September 2006

Assessment of resistance in multi drug resistant tuberculosis patients

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Screening of TB Patients for HIV Infection in Concentrated HIV Epidemic Setting in Sindh, Pakistan

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I AM Stopping TB

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BRIDGE SERVICE RESEARCH TRAINING

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ORIGINAL ARTICLES

Editorial

Tuberculosis in Pakistan: A decade of progress, a future of challenge

Sten H. Vermund,[1] Arshad Altaf,[2] Rab Nawaz Samo,[3] Rafiq Khanani,[4] Noor Baloch,[5] Ejaz Qadeer,[5] Sharaf Ali Shah,[3,4]

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Tuberculosis (TB) is a major public health problem in Pakistan. TB has been prevalent in Pakistan and unfortunately it has been one of the neglected health areas in the past. Pakistan ranks 8th amongst the countries with highest burden of TB in the world. Pakistan contributes about 44% of tuberculosis burden in the Eastern Mediterranean Region. According to the World Health Organization (WHO), the incidence of sputum positive TB cases in Pakistan is 80/100,000 per year and for all types it is 177/100,000. TB is responsible for 5.1 percent of the total national disease burden in Pakistan. The impact of TB on socio economic status is substantial.[1] The National TB Control Program, is responsiable for developing national guidelines, framing policies and generating resources for implementation of TB control measures at Provincial and district level. The DOTS was adopted as National Stretegy in 2000 and expanded to all public health facilities as part of primary health care. The Program was success ful in achieving 70 % case detection and 85 % treatment outcome of the global target set by STOP TB Partnership. Despite rapid expansion and consolidation of TB care there are still many issues related to TB Control. The disease is directly linked with socioeconomic status and 75 % patients are in productive age group.

Many patients consult untrained practitioners in the informal health sector with delays in diagnoses. Suboptimal case detection and treatment, lead to failure in acvhieving program target goals. This special supplement of the Journal of the Pakistan Medical Association presents several peer-reviewed papers originally published elsewhere[2-27] that we have assembled to provide an update on key issues of the Pakistani TB situation. In addition, there are three[28-30] original articles in this issue to stimulate debate as to how TB control and prevention can be revitalized in Pakistan.

Origin of this special issue

It is easier to make research results readily available to persons who need them now in the internet age. Nonetheless, there are many health professionals in Pakistan who do not have reliable access to the worldwide web. If a health professional or worker has a computer with excellent internet access, HINARI (http://www.who.int/hinari/en/) is a WHO-sponsored system that enables journal article access free-of-charge from computer networks in lower income countries. The PubMed system is used worldwide to read abstracts and increasingly has full reference access thanks to the PubMed Central system (http://www.ncbi.nlm.nih.gov/PubMed/) and liberalization of access by some journals, particular on-line journals. If someone does not have good internet access, but has a computer, eGranery (http://www.widernet.org/digitallibrary/) is an effort to bring global resources to an intra-net, rather than inter-net, i.e., one can access it from a local computer network without being logged onto the internet. This is important for institutions and individuals with computers whose internet access may be limited by availability, cost, or the low band width so familiar in many lower-income settings. However, for someone with no or limited computer access, there is still a need for a special supplement like this one to reach a diverse audience of front line service providers.

Many Pakistani researchers have overcome obstacles, both scientific and other, to make important contributions to TB research. Many are cited here, but space and costs prohibited accommodation of all eligible references. Hence, we provide a comprehensive list of 218 articles at the end of this editorial which is title "Special Bibliography", found in a PubMed search from 1997 through 3 December 2008. They include human-related articles published in English that came from searching "Pakistan AND tuberculosis". We have reproduced 26 papers selected from 1998-2007 in this special issue.[2-26] They are all original manuscripts. We hope that this will inspire government leaders and donors to recognize the research talent and opportunity in the nation, as well as the research need.

