CHAPTER 2

Literature review

2.1   INTRODUCTION

TB in children is a serious problem with public health implications, particularly in developing countries where paediatric TB notifications represent an underestimation of the true incidence because of diagnostic constraints and poor reporting and notifying systems (Osborne 1995:369).

Although the adequacy of TB diagnosis in children has been examined, very little is known about the ability of PHC nurses to diagnose TB in children. Baez (2000:10) indicates that the new PHC nurse-driven system requires that first line nurses be able to suspect, diagnose, treat and confirm the diagnosis of TB in children.

The global strategy for TB control, Directly Observed Treatment Short Course (DOTS), prioritises the management of patients with sputum smear positive TB (Enarson 2004:143). As pulmonary tuberculosis (PTB) in children was historically reported as rarely sputum smear positive, this led to a belief that children are not important in TB control. However, the rapid progression of TB is more frequent and dangerous in young children and, if not diagnosed and treated promptly, may lead to death or chronic morbidity (Cremin & Jamieson 1995:107). The diagnosis of TB in childhood remains challenging with TB in children only confirmed in 30,0 to 40,0% of clinically suspected cases (Schaaf, Beyers, Gie, Nel, Smuts, Scott, Donald & Fourie 1995:189).

In their study on TB treatment failure in children, Beyers, Gie, Schaaf, Van Zyl, Nel, Talent and Donald (1994:261) found that mortality and morbidity from

childhood TB may be adversely influenced by any delay in diagnosis or commencement of treatment and by poor compliance with treatment.

Van Rheenen (2002:435) states that one third of the world's population is infected with Mycobacterium tuberculosis. Moreover, with HIV co-infection the overall annual risk of developing active TB in dually infected people increases twenty-fold. The frequency of childhood TB in the population depends mainly on the number of adult infectious cases and susceptibility to infection (Van Rheenen 2002:435).

2.2   GUIDELINES AVAILABLE TO ASSIST THE SOUTH AFRICAN PHC NURSE TO DIAGNOSE TB IN CHILDREN

Two guidelines are available to South African PHC nurses to guide their diagnosis and treatment of TB in children:

(1) *South African tuberculosis control programme practical guidelines* (DOH 2000)
(2) *Tuberculosis: a training manual for health workers* (Balt et al 1998)

Between them these two manuals cover the areas of transmission of TB in children, clinical features of TB in children, approaches to the diagnosis of PTB in children, including the tuberculin skin test, chest radiography and contact history, impact of HIV on the diagnosis of TB in children, a score system for the diagnosis of TB in children, treatment of complications, diagnosis of TB meningitis in children, the development of TB infection in children, prophylaxis and other prevention measures, children who should be hospitalised, approaches to babies born to mothers who have sputum positive TB, and prevention of TB in the health care setting.

2.3   DIAGNOSTIC TOOLS/TESTS AVAILABLE TO THE PHC NURSE TO ASSIST IN THE DIAGNOSIS OF TB IN CHILDREN

Many patients are left undiagnosed because of the inadequacy, non-availability or incorrect application of diagnostic tools in disease endemic countries which results in increased morbidity, prolonged transmission and possibly even death (Perkins 2000:182-188).

Although a variety of tools are available, Schaaf et al (1995:192) emphasise that "the diagnosis of TB in childhood is an imprecise process, which, outside of referral centres where cultures can be undertaken, is dependent on a constellation of clinical symptoms and signs, chest x-rays, tuberculin testing, other special investigations and a history of close contact with an adult case of pulmonary tuberculosis".
The diagnostic tools and tests include tuberculin skin tests, chest radiography and contact tracing.

2.3.1 Tuberculin skin test

The diagnosis of TB in children still depends heavily on tuberculin skin tests (DOH 2000:32). There are several tuberculins. Harries et al (1996:65) describe a tuberculin as "a purified protein derived from tubercle bacilli. Thus another name is PPD (Purified Protein Derivative)." After infection with MTB a person develops hypersensitivity to tuberculin. "The tuberculin measures the degree of allergy and a positive test only shows that the person has at some time been infected with TB" (Crofton, Horne & Miller 1992:187). Tuberculin tests still used are the Mantoux and the Heaf tests. The use of the Tine, Patch and Von Pirquet tests has been abandoned (Crofton et al 1992:187).

