy (in the 1950 and 60s),

b) the demonstrated effectiveness of rifampicin in 1973,

c) the use of pyrazinamide as a first-line agent and the concept of Short Course

Chemotherapy (1974 - 1981).

These advances were mainly informed by 1) high resistance rates following monotherapy 2) early and sustained sterilisation and 3) low relapse rates.[32]

Allied to these advances was the use of intermittent therapy for the continuation phase of therapy, following a so-called initial intensive phase, which was based on the experimental work of Mitchison. Current thinking is that fully intermittent therapy is as effective as daily therapy,[11] provided that an initial intensive daily phase is desirable and that 4 drugs should be used. There is a difference in opinion as to whether thrice or twice weekly therapy is better. The WHO favours thrice weekly,[99] whereas the CDC favours twice weekly.[12, 13] Once weekly therapy has been proven to be ineffective.[72]

The trends and advances in the scientific experience with this form of treatment in adults are set out in Table A below. For tables A, B and C the standard abbreviated notation for tuberculosis regimens is used. There are slight variations in how this notation is used. A subscript following the drug abbreviation indicates the frequency of intermittent dosing. For some writers a subscript covers all preceding letters, but most use brackets or a subscript immediately following the each letter.[c] The latter method is used in this thesis because it can describe the treatment regimen more accurately.

Studies of the 1950s and 1960s

These are characterised by mono- and dual-drug therapy. Monotherapy fell out of favour because of rising resistance rates as the therapy progressed. Intermittent therapy twice weekly was shown to be as effective as daily therapy, but a dosing frequency of once weekly was ineffective.

The first large controlled follow-up study was performed in India by the Madras Tuberculosis Chemotherapy Centre, which showed that twice weekly supervised therapy was at least as effective as daily self-supervised therapy.[84] Although the initial

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[c] As illustration, a study of tuberculosis in childhood by Varudkar[92] has been differently reported as 6 $H_3R_3E_3$ by Starke,[77] and 6 HRE_3 by the original article, which assumed that the subscript covered all 3 preceding letters.

treatment duration was 12 months, there was still residual cavitation present at the end of treatment in a large number of subjects (31%), and these were continued with isoniazid monotherapy for 6 or 12 months.[61] A "logical consequence" study (as it was termed) done by the same group found that once weekly therapy was ineffective.[85]

Studies of the 1970s

There were two main advances in this period. The first was establishing the safety of rifampicin in intermittent therapy. While the Madras Tuberculosis Chemotherapy Centre was continuing with good studies on twice weekly therapy without rifampicin, others were starting to include rifampicin in treatment trials. The Poole study of 1971, which used a rifampicin dose of 1200mg in the intermittent phase, was terminated because of significant toxic effects and development of antibodies to rifampicin.[60] A later study - Fox et al of 1977 - used inter alia 900mg of rifampicin twice and once weekly, but found that a) once weekly therapy was ineffective and b) there were significant toxic effects with once weekly 900mg rifampicin.[71, 72] Thus rifampicin gained a reputation of being toxic. The study of Mitchison, Allen et al in Hong Kong in 1978, however, laid to rest the spectre of immunologic reactions to rifampicin, with few incidents either of the "flu" syndrome or rifampicin dependent antibodies.[43] Dutt's study of 1979, using a lower dose of 600mg of rifampicin, found that it was effective at this lower dose and also that it carried no toxic effects.[29]

The second advance was the use of pyrazinamide as a first-line agent. The trial of Mitchison, Allen et al in Hong Kong cited above also made the significant advance of using pyrazinamide with rifampicin as a first line agent and showed its worth a) in improved early sterilisation rates and b) in preventing relapse after therapy.[43] Pyrazinamide was shown to outperform both streptomycin and ethambutol.

Studies of the 1980s

These studies served to confirm that pyrazinamide should be used as a first-line agent as it gave lower relapse rates, and that intermittent therapy - whether fully or only partially intermittent - was indeed successful even over 6 months. Additionally, only 2 drugs were used for the "continuation phase" (after the "intensive phase" of the first 1 -

2 months).

Snider's study of 1982 was noteworthy in that the total duration of therapy was successfully shortened to 6 months using intermittent therapy.[75] Fully 29% failed to complete their therapy, but those with good adherence had early sterilisation and 0% relapse. The Singapore study of Fox and others, using 1 - 2 months of daily therapy and 4 - 5 months of thrice weekly dosing, showed a combined failure and relapse rate of <2% over 24 months' of follow-up, including those with drug-resistant bacilli.[73] This controlled trial showed the effectiveness of a regimen with just 3 drugs (isoniazid, rifampicin and pyrazinamide) in the initial phase, followed by isoniazid and rifampicin only, given intermittently. However, the regimen with 4 drugs for 2 months in the initial phase had the highest early sterilising activity. In Hong Kong, a study by Allen, Chan et al used 4 fully intermittent therapy regimens and 1 fully daily regimen for 6 months to work out optimal combinations of drugs.[44] The significant finding here was that the recurrence rate was three times greater with a regimen containing no pyrazinamide. Castelo et al (1989) showed that even where "skid-row" patients were not excluded, a partially intermittent regimen was effective in a clinic-based use-effectiveness setting.[10]

Studies in the 1990s

The main advance was calculating the optimal duration of pyrazinamide treatment.

Fredlund of South Africa showed that fully intermittent twice weekly therapy using 4 drugs was as effective on an out-patient therapy as it was for in-patients.[35] The out-patient regimen used ethambutol as the fourth drug, in addition to the usual rifampicin, isoniazid and pyrazinamide. In-patients were given streptomycin as the fourth drug. Girling, Chan et al of Hong Kong did a detailed clinical trial with out-patient fully intermittent thrice-weekly therapy.[47] All got isoniazid and rifampicin for 6 months, and streptomycin for 4 months. The different groups were given 2, 4 and 6 months of pyrazinamide. An additional group was given no streptomycin, but 6 months of pyrazinamide. This study showed that even with fully intermittent therapy, pyrazinamide can be given only for the first 2 months, and also argued that a fourth drug is necessary in the initial phase if the regimen is fully intermittent. In the presence of isoniazid

resistance, there was however an advantage in giving pyrazinamide for the whole 6 month period.

In summary, intermittent therapy was found to be as effective as daily treatment for uncomplicated pulmonary tuberculosis in adults.

TABLE A: Trends and advances in intermittent tuberculosis treatment in adults

Study, Year and Location	Number	Regimen	Results
Frimodt-Moller et al,[36] 1953	-	$3H_2$ v 3H	Similar CXR findings at 12 weeks
Katz et al,[50] 1954/5	-	S_2H_2 v HS_2	Inferior results with fully twice weekly therapy.
Tyrrell,[87] 1956	91	S_2H_2, In-patient S_2H_2, Out-patient	78% favourable outcome 80% favourable outcome
Holmes et al,[41] 1962	29	$3H_1$ only	Only 2 became culture negative.
Madras TB Centre,[84] 1963 India	165	12PH $12H_2S_2$	1 died; 89% negative at 9 months; 4.4% relapse 2 died; 93% negative at 9 months; 6.3% relapse
Poole et al,[60] 1971 England	49	$3HRS/(15)H_2R_2$	Trial terminated - see commentary
Menon, Tripathy et al,[86] 1973 India	247	0.5PHS/12PH $0.5PHS/12P_2H_2$	87% negative at 12 months, self supervised 88% negative at 12 months, clinic supervised

Notation: E = ethambutol; H = INH; P = PAS; R = rifampicin; S = streptomycin; Z = pyrazinamide.

$2HRZ/4H_2R_2$ means 2 months of HRZ followed by (/) 4 months of H and R, both $_2$ times a week. If no figure follows the letter, daily treatment is assumed.

NB. The details of some of the earlier studies are not always clear, and thus not shown. Outcome measures in the various studies differed.

TABLE A (continued): Trends and advances in intermittent tuberculosis treatment in adults

Study, Year and Location	Number	Regimen	Results
Fox et al,[71, 72] 1977 Singapore	481	0.5SHR/12-18H_2R_2 0.5SHR/12-18H_1R_1	No relapses in 18 month groups No relapses in 18 month groups
Mitchison, Allen et al,[43] 1978 Hong Kong	680	6SHR 2SHRZ/4-6$S_2H_2Z_2$ 2SHRE/4-6$S_2H_2E_2$ 4$S_3H_3R_3Z_3$/2-4$S_2H_2Z_2$	4% relapse by 6 months 3% relapse by 6 months - This regimen contained no Z, and had a 19% relapse rate by 6 months 5% relapse by 6 months
Dutt et al,[29] 1979 Arkansas, USA	315	1HR/8H_2R_2 only	95% bacteriologically negative at 3 months; 10 failures; 1 relapse.
Snider et al,[75] 1982 Poland	119	2HRZS/4H_2R_2 only	29% failed to complete therapy 71% completed therapy: 100% bacteriologically negative at 3 months; no relapses
Fox et al,[73] 1985 Singapore	420	2HRZS/4H_3R_3 1HRZS/5H_3R_3 2HRZ/4H_3R_3	1 Bacteriological failure; 1 relapse 4 relapses, including 3 with drug-resistance 1 relapse

Notation: E = ethambutol; H = INH; P = PAS; R = rifampicin; S = streptomycin; Z = pyrazinamide.

2HRZ/4H_2R_2 means 2 months of HRZ followed by (/) 4 months of H and R, both $_2$ times a week. If no figure follows the letter, daily treatment is assumed.