For this special issue, only Index Medicus-referenced articles were selected, with a priority given to those with public health importance focusing on pertinent issues in Pakistan. Thanks to the generosity of many publishers listed below, we were able to reproduce the publications of these key TB studies from Pakistan without cost, thereby increasing the convenience of their access to readers of the JPMA. There were a few articles which could not be included because publishers required a processing fee to reprint their articles; we preferred to devote our limited budget to purchase and distributions of additional copies of the supplement. We believe that the publishers demanding fees should reconsider these policies to permit free reproduction of articles for

legitimate purposes in the developing country where the research was conducted.

This supplemental issue seeks to reach practicing physicians, policy makers, health care managers, senior nurses, microbiologists, medical researchers, university faculty and students, and public health staff in Pakistan. We believe that an earlier analogous supplement met a similar need in the HIV/AIDS field.

Infrastructure and Tuberculosis Management Challenges in Pakistan

The WHO directly observed therapy-short course (DOTS) strategy was implemented in Pakistan in year 2001. It took four years to bring DOTS coverage to all public health facilities (by mid-2005), and the country remains far behind the global targets of case detection rate of 70% and treatment success rate of 85%. Among the important challenges for TB control in Pakistan are a lack of community involvement, limited engagement of the private sector, increasing number of multiple drug-resistant (MDR) cases and a recent rise in HIV cases among injection drug users who are also at much higher risk of TB.[30] We anticipate an increased burden of TB-HIV co-infection and continuing rise in the proportion of MDR-TB cases, unless there is aggressive intervention.

Pakistan spends a relatively small proportion of its gross domestic product (GDP) on health. In 2000, Pakistan spent 0.8% of GDP, lower than investments by its south Asian neighbors: India, 0.7%; Bangladesh, 1.7%; Nepal, 1.2%; Sri Lanka, 1.5%.[31,32] All are far below such nations as the United States with its 9.7% GDP investment in health in 2003.[33] Low health expenditures correlate with high military investments. Pakistan spent 22% of its total governmental budget on defense in 2000.[34] Medical and public health research investments are exceedingly low in Pakistan. The overall low governmental commitment to the health sector results in the particular neglect of prevention, as curative services command the lion's share of these scarce resources.

The articles in this special issue identify these specific needs of the Pakistani national TB control program:

1. ENGAGE THE PRIVATE SECTOR

A significant proportion of patients seek medical advice from private sector, including formal and informal sectors. Given the magnitude of the TB problem, the role of the private sector cannot be underestimated. The importance of private health care providers has also been recognized by the Stop TB Partnership with its emphasis on integrating private health care providers into DOTS strategy efforts. Well-organized educational efforts and logistical support to private sector health care providers can make it easier for them to follow standard TB control guidelines (both DOTS and DOTS-Plus for MDR-TB).[35] We had success in upgrading the syndromic management of sexually transmitted diseases by private providers in the informal sector in one Karachi study, but the government did not expand (or even continue) this model program.[36]

2. DRUG MANAGEMENT AND LOGISTICS

Proper anti-TB drug management is an essential component for success of TB DOTS strategy.[37] Frequent stock-outs of TB drugs and diagnostic supplies at first level care facilities are major impediments to the TB case detection and treatment, fueling incidence and MDR-TB.[38] The stock management systems at the central and district levels are weak such that distribution of TB drugs is far less reliable than distribution of most private sector products (e.g., petrol for autos and trucks, soft drinks, commercial goods).[37] Effective drug supply systems, inventory managment, methods of drug quality assurance, and proper use of anti-TB drugs by practitioners is essential.

3. SPECIAL FACILITIES

Targeted programs must engage prisons, jails, HIV/STD programs, specific high-risk occupational groups, illicit drug users, and persons living on the street. Links to community services are essential for persons leaving incarceration.