A negative tuberculin test does not exclude TB and the following conditions may suppress the tuberculin test: HIV infection, malnutrition, severe bacterial or viral infections, including measles, chickenpox and glandular fever, cancer and immunosuppressive drugs, including steroids (Harries et al 1996:66). Van Rheenen (2002:440) found only 9,0% reactivity to tuberculin in HIV-infected

children and points out that the usefulness of tuberculin skin testing (TST) to diagnose TB has decreased because of HIV-related cutaneous anergy. In a study of HIV-1 co-infected children hospitalised with TB in South Africa, Madhi, Huebner, Doedens, Adue, Wesley and Cooper (2000:448-454) found a similarly low figure. Van Beekhuizen (1998:155) states that the diagnosis of TB becomes much more difficult in the presence of malnutrition because the Mantoux reaction may be negative.

Arnadottir, Rieder, Trebucq and Waaler (1996:1) emphasise that infection with environmental mycobacteria might interfere with the tuberculin reaction because of the induction of tuberculin reactivity. Age and genetic factors may also influence the specificity of the tuberculin test (Arnadottir et al 1996:1). Arnadottir et al add that prior vaccination with Bacillus Calmette-Guerin (BCG) further complicates the interpretation of tuberculin test results. However, Benenson (1995:494) found that tuberculin skin testing positive as a result of BCG wanes over time and therefore a strong positive reaction should be considered indicative of TB infection.

Lienhardt, Sillah, Fielding, Bennett, Donkor, Warndorff, McAdam and Manneh (2003:615) found that TST is particularly useful in assessing the probability of TB infection in children, particularly those who live in the same household as individuals with infectious TB in areas with high BCG coverage.

Despite the frequency of negative results in early infancy, the Mantoux test is still an essential part of the evaluation of any child suspected of having TB but it is recognised to be more valuable when assessing an older child (Schaaf, Gie, Beyers, Smuts & Donald 1993:373).

According to Sadovsky (2001:2), it is important to recognise that up to 10,0% of children with culture-proven TB do not react to TST at the time of evaluation, but more become reactive after treatment is initiated. Furthermore, many children with TB meningitis or miliary TB have a skin test that is initially non-reactive, but when TB is suspected, any reaction to a tuberculin test should be considered

suggestive, although not diagnostic (Sadovsky 2001:2). Beyers et al (1994:265)
state that although greater utilisation of the TST would shorten the delay between
diagnosis and onset of treatment, various contradictions have dissuaded many
health workers from using the test.

2.3.2   Chest radiography

Donald et al (1999:154) state that "interpretation of a chest radiograph in a young
child is fraught with difficulty because of exposure of the film in expiration,
excessive lordosis, rotation of the thorax and faulty exposure or processing.
Chest radiography is perhaps the means by which diagnosis of tuberculosis in
childhood is most frequently supported. Unfortunately even experienced
observers will at times differ in their interpretation of children's chest radiographs
and in particular as to whether or not hilar adenopathy is present." Chest
radiography still plays a major role in the diagnosis of childhood TB, but its merit
continues to be debated (Schaaf et al 1995:193).

A non-resolving pneumonia should always lead to consideration of possible TB.
Chest x-rays in children with miliary TB are positive more than 90,0% of the time
but this proportion is less in other forms of TB (Hussey, Chisholm & Kibel
1991:834). However, a normal chest x-ray does not exclude miliary TB and
miliary changes may develop within several days (Schaaf et al 1993:373).

Osborne (1995:371) emphasises that "radiological findings do not always help,
particularly in small children, and can at times be confusing, as some cases show
extensive disease even when clinical examination has revealed little or nothing.
The picture becomes more confused when there is superadded bacterial
pneumonic findings in addition to those of tuberculosis. In HIV-infected children
some of the infections they are prone to have similar radiological findings as in
tuberculosis adding on to the difficulties." However, the correct interpretation of
chest radiographs may lead to early diagnosis of TB in infants with resulting early
initiation of treatment and thus lower mortality (Schaaf et al 1993:374).