TABLE A (continued): Trends and advances in intermittent tuberculosis treatment in adults

STUDY, YEAR AND LOCATION	NUMBER	REGIMEN	RESULTS
Allen, Chan et al,[44] 1987 Hong Kong	1207	$6(HRZSE)_3$	
		$6(HRZS)_3$	
		$6(HRZE)_3$	
		6HRZE	- These top 4 regimens had a 3.4% combined recurrence rate
		$6(HRSE)_3$	- This regimen, with no pyrazinamide, had a 10.3% recurrence rate
Castelo et al,[10] 1989 Brazil	667	2HRZ/4HR	17 died; 7% relapse
		$2HRZ/4H_2R_2$	10 died; 4% relapse
Fredlund,[35] 1990 South Africa	373	$6(HRZS)_2$	In-patients. 2 died; 4.3% relapse
		$6(HRZE)_2$	Out-patients. 2 died; 4.7% relapse
Girling, Chan et al,[47] 1991 Hong Kong	1386	$4H_3 R_3 S_3/2H_3 R_3 + 2Z_3$	No failures; 3% relapse rate
		$4H_3 R_3 S_3/2H_3 R_3 + 4Z_3$	No failures; 5% relapse rate
		$4H_3 R_3 S_3/2H_3 R_3 + 6Z_3$	No failures; 3% relapse rate
		$6H_3 R_3 Z_3$	Bacteriologic failure in 2% ($p<0.005$ v other regimens)

Notation: E = ethambutol; H = INH; P = PAS; R = rifampicin; S = streptomycin; Z = pyrazinamide.

$2HRZ/4H_2R_2$ means 2 months of HRZ followed by (/) 4 months of H and R, both $_2$ times a week. If no figure follows the letter, daily treatment is assumed.

2.4.2 Intermittent chemotherapy for tuberculosis - children

In contrast to adult studies where intermittent therapy largely kept step with the advances in daily therapy, research in the intermittent treatment of children started only in the 1980s, sparked by articles by Fox,[32] Smith[74] and possibly Kendig.[51] An excellent review of the entire subject of childhood tuberculosis therapy is provided by Starke.[77] Generally, the findings are similar to those in adults, i.e. the results of intermittent treatment are equal to daily treatment. It must be said, however, that the adult studies have been better conducted (much "tighter") scientifically, with larger numbers and better follow-up. The reason for this might be that endpoints in the treatment of childhood tuberculosis are more difficult to identify. By 1982 there were only 3 published papers on short course chemotherapy in children,[74] let alone intermittent short course chemotherapy. Trends and advances in the published studies are summarised in Table B.

The first study on intermittent therapy in children was from Chile.[48] The two groups were, however, not strictly comparable as their entry criteria as well as treatment regimens differed - those who were smear positive were put onto 4 drug therapy; those culture-only positive got 3 drug therapy. Nevertheless, satisfactory results were obtained.

Abernathy[1] reported in 1983 on a group of consecutively enrolled children put onto a 9 month regimen. Only the first month was daily therapy, with the months thereafter being twice weekly therapy only. "Excellent results" were reported by the researchers themselves, but no data were offered. It appears that all children were in fact cured by 9 months, although not unexpectedly, hilar adenopathy persisted on radiographs for 2 to 3 years. The first reported *fully* intermittent trial in children came from India in 1985.[92] There was a reported "excellent reponse" in 86% of the cases; again the claim was not further substantiated by statistics.

Biddulph's trial was notable for its sheer size and also for the high dropout rate: only 373 (58%) completed the 6 month course, and the follow-up rate was 34.9% of the inception cohort.[7,8] This study is said to have established the safety and efficacy of

short-course chemotherapy in children, but the claim cannot be accurate in view of the high dropout rate.

The small Starke/Taylor Watts study had no failures, relapses or toxicity.[76] In the Khubchandani study, three deaths occurred but it was not stated in which treatment group/s they occurred.[52] An interesting finding was that there was more toxicity in the fully daily group.

The Kumar trial was the first well-researched and documented study on *fully* intermittent therapy in childhood tuberculosis.[53] Both pulmonary tuberculosis and lymphadenitis tuberculosis were studied, making the numbers in each group small - approximately 20. Asymptomatic primary complex cases were excluded, and this might account for the relatively high death rate of 2.6%. Results obtained for the 2 groups were comparable.

In summary, despite the drawbacks mentioned, these studies have suggested that intermittent therapy is as efficacious as daily therapy in treating childhood tuberculosis.

TABLE B: Trends and advances in intermittent tuberculosis treatment in children

Study, Year and Location	Number	Regimen	Results
Ibanez and Ross,[48] 1980 Chile	54	$2HRZS/4H_2Z_2S_2$ $2HRZ/4H_2Z_2$	1 failure, related to resistance to isoniazid and streptomycin. No relapses. No failures, no relapses.
Abernathy et al,[1] 1983 USA	50	$1HR/8H_2R_2$ only	1 case of adverse effects of rifampicin. Excellent results stated.
Varudkar,[92] 1985: India	45	inter alia: $6\ H_3\ R_3\ E_3$	Excellent reponse in 86%.
Biddulph,[7,8] 1988 and 1990 Papua New Guinea	639	$2HRZS/4H_2R_2$ only	2% (12) died; 1% relapsed. 5/7 relapses were poor compliers. Only 373 (58%) completed the treatment.
Starke, Taylor-Watts,[76] 1989 USA	40	2HRZ/4HR $2HRZ/4H_2R_2$	No failures, relapses or toxicity.
Khubchandani et al,[52] 1990 India	118	2HRZ/4HR $2HRZ/4H_2R_2$	85% had significant clearing on chest radiograph; 9% toxicity 93% had significant clearing on chest radiograph; 3% toxicity

Notation: E = ethambutol; H = INH; P = PAS; R = rifampicin; S = streptomycin; Z = pyrazinamide.

$2HRZ/4H_2R_2$ means 2 months of HRZ followed by (/) 4 months of H and R, both $_2$ times a week. If no figure follows the letter, daily treatment is assumed.

TABLE B (continued): Trends and advances in intermittent tuberculosis treatment in children

STUDY, YEAR AND LOCATION	NUMBER	REGIMEN	RESULTS
Kumar et al,[53] 1990 India	76	$2HRZ/4H_2R_2$	1 died; 6 dropped out; 1 responded poorly.
		$2H_2R_2Z_2/4H_2R_2$	1 died; 4 dropped out; 1 responded poorly.

2.5 Studies on adherence in childhood tuberculosis

Studies which addressed adherence are chronologically summarised in Table C.

Only 2 studies, those by Dick[26] and by Oviawe and Ojemudia[59], dealt specifically with adherence. For the purposes of investigating adherence on different drug regimens, however, the study by Seth is the most instructive, because it researched adherence rates for 6 different regimens.[70] The best adherence was with a simple two-drug unchanging 6 month regimen. This was the only study to specifically state adherence rates (% doses taken/prescribed), but a weakness was that unlike other studies, therapeutic outcomes of each therapy group were not specified separately. As mentioned before, both adherence rate and therapeutic outcomes are ideally recorded.

Biddulph's study shows the benefits of short-course chemotherapy (SCC) in children.[6] Before SCC was introduced, over 40% of all paediatric beds were taken up by tuberculosis cases, and there was a 25% completion rate for the 18 month regimen. With the introduction of SCC, the completion rate increased to "approximately 75%". Additional benefits were reduced failure, relapse and toxicity rates. Weaknesses of his study were that there was no control group, and that the completion rates were not accurately measured.

The Nigerian study of Oviawe and Ojemudia investigated those who failed to complete their treatment, defined as non-attenders.[59] The mean duration of therapy prior to default was 20 weeks. The significant findings are shown in Table C: the non-attenders had a shorter initial hospitalisation, had more disruptive events in the family, and the level of maternal education was lower. This was not short-course chemotherapy, however.

Dick found that the rate of adherents (% adherent enrollees) was higher in those using a "community" supervision option, as opposed to supervision at the clinic.[26] This was short course chemotherapy, but the regimen used was not specified.

The study by Beyers et al showed that 88% of the children completed their treatment

by 6 months.[5] They used 80% as the categorical cut-off for adherence. Weaknesses were that therapy was not specified and that numbers were too small for statistical analysis. It was noted that those from urban squatter areas were possibly less adherent.

These studies have shed little extra light on the subject of adherence to tuberculosis therapy in children, and highlight the fact that little is known about this subject. Key points are that long duration of therapy - 12 and 18 months above - led to greater nonadherence, that high rates of adherence are possible with regimens of 6 months' duration and that maternal education and a stable family were associated with better adherence. A study by Seth showed that a simple unchanging daily regimen resulted in excellent adherence.

TABLE C: Studies dealing with adherence in childhood tuberculosis

Study, Year and Location	Number	Regimen	Results		
Seth,[70] 1986 India	168	6HR	79.9% adherence		
		2HRZ/4HR	71.1% adherence		
		2HRZ/4H_2R_2	66.1% adherence		
		12HR	64.0% adherence		
		2HR/4H_3R_3	63.0% adherence		
		0.5SHE/11.5HE	60.1% adherence		
Biddulph et al,[6] 1987 Papua New Guinea	321	2SHRZ/4H_2R_2	"Approximately" 75% completion rate		
		3SHRZ/3H	"Approximately" 75% completion rate		
		Probably 18SH	25% completion rate		
Oviawe and Ojemudia,[59] 1993 Nigeria	146	1SHT/17HT	Initial admission Mean (range)	Disruptive events in the family	Maternal education level - secondary +
	76	Attenders	57.7 days (35-111)	7	49
	70	Non-attenders	49.7 days (31-94)	20	17

Notation: E = ethambutol; H = INH; P = PAS; R = rifampicin; S = streptomycin; Z = pyrazinamide.

2HRZ/4H_2R_2 means 2 months of HRZ followed by (/) 4 months of H and R, both $_2$ times a week. If no figure follows the letter, daily treatment is assumed.