4. OPERATIONS RESEARCH

Operations research (OR) is necessary to address issues like now-uncontrolled private sector activities, poor management of defaulters, and lack of community involvement.[39] Field-based research at the community level is essential to better identify problems from patient, provider, and policy-maker perspectives; solutions to improve program utilization can then be much better informed.[35]

5. MDR-TB and TB/HIV

MDR-TB and TB/HIV are the emerging health issues in Pakistan and a great challenge to public health sector. In Pakistan, there is a lack of technical expertise in both areas. MDR-TB (through DOTS-Plus) and TB/HIV (via programme coordination and communication) are now identified as one of the challenges in broadening the activities of the National TB Programme beyond basic DOTS.[40]

These issues are very familiar to experts in TB, but may not be familiar to the diverse readership of the JPMA.

Role of future research in the fight against TB in Pakistan

We are confident that research will play a vital role in the fight against TB. We need answers to many questions:

- How should primary, asymptomatic TB be diagnosed and managed with high background BCG usage rates (complicating diagnosis) and INH resistance levels (complicating treatment)? Will isoniazid preventive therapy be appropriate or are alternatives needed?

- What strategies will work to maximize DOTS coverage, given Pakistani logistical challenges? Can we succeed in rural areas, including areas of civil strife, through community engagement?

- How do we optimize HIV and TB diagnosis and care, including program integration to enable simpler care logistics from a patient's point of view?

- Can we do better than the classic sputum examination to diagnose TB to diagnose TB? What is the most suitable resistance assay, given limitations in laboratories, especially in rural areas?

- What programs work best and why? What programs work most poorly and why?

- How can Pakistan's politicians and powerful business leaders be influenced to invest more into health?

These and many other questions remain unanswered for Pakistan, suggesting an urgent need for research, even as we seek to improve programs. Implementation science is a term for the work needed to increase coverage of programs that we already have in place.[41] Operations research is a component of implementation science that uses program process and outcome data in a feedback loop to improve program functioning. The guest editors are pleased that original articles have been provided for this special supplement and that publishers permitted reproduction of papers that we felt to be especially salient. We think they represent, in aggregate, a call-to-arms in the fight against TB in Pakistan.

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Prevalence and risk factors associated with tuberculin skin test positivity among household contacts of smear-positive pulmonary tuberculosis cases in Umerkot, Pakistan

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Abstract

Study Population and Setting: Household contacts of acid-fast bacilli (AFB) sputum smear-positive tuberculosis patients in the Umerkot Taluka, Sindh, Pakistan.

Objective: To estimate the prevalence of and identify risk factors associated with tuberculin skin test (TST) positivity among household contacts of acid-fast bacilli (AFB) sputum smear-positive pulmonary tuberculosis cases.

Design: A cross-sectional study of household contacts of AFB sputum smear-positive tuberculosis cases, registered at the Umerkot Anti-Tuberculosis Association clinic from August 1999 to September 1999. The contact's Mycobacterium tuberculosis infection status was assessed using TST. On the day of the TST, a predesigned questionnaire was administered to collect data on putative risk factors for TST positivity among contacts. The data were analysed using a marginal logistic regression model by the method of generalised estimating equations (GEE) to determine risk factors independently associated with TST positivity.

Results: The prevalence of TST positivity among household contacts of AFB sputum smear-positive index patients was 49.4%. The final multivariate GEE model showed that contact's age and sleeping site relative to the index case, the intensity of the index case's AFB sputumsmear positivity and the contact's BCG scar status were independent predictors of TST positivity among household contacts of AFB sputum smear-positive index cases.

Conclusions: The results suggest that the household contacts of AFB sputum smear-positive tuberculosis patients in a poor neighbourhood of rural Sindh had a high prevalence of M. tuberculosis infection as determined by TST. Poor housing conditions seem to contribute to the spread of M. tuberculosis infection. Early diagnosis of pulmonary TB through evaluation of TST-positive household contacts, followed by appropriate therapy, may prevent further spread of M. tuberculosis infection. We recommend an awareness programme to prevent household contacts from acquiring M. tuberculosis infection from smear-positive pulmonary TB cases.