2.3.3 Contact tracing

Although the main focus of TB control is the detection of culture-positive adults who primarily spread the disease, the early detection of children with TB will prevent progression of the disease in these children and should also lead to the tracing of infectious adult contacts (Gie, Beyers, Schaaf & Donald 1993:263).

Lienhardt et al (2003:610) found that "contact tracing is rarely done in non-industrialized countries, because of lack of resources". As TB is an airborne disease, the risk of infection in children is directly related to the intensity of exposure to individuals with infectious TB and these individuals' infectivity. There is a clear inverse association between household size and TST positivity as well as a positive association between the risk of TST positivity and the intensity of exposure to the individual with TB within the household (Lienhardt et al 2003:610).

Despite a history of BCG vaccination, a positive TST in a child who has had close contact with an adult with infectious TB probably indicates infection with MTB and treatment should be considered, especially if the child is younger than 5 years of age (Lienhardt et al 2003:610).

According to Schaaf, Donald and Scott (1991:223), a history of close contact with an adult with PTB offers strong support for the diagnosis of TB in a child. Osborne (1995:373) points out, however, that high BCG coverage rates in developing countries have in part contributed to complacency among the public and health workers regarding contact tracing. Health workers should always enquire about close adult contacts with PTB in a child with subacute systemic or respiratory disease as it could shorten diagnostic delay (Beyers et al 1994:265).

Although the main focus of TB control must remain the detection of smear positive adults who spread the disease, the early detection of children with TB will prevent progression of the disease in these children and help with identifying infectious adults (Gie et al 1993:263). The prevention of TB in early infancy relies on early detection and treatment of TB in expectant mothers or other members of the infant's household (Schaaf et al 1993:374).

Figure 2.1 illustrates Harries et al's (1996:68) approach to identifying and managing child contacts of infectious adults.

TB control programmes in developing countries have largely neglected the tracing of children in contact with infected individuals, mainly because of limited resources and planning challenges. In the absence of more specific markers of infection, TST continues to be used to screen for TB infection in children who live in the household of individuals with infectious TB, even in areas with high BCG coverage. Contact tracing is important in the control of TB in developing countries, as it can lead to early case detection and treatment (Lienhardt et al 2003:610).

Figure 2.1
How to identify and manage the child contacts of infectious adults
(Harries et al 1996:68)

2.3.4 Suspicion

A high degree of suspicion is important to ensure prompt diagnosis of TB in childhood (Gie et al 1993:263).   Suspicion should be prompted by a history of close contact with an adult diagnosed with PTB or previous repeated respiratory tract infections that have not responded to therapy.

According to Khan and Starke (1995:2), the natural history of TB consists of three stages, namely exposure, infection and disease:

1 Exposure implies that a child has had recent and substantial contact with an adult or adolescent who has suspected or confirmed contagious pulmonary TB. The development of hypersensitivity to tuberculin may take up to 3 months and in children under 5 years of age severe TB, especially meningeal and disseminated disease, can occur earlier, before the TST become reactive.
2 TB infection is first signalled by a reactive Mantoux TST – at this stage there are no signs or symptoms. TB infection is rarely discovered. In most industrialised countries children with a positive TST receive Isoniazid for 6 to 12 months.
3 TB disease occurs when signs and symptoms or radiographic manifestations caused by MTB appear. Studies show that in 40,0 to 50,0% of infants with untreated TB infection, disease develops within one to two years.

The first 6 to 12 months following infection represent a period of great danger as it is during this period that disease may progress, with pleural effusion development, progression of the primary focus to cavitation and the development of disseminated forms, such as miliary TB and TB meningitis (Kibel & Wagstaff 1995:278).

Recognition of clinical signs and symptoms of TB in children form an integral part of a high index of suspicion. However, many of the signs and symptoms

commonly used to aid the diagnosis of childhood TB are not very specific when applied in an endemic area therefore even with sufficient clinical findings to support a diagnosis of TB, continual reassessment of the correctness of the diagnosis is essential (Schaaf et al 1995:193).