TABLE C (continued): Studies dealing with adherence in childhood tuberculosis

Study, Year and Location	Number	Regimen	Results	
Dick,[26] 1994: Cape Town, South Africa	203	Not specified	Supervision Method	Adherer rate (the percentage who were adherent)
			Clinic	64%
			Community worker	82%
			School	85%
			Creches	75%
Beyers, Gie et al,[5] 1994 Cape Town, South Africa	131	Not specified	88% completed 80% of therapy in 6 months	

3. METHODS

3.1 Definition of terms:

Classification of tuberculosis in the children

Modified WHO criteria for childhood intra-thoracic tuberculosis were used to classify the children as suspect, probable or confirmed cases.[97] Suspect cases were those with suspicious chest radiograph and suggestive clinical features (cough, wheeze, failure to thrive). Probable cases were those with suggestive chest radiographs (hilar adenopathy with/without parenchymal lesions, a miliary pattern or pleural effusion); or suspicious chest radiograph (peri-hilar opacification with/without parenchymal lesions) with a positive tuberculin skin test or a positive contact. A Tine test where two or more papules were confluent was considered positive, and equivalent in significance to a Mantoux test of 15mm induration. Confirmed cases had a positive sputum or gastric washing culture for *M.tuberculosis*. Parenchymal disease was defined as those with initial chest radiographs displaying any of the following: segmental involvement, with or without hilar adenopathy; cavities; bronchogenic spread; or miliary disease.

Adherence

75% was the cut-off used operationally by the services at the time of the study.[26] Adherence was defined as 75% or more of doses taken/prescribed. Adherents were those who achieved 75% or greater adherence over the total treatment period, while nonadherents were those who achieved less. Para-adherers, a term coined by this study, included those who exhibited *any* sustained nonadherence. It therefore encompasses all the nonadherers, plus those classified as adherents, but who took <75% of doses over any block of four weeks. Excellent adherers were those who were not para-adherers. Adherence was measured over 24 weeks.

Crowding index

A value of >2.5 of this formula: (adults + [children <10 years]/2)/sleeping rooms indicates crowding.[18] The social data collected in this study included all children under 18 (and not under 10), so the formula was modified: (adults + [children <18 years]/2)/bedrooms. This method *under*estimated the crowding.

3.2 Study design and methods

Ethics

The study was a collaborative venture between the Western Cape Regional Services Council (now the Cape Metropolitan Council) and the Departments of Paediatrics and Child Health of the Universities of Cape Town and Stellenbosch. The study was approved by the respective Ethics and Research Committees of these institutions.

Design and sample size

The study was a clinic-based open randomised controlled clinical trial. The size of the cohort (an intended 103 in each group for an alpha error of 5% and a beta error of 20%) was constructed on the basis of the effectiveness of therapy - given an achievable 98% cure rate for the control group, a cure rate of less than 88.3% would be significantly different in the intervention group. Using the same sample size and a 65% adherent rate for the controls (as informed by the literature), a rate of 81.3% or above for the experimental group would be statistically significant. Enrolment stopped once 222 children were enrolled.

Setting and study population

The study took place at the Idas Valley Clinic, a regional referral centre for the diagnosis and treatment of tuberculosis in the greater Stellenbosch district. All children diagnosed as pulmonary tuberculosis in the district during the period June 1991 to June 1995 were admissable.

Inclusion and exclusion criteria

Inclusion criteria were: children <14 years with intra-thoracic tuberculosis; home address in the areas served by the following clinics: Delft, Dennemere, Hillcrest, Kleinvlei, Lwandle, Macassar, Malibu, Mfuleni, Northpine, Russell's Rest and Scottsdene; accompanied by parent or legal guardian to the Idas Valley Clinic. Exclusion criteria were: home address in a farming or rural area; no consent; previous tuberculosis; more than 30 days' hospital treatment; extra-thoracic tuberculosis.

Data measurement

At enrolment, a detailed clinical assessment was performed. This included a history of BCG immunisation, duration of illness, symptoms, details of tuberculosis contact and whether the contact was smear or culture positive for *M.tuberculosis*; socio-demographic details (age, sex, room occupancy, employment of adults in the household); a full clinical examination, including weight and height; tuberculin skin test and chest radiograph. Weight was measured using a Tanita baby scale for those who could only lie or sit, and a balance-arm scale for the rest. Length was measured in those under 3 years, and height was measured in those over 3 years. Only one set of measurements was done in each case. Nursing staff were trained at the outset in these procedures. All those enrolled were clinically assessed by the author of this dissertation. Sputum or gastric washings for *M. tuberculosis* culture were not done in the clinic, but were often available in those who had been referred by a hospital. Children diagnosed as having tuberculosis were randomised by household unit to receive either intermittent therapy (called Regimen 2 for two times a week) or conventional therapy (called Regimen 5 for five times a week) - see Section 3.3: Drug administration procedure. Randomisation was by random number tables: an odd number would assign the household to Regimen 2 and an even number would indicate Regimen 5. Households rather than patients were used in the randomisation process to avoid confusion in a household in the event of more than one child from a particular household being enrolled. A standard questionnaire was completed, along with the consent form (Appendices 1 and 2). Consent was taken *after* randomisation, for the purposes of informed choice or consent.

Follow up times were 3, 6, 12 and 18 - 30 months at which visits the children were assessed according to 4 criteria of change: history from the parent, clinical condition, weight and chest radiograph, and scored according to the schedule set out below:

	SCORE			
Criterion	**-1**	**0**	**+1**	**+2**
Parent's Assessment	Worse	Not better	Better	Much Better
Clinical Assessment	Worse	Same	Better	Much Better
Weight Gain	Lost weight	Same	Gained weight (ipsi-centile)	Significant gain (Crossing centiles)
Chest Radiograph	Worse	Same	Some clearing	Definite clearing

The score range for each criterion was -1 to +2, giving a possible combined score range at each visit of -4 to +8.

The data on adherence for each patient were recorded per dose by the community clinic nurse on the treatment sheets, by initialling a sequentially dated and numbered block for each dose given. The sheets (Appendices 3 and 4) were returned to the Idas Valley Clinic on completion of treatment for analysis. Exact dates for the adherence and default patterns were then recorded using a calendar by the following method: the first 24 weeks were divided into consecutive 4-week blocks. The number of doses taken during each block were counted. Should the adherence have been <75% for any block, it was noted as nonadherence. Blocks of four weeks were used in order to compare twice and five times weekly dosing - over any shorter period the adherence rates of the two regimens would not have been comparable, because the denominators are different. The first episode of non-adherence was then inspected, and the date of the first missed dose was entered as the date on which the default pattern began.

Standardisation and data quality

The author of this thesis collated all the initial and outcome data. Paediatricians on the research panel visited the Idas Valley Clinic twice a month to perform the diagnostic and radiological review for enrollees and follow-ups. They were blinded as regards the treatment regimen. The research technologist collated the adherence sheets, and classified the adherence as per the method above. She also entered all data into the database programme. As the study progressed, the coding list was revised and appears as Appendix 5. A complete audit of all data fields was done in November 1993, and at the end of the study. There was no independent checking of the database, nor sub-sample verification.

Analysis of the data:

The data were analysed using Epi Info database programme.[22] Non-parametric techniques were used to compare medians of groups (Kruskal-Wallis). Continuous variables were expressed as median (quartile 1 - quartile 3). The chi squared test was used for categorical variables and contingency tables. A P value of <0.05 was taken as significant. A small computer programme was written to derive data from the database (Appendix 6).

3.3 Drug administration procedure

All treatment was supervised, either professionally or by the parent. The parents and their children were required to present themselves at least weekly at the community clinic to collect the children's therapy, whatever the regimen. Those on intermittent therapy (Regimen 2) received isoniazid, rifampicin and pyrazinamide for 2 months, followed by isoniazid and rifampicin for 4 months ($2H_2R_2Z_2/4H_2R_2$). The doses were isoniazid 15 mg/kg/dose, rifampicin 15 mg/kg/dose and pyrazinamide 55 mg/kg/dose. Those on conventional therapy (Regimen 5) received 3 drugs Monday to Friday for 6 months ($6H_5R_5Z_5$) at the following doses: isoniazid 10 mg/kg/dose, rifampicin 10 mg/kg/dose and pyrazinamide 25 mg/kg/dose. Isoniazid and pyrazinamide were in tablet form, rifampicin was either a syrup or for the older child in capsule or tablet form. For both regimens, the dosages were rounded off to the nearest tablet. The dosages available were: isoniazid: 50mg, 75 mg, 100mg, 200mg and so on. Pyrazinamide was available in 500mg tablets, which could be quartered to give a multiple of 125 mg. Rifampicin was titratable to the nearest 20 mg up to 300mg in syrup form, and thereafter by 150 mg as a capsule or a tablet.

There was no direct cost to the patient for the medicines, the investigations nor for the transport to and from the referral clinic. No embargoes were placed on diet or exercise. Those on twice weekly therapy received a full 6 months' (= 26 weeks) therapy, whereas those on five times weekly therapy got the conventional $5^1/_2$ months' (= 24 weeks) therapy of the service at the time of the study.

4. RESULTS

4.1 ENROLLEES

There were 318 eligible for enrolment. 4 children were refused enrolment by their parents. The patient flow or trial profile is described in Table 1.

TABLE 1: Trial profile

	Total	Regimen 2	Regimen 5
Eligibles	318		
less Refusals	4		
Randomised	314	153	161
less Tuberculin and radiograph negative	24	12	12
less Tuberculin positive, radiograph negative	68	43	25
Enrollees	222	98	124
less Pre-treatment exclusions	9	3	6
Inception cohort	213	95	118
less Exclusions from analysis	7	6	1
Cohort analysed, by intention to treat	206	89	117

The data were analysed as initial data, outcome data and adherence data.

4.2 INITIAL DATA

Altogether 222 children were enrolled, 98 on Regimen 2 and 124 on Regimen 5. Recorded consent for their children's participation was obtained from the parents or guardians in all except 14 (6.3%) cases. All parents/guardians gave verbal consent.