Key Words: Mycobacterium tuberculosis; tuberculin skin test; household contact; cross-sectional study; risk factors; Pakistan.

Introduction

Tuberculosis (TB) is one of the leading causes of mortality, accounting for 26% of preventable adult deaths in the developing world.[1,2] An estimated onethird of the world's population (1.86 million) is infected with Mycobacterium tuberculosis, and during the last decade the incidence of tuberculous infection has increased even in industrialised countries.[3] Varying levels of endemicity of tuberculous infection have been reported worldwide, and South-east Asia seems to be the most afflicted: 44% of its population is reported to be M. tuberculosis infected.[3] Pakistan has been ranked fifth among the 22 highest-incidence countries of TB.[3]

Screening of high-risk populations for M. tuberculosis infection to identify individuals eligible for chemoprophylaxis is one of the strategies recommended to combat TB.[4,5] Contacts of TB cases constitute a high-risk group for acquiring M. tuberculosis infection,[6,7] as approximately 30% of close contacts demonstrate evidence of infection, and at least half of infected contacts exhibit progression to disease in the first 2 years.[8] So far, only a limited number of studies have evaluated the risk factors associated with acquiring M. tuberculosis infection among household contacts of index TB cases in other parts of the world.[9-12] However, comparable data on the frequency of tuberculous infection among household contacts of index TB patients are not available for Pakistan and other neighbouring countries. The magnitude and the predominant risk factors for M. tuberculosis infection among contacts of TB patients, particularly in rural areas of Pakistan, are uncertain. Furthermore, for primary prevention sound scientific knowledge about such risk factors is a prerequisite for suggesting preventive measures. We therefore conducted the present study to estimate the prevalence and identify the risk factors for tuberculin skin test (TST) positivity among household contacts of acid-fast bacilli (AFB) smear-positive index cases of pulmonary TB in Umerkot, a rural area of Sindh

province, Pakistan.

Study Population and Methods

Study design, setting and study population

A cross-sectional study was conducted in August and September 1999 in Umerkot, a remote district of Sindh covering an area of 5608 km2 with a population of around 0.7 million, 83% of whom live in rural areas. Topographically the Umerkot district has two distinct parts- the irrigated area in the north-west and rain-fed desert in the south-east. Agriculture is the main occupation in the area. About 57% of the housing units are single room houses with an average household size of 5.4 persons. The Muslim population constitutes 51% of the district's total population, and about 90% of the people speak Sindhi.[13]

Our study site, the Umerkot Taluka, an administrative sub-unit of Umerkot district, has a population of about 0.3 million. The local health care system is comprised of a government health centre, a nongovernmental organisation clinic-Umerkot Antituberculosis Association (UATA) clinic-and about 20 private clinics. TB control is provided for most patients of this study area by UATA clinic. The majority of patients are diagnosed and treated as out-patients.

Our study population was comprised of household contacts of index TB patients in Umerkot Taluka. An index TB case was defined as the first member of a household aged 15 years or more who presented and registered for TB treatment at the UATA clinic and was found positive on at least one AFB sputum smear. The initial TB diagnosis in an index case at UATA clinic is based on a combination of two or more methods including TST, radiography, AFB sputum smear status and bacterial culture.[9,14] A household contact was defined as any person over 3 months of age who had lived in the same house as the index case for at least 3 months and had slept in the same house for on average at least 4 nights per week, throughout this 3- month period.[15]

Selection of index cases and household contacts

The objectives of this study were to estimate the prevalence and determine factors associated with TST positivity among household contacts of index patients. For the estimation of M. tuberculosis infection prevalence among household contacts of index TB cases, we included 385 contacts of 77 index cases based on the following assumptions: an estimated prevalence of TST positivity of 0.5 among contacts of TB cases, with a bound on error of 0.05 at a significance level of 0.05.[16] This sample size was also sufficient for identification of factors associated with TST positivity, with an odds ratio (OR) _2 and a study power of at least 80%.[17]

To select household contacts of index TB patients, a list of 680 TB cases maintained at UATA clinic was obtained and used to select a simple random sample of 77 index cases. Using the Ziehl-Neelsen staining method,[18] each selected TB case was screened for AFB in three sputum samples, one on the spot and two on two consecutive days in the early morning. If a TB case turned out to be AFB smear-positive on at least one sputum smear, that case was enrolled as an index case and interviewed. If a registered TB case turned out to be AFB sputum smear-negative or declined to participate in the study, then the next TB case in the list was contacted and the screening procedure conducted.