Many of the symptoms and signs of childhood PTB are non-specific (Beyers et al 1994:261) thus one needs to integrate a constellation of physical signs (Gie, Beyers, Schaaf, Nel, Smuts, Van Zyl & Donald 1995:659). Symptoms of childhood TB include persistent cough and wheezing (Beyers et al 1994:264). Common conditions confused with TB are pneumonia, bronchopneumonia and asthma (Gie et al 1995:658-659). In areas with a high TB incidence, children from disadvantaged socio-economic backgrounds are often exposed to a variety of infections, parasitic diseases and allergens which, when causing disease, will often present with similar non-specific symptoms and signs and prompt initiation of inappropriate anti TB treatment (Gie et al 1995:659).

The most common chronic illnesses in children in sub-Saharan Africa, TB, HIV and malnutrition, often mimic each other and frequently co-exist in the same patient, resulting in tremendous diagnostic and therapeutic challenges for the health worker (Van Rheenen 2002:435). Furthermore, clinical signs of TB have become less specific in HIV-endemic areas (Van Rheenen 2002:440).

Pearson (1992:35) found loss of skin colour and hypomelanosis in the presence of weight loss to be an additional feature of TB in Africa and its occurrence should raise the index of suspicion for TB.

2.3.5 Tuberculosis score chart (TSC) for the diagnosis of TB in children

A score system is one way of trying to improve the diagnosis of childhood TB by the careful and systematic collection of diagnostic information (Balt et al 1998:88). Crofton, Horne and Miller's (1992) score chart (in Harries et al 1996:63) is a useful guide for clinical judgement (see figure 2.2). Van Beekhuizen

(1998:155) found the TSC to be a very useful, easy, cheap and quick method for diagnosing TB in children at primary health care facilities in Aitape, Papua New Guinea.

Crofton et al (1992:49) state that the TSC can be completed with a paediatric tuberculosis flow chart, which is generally advocated when a child has signs of pneumonia that have lasted more than 2 weeks (see figure 2.3).

Score chart for the diagnosis of TB in children						
SCORE IF FEATURE PRESENT						
Feature	**0**	**1**	**2**	**3**	**4**	**SCORE**
General						
Duration of illness (weeks)	<2	4		2-4		
Nutrition (%weight for age)	>80	60 – 80		<60		
Family history of TB	NONE	Reported by family		Proved sputum positive		
Tuberculin test				Positive		
Malnutrition				Not improving after 4 weeks		
Unexplained fever and night sweats			No response to Malaria treatment			
Local						
				Lymph nodes		
				Joint or bone		
				Swelling ab-dominal mass or ascites		
				CNS signs and abnormal CSF findings		
					Angle de-formity of spine	
TOTAL SCORE						

Figure 2.2
Paediatric TSC (courtesy of Dr Keith Edwards, University of Papua New Guinea)

(Harries et al 1996:63)

Figure 2.3
Paediatric TB flow chart

(Crofton et al 1992:49)

Many children appear to miss out on therapy because the score chart is not adequately applied (Osborne 1995:371). Its value may be negatively affected though in areas of HIV endemicity. In his study on the use of the paediatric TSC in an HIV-endemic area, Van Rheenen (2002:440) found a lower specificity compared with the 95,0% reported from Papua New Guinea, mainly because of the high prevalence of HIV-infection in the study population. However, Van Rheenen found that the TSC was still useful as a screening tool to identify children at the primary health care level who should then be referred for further diagnostic testing. Furthermore, the TSC needs to be refined in high prevalence HIV-endemic areas as low specificity could lead to over-diagnosis of TB and unnecessary use of costly anti-tuberculous drugs.

Migliori, Borghesi, Rossanigo, Adriko, Neri, Santini, Bartoloni, Paradisi and Acocella (1992:149) recommend including gastric washing in a score-based method (see figure 2.4).