Exclusions:

There were 9 exclusions for pre-treatment reasons:

Table 1a: Pre-treatment exclusions

	Total	Regimen 2	Regimen 5
Exclusions	9	3	6
Female/ Male	5/4	2/ 1	3/ 3
Reasons for exclusion:			
Prior tuberculosis treatment		1	2
Diagnosis change		1	2
Treatment incorrect		1	1
Incomplete initial data		0	1

There were no statistically significant differences between these small groups.

This left 213 children on the study, whose baseline data are given overleaf. All the data were analysed first for any differences between the two treatment regimens and then for any differences between the two groups identified retrospectively by the treatment records as adherent and nonadherent.

Table 2: Baseline data

	Total	Regimen 2	Regimen 5	P value
Number	213	95	118	-
Female/ Male	107/ 106	46/ 49	61/ 57	0.68
Age in months:	25.9	24.9	27.9	0.58
	(15.4-41.7)	(13.4-40.5)	(16.9-43.2)	
Weight in kg	12.0	11.5	12.1	0.23
	(9.4-14.0)	(9.0-14.0)	(10.0-14.4)	
Weight for age median %	93.1	89.6	96.6	0.015
	(84.0-103.1)	(82.4-100.7)	(86.1-104.0)	
Height in cm (N = 187)*	85.0	83.6	86.0	0.37
	(75.0-94.7)	(74.0-95.0)	(76.0-94.5)	
Height for age median %	95.3	95.0	96.2	0.09
	(92.9-99.9)	(92.6-99.3)	(93.2-100.8)	
Crowding index: (N = 205)*	3.3	3.3	3.3	0.66
	(2.3 - 4.3)	(2.2 - 4.1)	(2.3 - 4.5)	

*Please note that heights of 26 children (12.2%) were missing, as were the full data on crowding for 8 children (3.8%). Figures in brackets are the interquartile ranges.

Because of the use of the inception cohort/ intention-to-treat method,[102] there should have been no further exclusions. A further 7 children, however, were excluded because their adherence monitoring sheets could not be analysed properly, having been mislaid in 6 cases. The seventh sheet was indecipherable, the child having received both forms of therapy. Of the 7 children, 6 were on Regimen 2, the twice weekly regimen. This left 206 children in the study. Using the same criteria as above, the P values are very similar, as seen in Table 2a overleaf.

Table 2a: Baseline data - P values for N = 213 and N = 206

	Sex	Age	Weight	Weight/Age	Height	Height/Age	Crowding
(N = 213)*	0.68	0.58	0.23	0.015	0.37	0.09	0.66
(N = 206)*	0.69	0.62	0.32	0.030	0.24	0.11	0.90

*The numbers for Height, Height/Age and Crowding are fewer, as noted above

HISTORIES:

The histories did not differ between the 2 groups, and specifically not in the stated history of weight loss. Tuberculosis contacts: There were 142 (69%) children with a documented contact, with no difference between the treatment groups. These contacts were thoroughly reviewed in terms of their bacteriology, but again no difference could be found between the groups. Prior generation contacts were the commonest.

EXAMINATION:

The only difference in the examination is noted above - those on Regimen 2 had a significantly lower weight for age. As Regimen 2 was *not* the control regimen, this difference would not complicate the interpretation of the results.

DIAGNOSTIC CLASSIFICATION:

There were no differences between the groups in terms of diagnostic catagories.

Table 3: Diagnostic categories

	Regimen 2	Regimen 5	P value
Confirmed cases	4	4	
Probable cases	82	111	
Suspect cases	3	2	0.68
	89	117	

There were 67 subjects with parenchymal disease, 27 (30%) on Regimen 2 and 40 (34%) on Regimen 5, with no statistical difference between the groups (P=0.66). One

child with a miliary-like picture on the chest radiograph was treated as an out-patient with fully intermittent therapy from the start. The child was not ill enough to warrant hospitalisation, and was carefully watched clinically.

4.3 TREATMENT OUTCOME DATA

The first measure of adherence is *biological or therapeutic outcome*. There was no difference in the outcome between the 2 groups:

Table 4: Outcomes v Regimen

	Total	Regimen 2	Regimen 5	P value
No. discontinued therapy at scheduled time	199	85 (96%)	114 (97%)	0.59
3 months				
Number scored		70 (79%)	89 (76%)	0.40
Outcome score median		5 (4-6)	5 (4-7)	0.24
6 months				
Number scored		68 (76%)	94 (80%)	0.37
Outcome score median		6 (5-7)	6 (5-7)	0.90
Median weight gain by 6 months in kg*		1.5 (1.0-2.1)	1.75 (1.2-2.3)	0.21

*Weights for 167 (81.1%) children were collected at 6 months, 69 (77.5%) on Regimen 2 and 98 (83.7%) on Regimen 5. Ranges in brackets are the interquartile ranges.

There were no differences in the scores between the groups at 3 or 6 months, nor in the weight gain.

4.4 ADHERENCE DATA

The second measure of adherence used in this study was the percentage of doses taken/ doses prescribed:

Table 5: Adherence by Treatment Group

	Total	Regimen 2	Regimen 5	P value
Number	206	89	117	
Adherence %	91.5	93	91	0.29
	(76-97)	(75-100)	(77-97)	
Nonadherers				
Number (%)	46 (22.3%)	19 (21.3%)	27 (23.1%)	0.90
Median days to default	50.5	72	42	0.08
	(34-84)	(44-93)	(33-69)	
Para-adherers				
Number (%)	97 (47.1%)	40 (44.9%)	57 (48.7%)	0.69
Median days to default	74	88.5	57	0.07
	(39-110)	(50-126)	(35-105)	

Ranges in brackets are the interquartile ranges

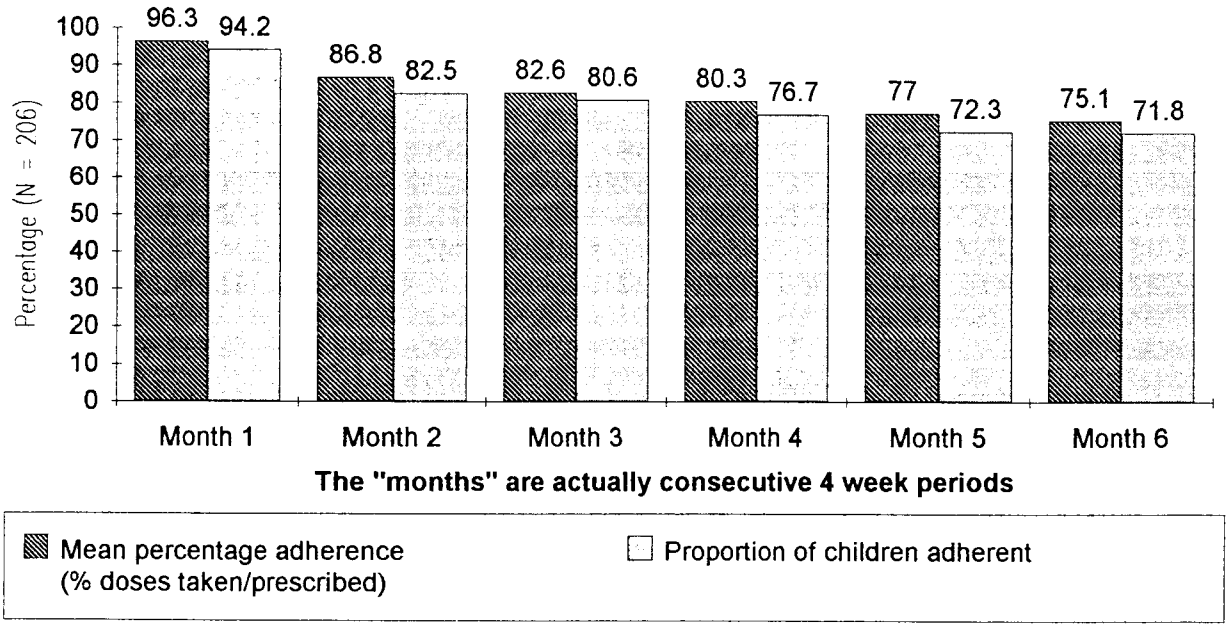
For clarity, the nonadherers are those whose total adherence % was <75%; the para-adherers include all nonadherers, plus those classified as adherents, but who took <75% of doses over any block of four weeks.

It is clear that a high adherence rate was achieved, and that there was no difference between the two treatment groups. It is also clear that some nonadherent behaviour was exhibited by nearly half the subjects. Time to default was longer for the twice weekly group, but the difference is not significant. The nonadherent group tended to default earlier than the para-adherers.

Thus the treatment results and the adherence rates achieved for both groups show no statistically significant difference.

The adherence over time for all subjects in the study is shown in the following bar graph, in terms of both adherence and adherent rates:

Figure 1: ADHERENCE v TIME



The falloff in adherence over time is clearly demonstrated.

In order to determine any differences between those adherent and nonadherent, the subjects were grouped using 75% of total doses taken/prescribed as a cutoff. The adherence over the first month is compared to adherence over the rest of the therapy period using the median (100%) as the cutoff.