During the first household visit, verbal informed consent was obtained from all persons aged 12 years or more and from the parents of household contacts less than 12 years of age who fulfilled our contact definition. The study protocol was reviewed and approved by the departmental ethical review committee.

Tuberculin skin test and data collection

In addition to the principal author, three medical graduates (two male and one female) who had at least 2 years of experience in the field since graduation were recruited for interview purposes. All were quite fluent in Sindhi. The principal author briefed the team on the interviewing process during a training session which included obtaining the subject's consent, being polite and considerate, using a standardised delivery of questions, recording the responses and performing the TST.

A pre-designed and pre-tested questionnaire was used to collect data on potential risk factors from the index case and from household contacts. Information on household level variables was collected from the head of household or a representative on the day TST was performed. For household contacts aged < 12 years, the mother or guardian answered the questions on behalf of the contact. Bacille Calmette-Guérin (BCG) vaccination status was assessed by physical examination for the presence or absence of BCG scar. However, vaccination records were not available for most of the contacts for verification of BCG vaccination history.

Household contacts of index cases were subjected to TST using the Mantoux method, a recommended technique for mass screening of M. tuberculosis infection in epidemiological studies.[19,20] It was performed on the volar aspect of the forearm with 0.1 ml of Tubersol (purified protein derivative [PPD] RT 23, 5 tuberculin units; Connaught Laboratories, North York, Ontario, Canada). Contacts were visited again 72 hours later to read the TST.

During that visit any household contact who had not been present on the first visit was also interviewed, subjected to TST and revisited 72 hours later to read the result. Non-BCGvaccinated household contacts of an index case were considered M. tuberculosis infected if the skin induration was ≥ 10 mm at 72 hours post TST. For BCGvaccinated household contacts, a cut-off value of ≥ 15 mm at 72 hours post TST was used as an indication of M. tuberculosis infection, otherwise the contact was regarded as non-M. tuberculosis-infected.[20]

The participation rate was nearly 100% when the contacts were explained the benefits of TST and when it was followed by appropriate free prophylactic or curative TB therapy.

Statistical Analyses

Data were processed using software Epi-Info version 6.04 (CDC, Atlanta, GA, USA). All the analyses were performed using SAS software (SAS Inc, Cary, NC, USA). The summary statistics were generated by computing means (±SD) for continuous variables and frequencies for categorical variables. We used generalised estimating equations (GEEs) to arrive at a marginal multivariate logistic regression model predicting positive M. tuberculosis infection status as detected by TST. The GEE corrects for correlation and lack of independence of responses for contacts with an index TB case in common (clusters within households) using quasi likelihood methods and robust variance estimators. Univariate GEE analyses were carried out to evaluate each variable of interest for its unadjusted association with the infection status of contacts. A multivariate GEE model was then used to estimate the independent effect of each variable on the infection status of the contact. All independent variables significantly ($P \leq 0.1$) related to an outcome variable in univariate analyses were considered for inclusion in the multivariate GEE model.[21] The variables meeting the above selection criteria were all entered in a multivariate model. We arrived at the final model by the backward elimination method. The adjusted ORs and their 95% confidence intervals (9%CIs) were computed using the parameters' estimates of the final GEE model and used for the interpretation of the results.