2.3.6   Acid-fast bacilli (AFB) microscopy

Mycobacteria are acid- and alcohol-fast bacilli (AFB) (Harries et al 1996:39). Examination is done by the Ziehl-Neelsen (ZN) staining method. In adults, sputum smear microscopy is the most reliable and cost-effective way of diagnosing TB (Balt et al 1998:23; Perkins 2000:182). Sputum is by far the best clinical material for the bacteriological diagnosis of PTB, but children can often not produce sputum (Donald et al 1999:7) The "gold" standard test for adults with TB is sputum smear microscopy, but there is no such "gold" standard test in

children (Harries et al 1996:6). The diagnosis of TB in children is nearly always presumptive with bacteriological confirmation not being possible (Harries et al 1996:63). Sputum induction in infants and young children can be done safely and effectively. Where feasible, this could provide a more convenient specimen for bacteriologic confirmation of pulmonary TB in children (Zar, Tannenbaum, Apolles, Roux, Hanlo & Hussey 2000:1151). Shortcomings of AFB microscopy seriously limit both the extent and quality of its application and, ultimately, its impact on TB control (Perkins 2000:182). This is further complicated by the rising incidence of smear-negative disease in regions where HIV infection is prevalent, such as in sub-Saharan Africa. The need for two or three sputum examinations further compounds its application in developing countries.

Figure 2.4

Proposed criteria for the diagnosis of PTB in childhood

(Migliori et al 1992:149)

2.3.7 Culture of the specimens submitted for microscopy

Culture makes a definite diagnosis possible in milder cases, which are negative
on microscopy (Crofton et al 1992:20).

2.3.8 "Road to Health" card

The "Road to Health" card is an additional tool that the PHC nurse can use to
assist diagnosis of TB in children (Donald, Schoeman & Van Schalkwyk
1985:117). A weight card can be most useful in the diagnosis of TB in the young
child. It is very useful in the case of TB meningitis (TBM) and has proven a
sensitive and simple aid to early diagnosis. The prodromal phase that usually
lasts for a week to 10 days is preceded by a considerably longer period of failure
to gain adequate mass, which may be detected by using the "Road to Health"
card. This period may vary from 4 to 28 months. Failure to gain adequate mass
is a sensitive sign of the presence of TBM and should assist the peripheral health
worker in deciding on the initiation of anti-TB drugs (Donald et al 1985:117).

It should be noted that it is the direction of the growth curve rather than the
precise percentile that is important (Donald et al 1999:160). Not all children in
need of anti-TB treatment will fail to gain weight or lose weight, but all children
who fail to gain or lose weight should be evaluated for TB.

As TB and malnutrition often co-exist in children, and differentiating between the
two is not easy, every clue to the presence of TB is worth noting (Pearson
1992:35). Where children attend an under-five clinic with well-kept growth charts,
the growth chart might help to distinguish one from the other. Progressive weight
loss, with a downward curve, is more likely to be TB. Failure to gain weight, with
a flat curve, is more likely to be malnutrition (Pearson 1992:35). Failure to thrive
in children must always lead to consideration of the possibility of TB (Donald,
Schoeman, Cotton, Van Zyl & Strachan 1990:78).

2.3.9 Alternative specimens that can be used for microscopy (AFB) and TB culture

2.3.9.1 Bronchial washings

Bronchial washings should be submitted for culture. The procedure often results in the patient being self-productive of sputum for several days (Donald et al 1999:158).

2.3.9.2 Urine

The specimen of choice is the total morning, cleanly voided specimen rather than a 24-hour pooled specimen for diagnosing TB of the genitourinary tract. A series of 3 specimens should be submitted to the laboratory. Urine specimens should be refrigerated prior to dispatch to the laboratory (Donald et al 1999:158).

2.3.9.3 Laryngeal swabs

This technique requires some degree of expertise and should only be undertaken by those trained to visualise the vocal cords. Laryngeal swabbing is unpleasant for a child and has a low yield. The procedure often causes the child to cough violently and this poses a risk of infection to the person taking the specimen, who should wear a mask or a visor (Donald et al 1999:8).

2.3.9.4 Pleural, ascitic, peritoneal and joint fluids

These specimens often contain very few bacilli therefore culture should always be performed if TB is suspected in these anatomical sites (Donald et al 1999:1590).

2.3.9.5 Cerebrospinal fluid

"Cerebrospinal fluid (CSF) should be sent directly to the laboratory in sterile containers. Examination of CSF for MTB is an emergency investigation when TB meningitis is suspected and the laboratory should be contacted directly by the submitting clinician" (Donald et al 1999:159).

2.3.9.6 Biopsy/histology

Biopsy of liver, bone marrow, pleura or lymph nodes may assist in the diagnosis of TB of these organs and material must be sent for both histology and culture (Cremin & Jamieson 1995:159).