Table 6: Adherers v Nonadherers

	Total	Adherent	Nonadherent	P value
Number	206	160 (78%)	46 (22%)	
Regimen 2	89	70 (79%)	19 (21%)	
Regimen 5	117	90 (77%)	27 (23%)	0.90
First month's adherence				
100%	140 (68%)	119 (85%)	21 (15%)	
< 100%	66 (32%)	41 (62%)	25 (38%)	0.000 2
Crowding index median	3.3	3.0	4.3	
	(2.3-4.3)	(2.2-4.0)	(3.0-5.0)	0.002
Median age	26.1	30.1	20.7	
	(15.4-41.7)	(16.6-46.0)	(9.5-32.1)	0.001
Outcome score median				
at 6 months (n=162)	6 (5-7)	6 (5-7)	6 (5-6)	0.10

Ranges in brackets are the interquartile ranges

It is clear that crowding, and adherence over the first month are powerfully related to nonadherence over the entire period of treatment. Younger age seems to be a factor which mitigates against good adherence. There was no difference between the disease outcome score for the two groups

The results for crowding and adherence over the first month are even more marked if one takes the nonadherent group as those defaulting at *any* stage of therapy:

Table 7: Excellent adherers v Para-adherers

	Total	Excellent adherers	Para-adherents	P value
Number	206	109 (53%)	97 (47%)	
Regimen 2	89	49 (55%)	40 (45%)	
Regimen 5	117	60 (51%)	57 (49%)	0.59
First month's adherence				
100%	140	89 (64%)	51 (36%)	
< 100%	66	20 (30%)	46 (70%)	0.000 02
Crowding index median	3.3	3.0	4.0	
	(2.3-4.3)	(1.9-3.9)	(3.0-5.0)	0.000 2
Median age	26.1	30.2	25.1	
	(15.4-41.7)	(16.3-45.8)	(13.3-36.3)	0.14
Outcome score median at 6 months (n=162)	6 (5-7)	6 (5-7)	6 (5-7)	0.28

Ranges in brackets are the interquartile ranges.

For clarity, the para-adherers include all nonadherers, plus those classified as adherents, but who took <75% of doses over any block of four weeks. Excellent adherers are the rest.

The value of P is enhanced by comparing any period of default during the treatment period against the crowding and adherence over the first month. The association remains if the adherence over the first month is compared against the subsequent adherence. So the propensity to nonadherence is strongly associated with these variables in this study. The association between nonadherence and young age has become nonsignificant when the definition of nonadherence was broadened.

Table 8: Adherence and Treatment Clinic

Clinic	Nonadherent	Para-adherent	Adherent	P value
Delft	0	0	3	
Dennemere	0	2	10	
Hillcrest	0	0	2	
Kleinvlei	6	12	26	
Lwandle	17	8	11	
Macassar	5	4	23	
Malibu	0	1	1	
Mfuleni	5	7	9	
Northpine	0	0	3	
Russells Rest	0	5	10	
Scottsdene	13	12	11	
TOTALS	46	51	109	0.0002 - 0.0008

It is clear that adherence rates differed markedly between clinics. Those clinics with more nonadherence are also those intuitively in the poorer suburbs, but there are no easy objective means of testing this.

Negative findings

There was no difference between the treatment groups in the falloff in adherence over time. There was no difference in the duration of illness prior to finding help between the two therapy groups, between the adherence groups, nor if tested against disease severity. There were no notable side-effects of treatment, apart from initial vomiting in children on twice weekly pyrazinamide at 62.5 mg/dose. When the dose range was lowered to 55 mg/dose, this problem did not recur. Except for persistent vomiting (there were no such cases), adverse drug events were not systematically recorded. One subject (#63), on Regimen 5, developed a mild rash of short duration.

5. DISCUSSION

This was a clinic-based open randomised controlled clinical trial to assess the effectiveness of and adherence to twice weekly therapy for childhood tuberculosis. The evaluation of this study according to the scoring system developed by Haynes, Taylor and Sackett[40] for studies on adherence, "Methodologic standards for compliance research reports", follows. There are six categories which are separately scored with the maximum score in brackets:

	This study	Score
Study design (4 +1*)	Randomised trial	4 +1
Selection & specification of study sample (3 +1)	Referral centre	2 +1
Specification of the illness or condition (3 +1)	Replicable criteria	3
Compliance measures (4 +1)	Pill count/Rx refill	2 +1
Definition of the therapeutic regimen (2 +1)	Complete description	2
Definition of compliance (2)	Replicable	2
TOTAL (18 +5)		15 +3

*Bonuses are scored if certain specifications are met.

It is clear that by this estimation, this study rates highly in terms of "adequacy of methods" that produced the results.

5.1 Limitations

5.1.1 Design:

Randomisation controlled for confounding. The possible bias that blinding could have had on the study needs to be considered. It should be noted that this was an effectiveness trial, therefore patient blinding was not a consideration, as this would have negated the aim of testing twice weekly therapy under field conditions. As regards researcher blinding to the study regimens, the clinician who saw the patients was not blinded, but the review paediatricians who did the outcome measure scoring were. As the main outcome measure for the effectiveness of therapy was based on the scoring done by the blinded panel, it is unlikely that this aspect created a bias. Lastly, it is noted that placebo control was considered unethical.

5.1.2 Subject selection:

The subjects were selected from clinics in urban and peri-urban areas only, not from the farming areas which are served by mobile clinics. The farming areas were omitted because they could not be monitored on a daily basis. An urban or peri-urban bias thus occurred. Additionally, for the purposes of informed consent, the parent had to be present at the initial interview. In most instances, this was conducted at the Idas Valley Clinic in Stellenbosch, some 20 - 30 km from each of the clinics mentioned above. The parent was thus bussed in with the child. Those unwilling to accompany their children were then automatically excluded. Consent was taken after the parent was told "... should you decide to enrol your child onto the study, s/he will be given 2/5 times a week treatment ..." It is unlikely that this process biassed entry onto the study, as there were 4 refusals only. Although this study was done in a regional referral centre where all tuberculosis patients in the area of jurisdiction of the clinic were bussed in for initiation of out-patient therapy, the patients were by no means consecutive admissions. This was mainly because among the different doctors doing the tuberculosis sessions, only the project leader was considered expert enough in childhood tuberculosis to enrol patients onto the study. The logistic time constraints of enrolling a patient also curbed the number entered onto the study.

5.1.3 Data not collected:

The enrolment refusals should have been systematically recorded with regard to the stage at which they refused and their intended treatment group. They would also constitute part of the inception cohort in its most liberal definition of intention to treat. For the purposes of an adherence study, more data on the families of the subjects should have been collected, like parental income, parental ages, education status, employment/professional status, marital/family status, and possibly race. Other data of importance would have been the distance and/or the time to the clinic from home, which could have influenced the adherence. The clinics are by and large situated in the communities they serve, so the effect of this variable is not expected to be great.

Data on who supervised each dose - parent or professional could have been collected, and could have been a source of bias. It could be argued that parental supervision is

a form of self-supervision. Both methods of supervision, professional or parent, fall however into the same category of Haynes, Taylor and Sackett, being "Objective indirect measures".[40] Because the adherence study was tagged on, these data were largely irrecoverable, inter alia because of the time elapsed.

Co-morbidity should have been described. This would have determined whether adherence was associated with other illnesses. Compliance estimation would have improved had a better method been used, eg. random urine testing for isoniazid. No co-interventions were noted. A record of all side effects and unusual events that occurred during therapy should have been kept, as well as action taken by the services. The time spent at the initial interview was not recorded: one group could have been more intensively counselled.

5.1.4 Data not analysed:

The address of the patient could have been analysed for distance to the clinic, and the effect on adherence. The effect of no consent was not analysed for adherence.

5.1.5 Categorisation:

Data were categorised for ease of data handling. Some of the significant associations could not have been produced using the Epi Info programme had the data not been categorised, eg. age v nonadherence and crowding v doses taken.

Despite the above limitations, the high score obtained on the Haynes Taylor and Sackett assessment method, and the fact that the biases and limitations have little impact on the categorisation of the subjects into different groups - treatment regimen and adherence - on which the results are based, allows one to conclude that the methods are acceptable. One can thus continue to discuss the results.

5.2 Discussion of Results

5.2.1 RESULTS BY REGIMEN

Randomisation:

Almost half (48.7%), of the 314 were randomised to Regimen 2. The final cohort analysed, however, contained only 43.2% on Regimen 2 mainly because there were many more on Regimen 2 who were tuberculin positive yet radiograph negative than on Regimen 5.

Exclusions:

The nine subjects (4%) of Table 1a were excluded for pre-treatment reasons. This is a common phenomenon in clinical trials, and there was no obvious bias here. Seven of the treatment sheets were indecipherable or mislaid. Six of these were from the twice weekly group, but the numbers were small and the baseline P values for the original group of 213 and the subsequent 206 assessable were no different when the two therapy groups were compared, so this was not a significant source of bias.

Baseline data: (Table 2 and Table 2a)

The weight for age median was statistically lower for the test group. This was a random variation in data, and had no further effect on the study, as is seen by the weight gain at 6 months. The missing data were irretrievable, as both height and crowding data change with time. The results showed clearly that the other data at inception were no different between the groups.

Diagnostic classification:

Table 3 shows that most children were classified as WHO probable cases. This is expected in a clinic based study where facilities for gastric aspiration are not available or feasible. When gastric aspirates have been evaluated in clinic based studies, little more than 10% of cultures have been positive for *M.tuberculosis*.[4]

Outcomes: (Table 4)

Almost 97% of the subjects had their therapy discontinued at the scheduled time. This is excellent for a study testing adherence and two different regimens as further doses

then do not contaminate the results. There were no differences between the therapy groups in the clinical outcomes measured at 3 or 6 months.

Adherence rates:

High overall adherence rates were achieved for both regimens. These are somewhat higher than found in the studies mentioned in the literature review. The differences are explainable in that it is the *adherence rate* reported here, which can be higher than the *total adherer rate* - which in this case is 78% (yet the median adherence is 91.5%). It may also reflect the Hawthorne effect, namely the positive effect on adherence merely because the subjects knew that they were being studied. The falloff in adherence over time needs no elaboration here, being well documented in many adult tuberculosis studies.[10] It is notable that the falloff phenomenon is reflected in this childhood study, and is probably a function of care-giver (adult) adherence. The nonadherer rate is essentially the same as that of other studies, and the para-adherer rate of nearly half confirms very well the views expressed by Rouillon[64] and Dick[26] that it is normal to default. It is also clear that the adherence rates for the two regimens are no different. The time prior to default in both the nonadherers and para-adherers is longer for the twice weekly regimen, but as seen, is not statistically significant.