Results

The means (±SD) and median number of contacts per case interviewed and tested for TST positivity were respectively 5.4 ± 3.1 and 4.0. The prevalence of M. tuberculosis infection among household contacts was 49.4% (95%CI 46.9-51.9%). Their demographic characteristics are given in Table 1. The distribution of M. tuberculosis infection status as assessed by TST positivity with respect to age, sex, marital status, education, relationship of contact with index case and BCG scar status is given in Table 2. In general, the prevalence of M. tuberculosis infection was higher among the contacts who were of male sex, had no formal schooling, had never married, were children of index patients, or who did not have a visible BCG scar. There was

Table 1: Demographic characteristics of household contacts of the smear-positive tuberculosis cases recorded during a cross-sectional study of risk factors associated with tuberculin skin test positivity among household contacts of index cases, Umerkot, Pakistan, August–September 1999 (n=385)

Variables	n (%)
Age of household contact	
4 months–4 years	68 (17.7)
5–14 years	83 (21.6)
15–24 years	103 (26.8)
25 years	130 (33.9)
Sex	
Male	205 (53.2)
Female	180 (46.8)
Education (years of schooling)	
Nil	277 (71.9)
1–5	36 (9.4)
6–10	45 (11.7)
>10	27 (7.1)
Marital status	
Never married	236 (61.3)
Ever married	149 (38.7)
BCG scar	
Present	57 (14.8)
Absent	327 (85.2)
Relationship of contact with index case	
Husband	28 (7.3)
Wife	34 (8.8)
Child	184 (47.8)
Sibling	23 (6.0)
Father	8 (2.1)
Mother	8 (2.1)
Grandparent	1 (0.3)
Uncle/aunt	2 (0.5)
Others	97 (25.2)

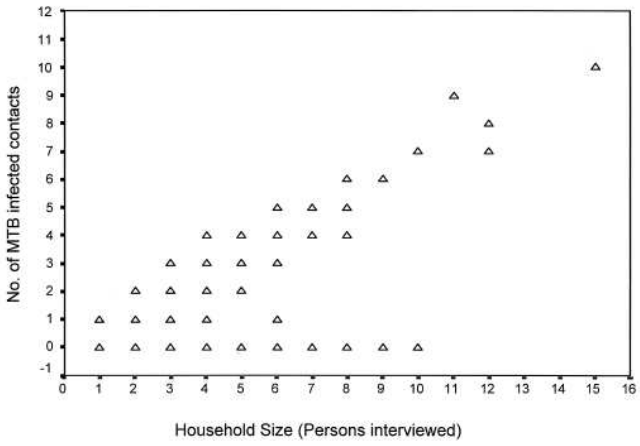

Figure: Distribution of Mycobacterium tuberculosis-infected household contacts of acid-fast bacilli smear-positive index patients by household size in Umerkot, Sindh, 1999.

Table 2 Univariate GEE analysis of risk factors from a cross-sectional study of TST positivity among household contacts of smear-positive tuberculosis cases, Umerkot, Pakistan, August–September 1999 (n 360)*

Variables	Infected contacts‡ 179 (%)	Non-infected contacts‡ 180 (%)	Odds ratio	95%CI
Age of contact				
4 months–4 years	14 (7.8)	46 (25.6)	1.0	—
5–14 years	39 (21.8)	36 (20.0)	2.7	1.4–4.9
15–24 years	46 (25.7)	53 (29.4)	2.3	1.3–3.9
25 years	80 (44.7)	45 (25.0)	3.5	2.0–6.0
Sex				
Female	90 (47.4)	90 (46.4)	1.1	0.7–1.5
Male	100 (52.6)	104 (53.6)	1.0	—
Education				
Illiterate†	142 (79.3)	117 (65.0)	1.2	0.8–1.8
Literate	37 (20.7)	63 (35.0)	1.0	—
Marital status				
Ever married	87 (48.6)	56 (31.1)	1.3	0.7–1.9
Single	92 (51.4)	124 (68.9)	1.0	—
Relationship of contact with index case‡				
Spouse	41 (22.9)	21 (11.7)	2.0	1.1–3.6
First degree	103 (57.5)	112 (62.2)	1.2	0.8–1.9
Second degree	35 (19.6)	47 (26.1)	1.0	—
BCG scar in contact				
Present	34 (19.0)	21 (11.7)	1.8	1.2–2.5
Absent	145 (81.0)	159 (88.3)	1.0	—
Sleeping site relative to index case				
Same bedroom	118 (65.9)	93 (51.7)	1.9	1.3–2.8
Different bedroom	61 (34.1)	87 (48.3)	1.0	—
Sharing of utensil with index case				
Yes	130 (62.0)	102 (58.0)	1.6	1.1–2.4
No	47 (26.6)	74 (42.0)	1.0	—
Intensity of AFB sputum-smear positivity of index case				
≤ ++	111 (62.0)	147 (81.7)	1.0	—
> ++	68 (38.0)	33 (18.3)	3.2	1.7–5.9