2.3.9.7 Gastric aspiration/gastric washing

Pomputius, Rost, Dennehy and Carter (1997:225) studied the standardisation of gastric aspirate technique. The examination of gastric aspirates for the presence of AFB has produced variable results. A smear of gastric aspirates is an acceptable substitute when sputum cannot be produced and therefore is particularly suitable in young children. It can also be used to monitor response to treatment when performed monthly. Gastric washing and direct microscopy may be used for routine hospital diagnosis of TB in childhood just as gastric lavage, sputum and bronchial washing are used for TB culture in developed countries (Migliori et al 1992:149).

Schaaf et al (1995:193) found a lack of facilities in clinics for taking gastric aspirates and the necessity of early morning specimens further frustrates attempts to confirm the diagnosis.

2.3.9.8 Stools

Stool microscopy and culture for MTB has been used for diagnosing PTB especially where sputum or gastric washing cannot be obtained (Osborne 1995:371).

2.3.9.9 ELISPOT test

This rapid, blood test for MTB infection, in its current form, with the need for a microscope, centrifuge, and incubator, has limited usefulness in smaller health centres without such equipment (Liebeschuetz, Bamber, Ewer, Deeks, Pathan & Lalvani 2004:2197). Liebeschuetz et al (2004:2202) recommend that TST and ELISPOT be used together to improve diagnostic sensitivity in African children with suspected active TB.

2.3.10 Classification of children as having suspected, probable or confirmed respiratory TB

Kibel and Wagstaff (1995:280) state that, given the difficulties inherent in the diagnosis of TB in childhood, "the WHO, based on work conducted in Kenya, has suggested a graduated approach to diagnosis that better reflects the degree of uncertainty characterising diagnosis of childhood TB. They suggest classifying children as having suspect, probable or confirmed respiratory TB." This approach might assist the PHC nurse to decide whether to place the children on treatment or prophylactic treatment.

Schaaf et al (1995:189-194) describe the WHO provisional guidelines for the diagnosis of pulmonary tuberculosis in children (see figure 2.5).

2.3.11 New diagnostic tools for TB

The Foundation for Innovative New Diagnosis (FIND), an independent non-profit foundation launched in 2003 by the Special Programme for Research and Training in Tropical Disease with funding from the Gates Foundation, chose TB

as its first target. Several innovative and rapid tests are being developed with the support of FIND (Mwinga 2005:98).

Figure 2.6 depicts Donald et al's (1999:157) suggested diagnostic pathways for children with possible PTB.

Figure 2.5

The WHO provisional guidelines for the diagnosis of PTB in children

(Schaaf et al 1995:189-194)

Figure 2.6

Suggested diagnostic pathways for children with possible PTB

(Donald et al 1999:157)

2.4   FURTHER RESEARCH NEEDED

The literature review indicates the pivotal role of the primary practitioner, who in the rural South African context is a PHC nurse, in suspecting and diagnosing TB in children. There are definite gaps in the research literature that need to be examined, including:

1   What knowledge is necessary for the PHC nurse to effectively diagnose TB in children?
2   What is the present knowledge base of the PHC nurse to enable diagnosis of TB in children?
3   Is the PHC setting equipped to diagnose TB in children?
4   The diagnosis of TB in children has already been explored. Is it possible to combine the findings into an appropriate plan of action (guidelines) to assist PHC nurses in diagnosing TB in children?
5   What are the potential usefulness of a contact register and the role of the PHC nurse in administering the register?
6   How useful is the score chart in the South African context?
7   How does co-infection of TB/HIV influence the PHC nurses' ability to diagnose TB in children?

2.5   CONCLUSION

The literature review reflects the difficulty inherent in making an early diagnosis of TB in children. However, it also highlights specific tools and approaches that have proven useful in diagnosis. Some valuable algorithms were also reviewed.

The researcher found no direct reference in the literature review to the pivotal role played by PHC nurses in diagnosing TB in children. The new South African PHC nurse-driven system demands that first line nurses be equipped to suspect, diagnose, confirm the diagnosis and treat TB in children (Baez 2003:1). Their ability to effectively perform this important task deserves close study.

Chapter 3 describes the research design of the study.