5.2.2 RESULTS BY ADHERENCE (Tables 6 and 7)

77.7% of the subjects were adherent, having taken at least 75% of the doses prescribed. The statistically significant findings were that the first months' adherence was predictive of subsequent adherence, that crowding was statistically higher in the nonadherent group, and that those nonadherent had a younger age. Broadening the definition of nonadherence consolidated only the first two of these findings.

The outcome scores at 6 months showed no difference by adherence status. This finding is not unexpected, as the natural history of primary pulmonary tuberculosis is spontaneous resolution, especially if the patient is well enough to get clinic treatment, as was the case here. As noted in the literature review, the level of adherence needed for safe resolution of primary pulmonary tuberculosis is unknown, but it is likely that 4 months' therapy is sufficient, based on work in adults with smear-negative

tuberculosis.[30,45] It may well be that this unknown level was achieved by those nonadherent in this study. It is noted that the latest regimens for childhood TB in South Africa recommend 4 months' treatment for pulmonary tuberculosis.[25]

Young age and adherence:

Table 6 shows a significant association between younger age and nonadherence, but this is not reflected in Table 7, where the definition of nonadherence is broadened. One feels intuitively that younger age would result in greater adherence - the care-givers being more concerned - yet this finding shows the opposite. It could be an effect of being more difficult for the care-giver to get the younger child to the clinic. More likely it could be a true random finding, because the association disappears when the definition of nonadherence is broadened.

First month's adherence and subsequent adherence:

This finding was expected, as was highlighted by Sumartojo.[79] This phenomenon could be used by the clinic staff to predict and prevent subsequent nonadherence.

Crowding and adherence:

Crowding is probably a proxy for socio-economic status. Crowding was negatively associated with adherence. This was a new finding. It is exciting because, if proven elsewhere also, could be an easily measured demographic characteristic which can be used to predict nonadherence, and so spark preventive management. Nurses usually take down family details in order to trace contacts, so this would entail little extra work. There were insufficient factors studied to more fully explore the relationship between crowding and nonadherence, like parental education status. An unmeasured or unknown confounder is possible here. Nonetheless, an association is present, and could be used in practice.

Address and adherence:

The busier and poorer area clinics were associated with poorer adherence. In the absence of research-measured comprehensive data on the clinics' activities, it is difficult to draw accurate conclusions from this data.

6. CONCLUSION

There were no differences in the disease outcome criteria. There was no difference in the adherence rates between the regimens. The null hypotheses thus cannot be rejected, as there were no differences in the clinical outcomes nor in the adherence rates between the two forms of treatment. A higher crowding index was predictive of poor adherence. Adherence in the first 4 weeks was predictive of adherence over the rest of the therapy period.

The finding that adherence in the first month was predictive of adherence over the entire treatment period is not new, but has once again been strongly validated. Another and maybe more important finding was that one could predict nonadherence using an easily measured and computed crowding index. Although this finding was made in a childhood study, it is new to the literature, and is contrary to assertions that demographic data are "poor predictors of adherence" (Sumartojo[79]). The fact that crowding was predictive of nonadherence over the entire period of treatment and for *any* 4 week period of nonadherence, and that the second group was double the first, shows that this finding is robust.

This research cannot answer questions like why clients (or their parents) fail to adhere, and why do they not come earlier or at all for therapy. These considerations are highlighted by Sumartojo[79], and by Dick.[26] Quantitative research such as this will not address these larger questions in adherence, but can identify areas for improvement and be used to monitor programmes' success or failure. Although the treatment of children is not important in the control of tuberculosis (this lies mainly in the proper treatment of infectious adult cases and in socio-economic upliftment of our society) large numbers of children do fall ill with tuberculosis. This is related to the extent of the epidemic and the high annual risk of infection. These children place a burden on the tuberculosis control programme and the health services in general. Furthermore, a primary infection successfully survived is thought to generate a 60 - 80% protection against subsequent pulmonary tuberculosis from re-infection.[80]

7. RECOMMENDATIONS

The findings show that in terms of treatment for childhood tuberculosis, the outcomes and adherence achieved with either treatment modality are identical. This is good news for the services, which should be looking to converting all therapy to intermittent, based on studies such as these. It is possible to supervise all therapy if it were intermittent, but it is not possible to supervise all therapy in the current setup of daily treatments. This point was made as far back as 1967,[31] and reiterated in 1996.[96]

It is recommended from this study that routine clinic based tuberculosis therapy for children be changed to fully twice weekly - demonstrated by this study to be no different in terms of outcome and adherence - provided that the long term follow-up of the intermittent therapy group shows no significant relapse rate. Although a rural setting was not studied, there is no reason to believe that this form of treatment delivery would not be generalisable to a rural setting. This would reduce the workload on the services, as well as being cheaper, by 40 - 60%.[10,39]

There may be concern about the possible emergence of drug-resistance with intermittent treatment. With regard to childhood tuberculosis, the disease is paucibacillary, and it is only where one has cavitation with of the order of 10^9 organisms that drug-resistance is a threat. With regard to adult tuberculosis, the chance of resistance is greater because of the greater loads of bacilli present. There is theoretical evidence, however, to suggest that pulsed intermittent dosing is more likely to eliminate the emergence of secondary resistance, by targetting the bacilli in the growth phase.[57] Also, the logistical possibility of all doses being supervised is greater with the reduced workloads in intermittent therapy, thus reducing the emergence of secondary resistance, which is the commonest form of drug resistance.

In terms of the proactive management of adherence in childhood tuberculosis, the recommendations from this study are that:

1. crowding be measured at the start of therapy to identify possible nonadherers, and
2. adherence over the first month be measured.

Should either measurement be suboptimal as regards predicting nonadherence, action should be instituted to ensure or enhance adherence. The clinic staff would in these ways be able to manage nonadherence preventively, having identified those at risk, instead of managing it once it occurred. This process should be monitored in practice to ensure that the predictability of nonadherence was not merely a research phenomenon.

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10. APPENDICES

Appendix 1: Standard Questionnaire.

Appendix 2: Consent form.

Appendix 3: Adherence sheet for Regimen 2.

Appendix 4: Adherence sheet for Regimen 5.

Appendix 5: Coding list.

Appendix 6: Programme written to derive data from the database.

Appendix 7: Map of the area.

STELLENBOSCH RSC TB STUDY

DATE

DATA COLLECTION FORM

RING EITHER THE Y or N

Name.....(surname)..... Date of Birth ../../..
Clinic number ...../Hospital..... No. .....

Address .....

History: Duration of illness ..... weeks
Cough Y/N Fever Y/N Wheeze Y/N
Loss of appetite Y/N Loss of weight Y/N Sweats Y/N
Listlessness Y/N Breathless Y/N
Recently in Hospital?/Other (list) . . . . . .
. . . . . .

Contact: Specify who .....
Contact microscopy + Y/N
Contact culture positive Y/N
Contact is a retreatment case Y/N
Contact = good compliance (>75%) Y/N
Contact = defaulter (>2 months off Rx) Y/N

BCG: Date given .../.../... Scar present Y/N

Social: Number of adults ... Number of children ...
Sleeping rooms per house ... Number of adults employed ...

Examination: Weight ..... kgs; %EW.....
Height/length ..... cms; %EH.....
Wt for Ht Green/ yellow/ red/ brown

Lymphadenopathy Y/N Site and size .....
E.N... Y/N P.C ..Y/N Abd glands Y/N
Hepar Y/N , size ....cm Spleen Y/N , size ....cm
Resp Distress Y/N Rate.....acc.muscles/ grunts/ cyan
Other . . . . . .

Investigations:
TST - Tine grade ..... or Mantoux ..... mm
CXR - NAD Y/N
hilar adenopathy only Y/N - segmental lesion only Y/N
- both of the above Y/N - pleural effusion Y/N
- cavitatory disease Y/N - miliary Y/N
- bronchogenic Y/N - merely suspicious Y/N
(Sputum investigation Y/N: microscopy + / - ; culture + / -)

Diagnostic category:
Intrapulmonary -TB .. Y/N
Extrapulmonary -TB... Y/N Specify .....
Case Definite Y/N Probable Y/N Suspect Y/N
Tuberculin reactor Y/N
Contact only Y/N

Treatment allocation: No. in the study.....

WESKAAPSE STREEKSDIENSTERAAD

Stellenbosch Streekskantoor

Toestemming tot insluiting in 'n navorsingsprojek

Afwisselende T.B. Behandeling Studie ("die Studie"): Goedgekeur deur die Etiese Komitees en Liggame van Weskaapse Streekdiensteraad Gesondheidsdienste, Rooikruis Hospitaal en Tygerberg Hospitaal.

Pasient: NAAM: . . . . . (van) . . . . . .

GEBOORTEDATUM: . . . . . .

U kind is gekies om standaard/2 dae per week* behandeling te ontvang. Dit is noodsaaklik dat u kind die volle duur van die behandeling voltooi.

Ek, Dr J.M. te Water Naude verklaar hiermee dat ek die aard, doel, risiko's en moontlike gevolge van die Studie aan die ondergenoemde OUER/VOOG* wat regsbevoeg is om toestemming te gee, verduidelik het.

. . (handtekening van genoemde) . .//. . (datum) . .

Ek, die ondergetekende . . . . . (naam en van) . . . . . in my hoedanigheid as OUER/VOOG* gee hiermee toestemming tot die insluiting van my kind in die Studie, die geaardheid waarvan deur Dr J.M. te Water Naude aan my verduidelik is en ek sertifiseer dat:

1. Die aard, doel, risiko's en moontlike gevolge van die Studie aan my verduidelik is.
2. Ek die implikasies van die Studie en die risiko's daaraan verbonde aanvaar.
3. Die volgende prosedures uitgevoer mag word as deel van die Studie:
   i) kliniese mediese ondersoeke
   ii) toepaslike X-Straal ondersoeke
   iii) Tuberkulien vel toetse ("tjappies")
   iv) enige verdere spesiale ondersoeke wat klinies aangedui is.
4. Ek bevoeg is om hierdie toestemming te gee.