*A contact was considered to be M. tuberculosis infected if the skin induration was 10 mm without BCG vaccination and 15 mm with BCG vaccination at 72 hours post tuberculin test; otherwise the contact was regarded as non-M. tuberculosis-infected.
† Illiterate: had no formal school education; literate: had one or more years of schooling.
‡ Relationship of contact with index case: spouse (husband or wife); first degree (child, sibling, and parents); second degree (uncle, aunt, brother-in-law, and sister-inlaw, others).
GEE = generalised estimating equations; TST = tuberculin skin testing; CI = confidence interval; AFB = acid-fast bacilli.

also a direct linear relationship between the household size and the number of M. tuberculosis infected contacts (Figure).

For further GEE analysis, contacts from household size of nine or fewer were used. Six households of size 10 or more were dropped, as by their inclusion the GEE model did not converge for parameter estimation owing to sparse data. In the univariate analysis, factors associated with M. tuberculosis infection status included contact age (P = 0.022), relationship with index case (P = 0.028), BCG scar status (P = 0.003), sleeping site relative to index case (P < 0.001), sharing of utensils with index case (P = 0.026), and intensity of AFB sputum smear positivity in the index case (P = 0.002) (Table 2). No association was found between M. tuberculosis infection status and the variables sex, marital status and education.

The final multivariate GEE model (Table 3) revealed that compared to non-infected contacts, M. tuberculosis infected contacts were more likely to be older by 5 years or

Table 3 Multivariate GEE analysis results of risk factors for TST positivity among household contacts of smear-positive tuberculosis cases, Umerkot, Pakistan, August–September 1999 (n = 360)

Variables	Adjusted OR	95%CI	*P* value
Age of household contact			
4 months–4 years	1.0	—	
5–14 years	3.0	1.6–5.8	
15–24 years	4.9	2.4–10.0	
25 years	6.7	3.5–12.8	0.001
Sleeping site relative to index case			
Different bedroom	1.0	—	
Same bedroom	2.5	1.5–4.0	0.0003
Intensity of AFB sputum-smear positivity of index case*			
≤ ++	1.0	—	
< ++	2.8	1.6–4.8	0.0003
BCG scar			
Absent	1.0	—	
Present	1.6	1.1–2.6	0.0276

* Intensity of sputum-smear-positivity: + = 1–10 AFB in the whole slide; + + = 1–10 AFB per microscopic field (x 1000); + + + = more than 10 AFB per microscopic field.
GEE = generalised estimating equations; TST = tuberculin skin test; OR = odds ratio; CI confidence interval; AFB = acid-fast bacilli.

more (5-14 years vs. 4 months-4 years, adjusted OR 3.0, 95%CI 1.6-5.8; 15-24 years vs. 4 months-4 years, adjusted OR 4.9, 95%CI 2.4-10.0; _25 years vs. 4 months-4 years, adjusted OR 6.7, 95%CI 3.5-12.8), to have slept in the same bedroom (adjusted OR 2.5, 95%CI 1.5-4.0), to have lived with an index case with an AFB sputum smear positivity index of 2 or more (adjusted OR 2.8, 95%CI 1.6-4.8) or to have had a visible BCG scar (adjusted OR 1.6, 95%CI: 1.1-2.6).