. . . . . .
(HANDTEKENING VAN OUER/VOOG*)

Getuies: 1. .....

DATUM: . . . . . .

2. .....

* *SKRAP WAT NIE VAN TOEPASSING IS NIE*

Appendix 3: Adherence sheet for regimen A

T.B. kontrolevorm: Intermitterende Behandeling

Naam: Shaun Abrahams
Adres:
16 Lescodua Crt
Scottsdene

Geb. datum: .....
Oud: 3j.
Toesighouer: Klimek
Toelatingsgewig: .....
X-Straal no: ...71...
Tinetoets : .....

Behandelingskedule:

Opvolg X-Strale

6/12 .....
12/12 .3/2/93....
30/12 .3/2/94....

Datum Rx begin: 3/2/92

Weke	Maan. 3/2	Don. 5/2	Totaal van Dosisse	Opdragte Feb	Weke	Maan.	Don.	Totaal van Dosisse	Opdragte
1	✓	✓	2/2		15	4/5 ✓	✓		
2	10/2 ✓	12/2 ✓	2/2		16	✓	✓		
3	17/2 ✓	20/2 ✓	2/2		17	18/5 ✓	21/5 ✓		
4	24/2 ✓	27/2 ✓	2/2	8/8-100%	18	✓	✓	5/8 100%	
5	2/3 ✓	5/3 ✓	2/2	Mrt.	19	11/6 ✓	✓	8/8 JUNE	
6	9/3 ✓	12/3 ✓	2/2		20	✓	✓	8/8	
7	16/3 ✓	19/3 ✓	2/2		21	✓	✓	16/9-66,6%	
8	23/3 ✓	26/3 ✓	2/2		22	✓	✓		
9	30/3 ✓	/	1/1	9/9-100%	23	✓	✓		
10	2/4 ✓	/	1/1	Apr.	24	✓	✓	8/8 July 92	
11	6/4 ✓	9/4 ✓	2/2		25	✓	✓	8/8	
12	13/4 ✓	16/4 ✓	2/2		26	✓	✓	4/8 = 4 Hitte	
13	20/4 ✓	23/4 ✓	2/2	8/8-100%	27	✓	✓		
14	27/4 ✓	✓	1/1		28	✓	✓		

Appendix 4: Adherence sheet for regimen B

TIPE

W.K.S.D.R. STELLENBOSCH

NAAM: Glenville Alexander
17 Circle Rd
Forest Park

OUD.: 6/12

TOESIGHOUER:

VDRL:

BEHANDELING:

24/9/92 ...

BEHANDELING VANAF: 25.6.92 **X-STRAAL NR.:** 82

										GEWIG	COMPL.
1	2	3	4	5	6	7	8	9	10		
11	12	13	14	15	16	17	18	19	20		
21	22	23	24	25	26	27	28	29	30		
31	32	33	34	35	36	37	38	39	40		
41	42	43	44	45	46	47	48	49	50		
51	52	53	54	55	56	57	58	59	60		
61	62	63	64	65	66	67	68	69	70		Okt. 23/10
71	72	73	74	75	76	77	78	79	80		
81	82	83	84	85	86	87	88	89	90		

Sputumbottels: 90 dosis ....

X-strale : 100 dosis ....

91	92	93	94	95	96	97	98	99	100	Nov	
101	102	103	104	105	106	107	108	109	110		
111	112	113	114	115	116	117	118	119	120		
121	122	123	124	125	126	127	128	129	130		
131	132	133	134	135	136	137	138	139	140		
141	143	143	144	145	146	147	148	149	15C		
151	152	153	154	155	156	157	158	159	160		
161	162	163	164	165	166	167	158	169	17C		
171	172	173	174	175	176	177	178	179	180		

STELLENBOSCH RSC TB STUDY

Appendix 5: Coding list

CODING LIST
(stb.rec file)

1. Name (NAME):
   Child's name and surname
   If "=" next to surname, consent obtained
   If "#" next to name, slight calcification visible on CXR (mark for radioligist study)
   If "@" interesting CXR
   If "$" next to name, child keeps on vomiting on treatment.
   If "%" next to name, Dr. Gie's study (Lymphobronchial TB)

2. Sex (SEX):
   M = male
   F = female

3. Age (AGE):
   mos = in months
   yrs = in years
   (This calculation is automatically done by DOMEAS by entering birthdate and visitdate of child)

4. Date of birth (BIRTHDATE):
   American date order
   If date of birth is unknown, 01/01/year of birth

5. Date treatment commenced (VISITDATE):
   American date order
   Date treatment commenced

6. Initial weight (WEIGHT):
   Initial weight in kilogram - numeric value

   (LBS and OZS are not used in this study - this variables remain empty)

7. Height for age percentile (HAP):
   Percentage of expected height/length - numberic value

8. Height for age Z-score (HAZ):

9. Height for age %median (HAM):

10. Initial height (HEIGHT):
    Initial height if child >3 years

Initial length if child <3 years - numeric values in centimeters
(FT and IN are not used in this study - this variables remain empty)

11. Weight for age percentile (WAP):

12. Weight for age Z-score (WAZ):

13. Weight for age %median (WAM):

14. Weight for height percentile (WHP):

15. Weight for height Z-score (WHZ):

16. Weight for height %median (WHM):

17. Flag (FLAG):

18. Study no (STELLENBOS):
2 = intermittent therapy
5 = standard therapy
6 = intermittent therapy - excluded from study, but still for follow-u
7 = standard therapy - excluded from study, but still for follow-up
8 = intermittent therapy - excluded from study, not for follow-up
9 = standard therapy - excluded from study, not for follow-up

19. Clinic number
(a) (CLINICNUMB):
First letter of surname - Capital letter
(b) (CLINICNUM1):
Folder number on left hand corner of folder envelope - numeric valu

20 . Hospital (HOSPITAL):
Big referral hospitals - not local hospitals and day hospitals
eg. Tygerberg Hospital
Somerset Hospital
Red Cross Hospital
Use abbreviations eg. RXH

21. No (NO):
Child's hospital number - numeric value

22. Address (ADDRESS):
Name of area - full address not necessary
Name of area is written on top of folder envelope in pencil

23. Holiday (HOLIDAY):
1 = Transkei
2 = Ciskei
3 = Montagu
Parents must report leave to clinic sister for arrangements re treatme
and follow up - if not, defaulter and therefore not suitable for this
category

22.1 Address (ADDRESS01):
Street address of child
1moved = child moved outof study-area - didn't complete treatment
moved = moved, but completed treatment
(This is used for monthly follow-up recalls - to make it easier for the clinic sister to find the child)

24. History - Duration of illness (HISTORYDUR):
Numberic value counted in weeks

25-32. Cough (COUGH), Fever (FEVER), Wheeze (WHEEZE), Loss of appetite (LOSSAPPETI), Loss of weight (LOSSWEIGHT), Sweats (SWEATS), Listlessness (LISTLESSNE), Breathless (BREATHLESS)
"y" = yes
"n" = no

33. Other (list) (OTHERLIST):
If recent admission to a hospital; name of hospital, reason of stay duration of stay
Comments by medical docter - if no comments; type in "none"

34. Contact Specify who (CONTACTSPE):
Only adult index cases are important
Folder number next to name eg. Nel,Jan X1

34.1 Record number of CONTACT.REC (CONTACTSP1):
Detailed information of specific child's contact in CONTACT.REC - record number specified

35. BCG Date given (BCGDATEGIV):
American date order

36. BCG Scar present (SCARPRESEN):
"y" = yes
"n" = no

37-40. Social Number of adults (SOCIALNUMB), Number of children (NUMBERCHI Sleeping rooms per house (SLEEPINGRO), Number of adults employed (NUMBERADUL):
Numeric values

41,43-46,
48,50,52,
53,54. Lymphadenopathy (LYMPHADENO), Erythema nodosum (EN), Phlytenular conjunctivitis (PC) Abdominal glands (ABDGLANDS), Hepar (HEPAR), Spleen (CMSPLEEN), Respiretory Distress (RESPDISTRE), accessory muscle use (ACC), grunting (GRUNT), cyanosis (CYAN):

"y" = yes
"n" = no

42. Site and size (SITESIZE):
Short comments by medical docter re lymphadenopathy

47,49,51. Size (SIZE), size (SIZE01), Rate of breathing if has respiratory distress (RATE):
Numeric values

55. Other (OTHER):
Remarks by medical docter re the physical condition of the child eg. Scabies, orange hair etc.

56. Investigations TST (Tuberculin Skin Test) tine grade (TSTTINEGRA):
Numeric values 1 - 4
Initial tine test result

57. Mantoux (ORMANTOUX):
Numeric value in millimeters
Initial skin test result

58. Tine grade 12 mth (TINEGRADE1):
Numeric value 1 - 4
Tine test result - 12 mth's after treatment commenced

59-67. CXR hilar adenopathy only (CXRHILARAD), segmental lesion only (SEGMENTALL), both of the above (BOTHABOVE), pleural effusion (PLEURALEFF), cavitatory disease (CAVITATORY), miliary (MILIARY), bronchogenic (BRONCHOGEN), merely suspicious (MERELYSUSP), NAD (NAD)
y = yes
n = no
This part of the questionnaire is filled in after the panel of specialists evaluated the x-rays of the children.

68. Sputum investigation (SPUTUMINVE):
y = yes
n = no

69. microscopy + (MICROSCOPY):
y = yes
n = no

70. culture + (CULTURE):
y = yes
n = no
(68 -70 - sputum investigations in children are very seldom done)

71,72,74-79. Diagnostic category: Intrapulmonary -TB ... (INTRAPULMO), Extrapulmonary -TB ... (EXTRAPULMO), Case Definite (CASEDEFIN Probable (PROBABLE), Suspect (SUSPECT), Tuberculin reactor (TUBERCULIN), Contact (CONTACT):

y = yes
n = no
This part of the questionnaire is filled after the panel visi

Cases (CASES): Numeric value (used by research-assistant)
1 = Definite case
2 = Probable case
3 = Suspect case

73. Specify (SPECIFY):
Short comment by specialists.

80. (a) Follow up date (FOLLOWUPDA):
American date order
Recall date for chest X-rays, clinical investigation by medical docter
Usually at 3,6,12,30 months after treatment has started.
(b) Followup date (FOLLOWUPD1):
A numeric value of "12" is typed in if it's time for the 12 month foll
up. This is done to remind the clinic sister to repeat the tine test.
This information is used by the research-assistant to recall children
monthly.
"99" is typed in if the respondent was already discharged, but
still for follow-up.

81-85. Date3 mth assess (DATE3MTHAS), Date6 mth assess (DATE6MTHAS),
Date12 mth assess (DATE12MTHA), Date30 mth assess (DATE30MTHA),
The follow-up assessments are based on the quantity of doses the
child received to date - the real time aspect is not always reliabl

The "12" and "30" month follow-up though are respectively based
on the time after treatment commenced - "12 month follow-up" 10-17
months after treatment commenced and "30 month follow-up" 18-30
months after treatment commenced.
(DATE30MTH1) This numeric value represents the exact time the 30
month follow-up was performed.

85,86. Weight3 (WEIGHT3), Height3 (HEIGHT3):
Numeric values
Weight measurement and height if the child is >3 years old, length
measurement if the child is <3 years old. The child has completed
26 or 60 doses respectively.

88,89. Weight6 (WEIGHT6), Height6 (HEIGHT6):
Same as 74,75
The child has completed 52 or 120 doses respectively.

91,92. Weight12 (WEIGHT12), Height12 (HEIGHT12):
Same as 74,75

Measurements taken 10-17 months after treatment commenced.

94,95. Weight30 (WEIGHT30), Height30 (HEIGHT30):
Same as 74,75
Measurements taken 18-30 months after treatment commenced.

87,90,93,96. Outcom3 score (OUTCOM3SCO), Outcom6 score (OUTCOM6SCO), Outcom12 score (OUTCOM12SC), Outcome30 score (OUTCOM30SC):
Numeric value -4 to +8
Scoring is done by the medical doctor in co-operation with the specialists.
See protocol by Dr te Water Naude
Twice Weekly:
3 month score = (20 - 40) doses
6 month score = (33 - 77) doses
Standard regime:
3 month score = (46 - 94) doses
6 month score = (95 - 135) doses
(The following codes are used by the research-assistant:
20 = wait for chest X-rays
21 = wait for sisters-report
22 = impossible to score
23 = didn't come for follow-up
24 = moved)
25 = administrative error

97,99,101,103. Outcome Compliance: Doses3 (DOSES3)AND(DOSES4), Doses6 (DOS AND(DOSES7), Doses9 (DOSES9)AND(DOSES10), Doses12 (DOSES12) AND(DOSES13):
Numeric values
This represents the actual amount of treatment the child received over 3 months over the presumed amount of treatmen over a calendar time of 3 months.

98,100,102,104. Compliance3 (COMPLIANCE), Compliance6 (COMPLIANCEO1), Compliance9 (COMPLIANO2), Compliance12 (COMPLIANO3):
Percentage of 86,88,90,90 respectively

105. IIT Completed: Month (IITCOMPLET):
Numeric value
Presumed duration of treatment expressed in months.
(The following code words are used by the research-assistant:
3* = Treatment was incorrectly stopped; error was discovered 2 months after it was stopped

2TS = Two treatment sheets in file - child had received TB-Rx before.

62+5 = received Intermittent therapy and Standard therapy during the period of treatment - reasons: administrative errors, admitted in hospital, study MO changed therapy (rec 116), took therapy twice weekly on standard therapy regimen,

took therapy 5 days/week on twice weekly regimen.

6+6 = child received 6 months treatment, compliance was poor, specialists decided on another 6 months of Rx.

6+R = child was seen by other MO; by mistake put on Rifater 40 doses.

8H = received Rx for 2 months in hospital + 6 months of ST with us.

9 = child never came for 3 and 6 month follow-up, after 9 months saw MO and Rx was stopped.

11 = Enrolled to take ST for 6 months, vomited and specialists decided on Rx for another 30 doses (TBH - enterocolitis).

12 = Child was enrolled to take ST for 6 months, by mistake received IT (120 doses).

wait = wait for completed treatment sheet from the clinic

lost = treatment sheet is lost; impossible to complete question

notb = specialist changes diagnoses; received TB treatment but not really TB-sufferer

ros = regime other than study

106. Doses (DOSES)AND(DOSES1):
Numeric values
The doses the child received from day one of treatment till the day treatment is stopped, over the presumed amount over the exact calenda period of treatment.

107. Compliance (COMPLIANO4):
Numeric value
Percentage of 95.

108. Defaulter (DEFAULTER)AND(DEFAULTER1):
(a) y = yes
n = no
(b) 1 = bad compliance
2 = defaulted for >2 months

109. Excluded form study (EXCLUDEDFR):
1 = moved to homelands (Transkei, Ciskei)
2 = moved out of study-area

3 = defaulted
4 = diagnosis (changes in opinions)
5 = incomplete initial data
6 = drug reaction while on or reaction to treatment
7 = previous TB treatment
8 = ineligible for enrollment
9 = hospital admission
10 = Treatment incorrect
11 = other

110. Relapsed (RELAPSED):
If "Y" = child possibly relapses - for specialists' evaluation.

111. N12score and N30score
On the 11/9/94 it was decided to exclude the mother's assessment from the score criteria at 12 and 30 months.
A new numeric variable was created with the denominator = 6.
Previous scores were re-entered subtracting the points for the mother' assessment.

Appendix 6: Programme written to derive data from the database

```
Please note: this is a number of programmes combined.
Read C:\epi6\data6\stb.rec
define case #
If cases =1 or cases =2 or cases =3 then case =1 else case =0

If cases =1 or cases =2 or cases =3 then cases =6

If stellenbos =6 or stellenbos =8 then stellenbos =2
If stellenbos =7 or stellenbos =9 then stellenbos =5

Let deftime = ( DATEFIRSTD - VISITDATE)
Define cramin ###.##
let cramin = ( SOCIALNUMB + NUMBERCHIL/2) / SLEEPINGRO
Define dose% ###
if stellenbos = 2 then dose% = 100 * ( N1ST4WEEKS + N2ND4WEEKS + N3RD4WEEKS
if stellenbos = 5 then dose% = 100 * ( N1ST4WEEKS + N2ND4WEEKS + N3RD4WEEKS
Define dosecat #
if dose% >=75 then dosecat =1
if dose% < 75 then dosecat =0
Define cramcat #
if cramin >2.5 then cramcat =1
if cramin <=2.5 then cramcat =0
Define discat #
If SEGMENTALL = "Y" or BOTHABOVE = "Y" or CAVITATORY = "Y" or BRONCHOGEN =

define contaxcat #
if CONTACTSPE = "no adult contacts" then contaxcat =0 else contaxcat =1
define d%1 ###
let d%1 = 100 * n1st4weeks/ n1st4week1
define d%2 ###
let d%2 = 100 * n2nd4weeks/ n2nd4week1
define d%3 ###
let d%3 = 100 * n3rd4weeks/ n3rd4week1
define d%4 ###
let d%4 = 100 * n4th4weeks/ n4th4week1
define d%5 ###
let d%5 = 100 * n5th4weeks/ n5th4week1
define d%6 ###
let d%6 = 100 * n6th4weeks/ n6th4week1
define d1 #
if d%1 < 75 then d1 = 0
if d%1 >=75 then d1 = 1
define d2 #
if d%2 < 75 then d2 = 0
if d%2 >=75 then d2 = 1
define d3 #
if d%3 < 75 then d3 = 0
if d%3 >=75 then d3 = 1
define d4 #
```

```
if d%4 < 75 then d4 = 0
if d%4 >=75 then d4 = 1
define d5 #
if d%5 < 75 then d5 = 0
if d%5 >=75 then d5 = 1
define d6 #
if d%6 < 75 then d6 = 0
if d%6 >=75 then d6 = 1
define d12 ###
let d12 = d%1 + d%2
define d1-100 #
if d%1 < 100 then d1-100 = 0
if d%1 >=100 then d1-100 = 1
define d12-175 #
if d12 < 175 then d12-175 = 0
if d12 >=175 then d12-175 = 1

route C:\06a\resultz.6a3
tables cases stellenbos
select cases =6
tables sex stellenbos
means age
means age stellenbos
means weight
means weight stellenbos
means wam
means wam stellenbos
means height
means height stellenbos
means cramin
means cramin stellenbos
select ham <999
means ham
means ham stellenbos
select cases =6
select outcom3sco <20
means outcom3sco stellenbos
select
select cases =6
select outcom6sco <20
means outcom6sco stellenbos
tables dosecat STELLENBOS
tables STELLENBOS dosecat
select
means D1-100 dosecat
means cramin dosecat
means cramin any
tables D1-100 any
define d23456 ###
if STELLENBOS =2 then d23456 =100*( N2ND4WEEKS + N3RD4WEEKS + N4TH4WEEKS +
if STELLENBOS =5 then d23456 =100*( N2ND4WEEKS + N3RD4WEEKS + N4TH4WEEKS +
```

Appendix 7: Map of the area