Discussion

This cross-sectional study demonstrated that in this study population in Umerkot, Pakistan, 49.4% of household contacts of smear-positive index TB cases were M. tuberculosis infected as assessed by TST. To our knowledge no similar data from the study area or other areas of Pakistan are available for comparison. However, comparable data on the prevalence of M. tuberculosis infection among household contacts of index cases have been reported from other countries. For example, prevalences of M. tuberculosis infection among contacts of TB patients of as high as 44% in Spain and 55% in Peru have been reported.[22-24] Also, in another study in an area with high TB incidence, 34% of children under the age of 5 years living in the same household as an index TB case were diseased and 14% were infected.[25] Therefore, the results of the present study corroborate the findings of previous studies and show that contact with AFB sputum smearpositive index case poses a substantially higher risk of acquiring M. tuberculosis infection. We could not assess the sputum smear status of the TST-positive contacts, but one could speculate that considerable numbers of these could have active TB and contribute to the continued spread of M. tuberculosis infection in their households and in the community.

Consistent with previous findings, a trend of increasing odds of TST positivity with increasing age was observed in this study.[23] Plausible explanations for this result may include the extended duration and frequency of contacts with an index case and/or that contacts with increasing age might have been exposed to other AFB smear-positive TB cases in this neighbourhood with a high burden of TB.

The intensity of sputum smear positivity of the index case was associated with increased odds of TST positivity of the contact in this study. It has previously been shown that the number of contacts infected by a person with TB also depends on the severity of disease in the index case,[11] and on the number of organisms excreted in the sputum.[26]

In this study M. tuberculosis infected contacts were significantly more likely than non-infected contacts to have had slept in the same bedroom as the index case. This type of behaviour seemed to result from over-crowding, as most of the housing units in the study area are one bedroomed, with an average household size of 5.4. The presence of BCG scar in contacts was also associated with positive M. tuberculosis infection status. BCG may induce cross-reactions for a prolonged period after vaccination.[27] However, the recommended cut-off value of $\geq$ 15 mm skin induration on TST was used as an indicator of M. tuberculosis infection in the study. Furthermore, BCG vaccination reportedly does not prevent infection but protects against the consequences of infection.[28] Recently, a prevalence of M. tuberculosis infection of 7.5% among those with BCG scar was reported in another Asian population.[29]

Several limitations of our study need to be acknowledged. Firstly, the study is limited by its cross-sectional design, so temporality (cause-and-effect relationship) can not be established. Second, the first subject from a given household registered for treatment at the UATA clinic was assumed to be the index case. We are, however, uncertain whether this is indeed the first person to be infected or whether it is a secondary contact of another infected member in the household who exhibited disease earlier than the other infected household member. Third, after exposure to M. tuberculosis the ability of TST to detect delayed type hypersensitivity reaction is on average 4-12 weeks.[30] Therefore, some infected household contacts might have been incubating M. tuberculosis but were not detected by TST and were labelled as non-infected, thus directing the results towards null. Fourth, the duration of contact of each household member with the index case could not be ascertained, since the exact dates of diagnosis of M. tuberculosis infection in most of the index cases were not available. Fifth, as all the index cases were AFB smear-positive, we cannot draw any inference regarding the risk of M. tuberculosis transmission in the household of AFB sputum smear-negative index cases. And finally, in this study we could not assess the intra-observer and inter-observer variability of reading the TST results. However, we believe that such variation was probably minimal because all the interviewers were medical graduates and their training before the start of the actual study should have given them sufficient experience to conduct TST and objectively measure the results.

We could not evaluate whether or not index patients were suffering from multidrug-resistant TB. The evaluation of such TB patients and the treatment required should be prioritised to help shrink the pool of infectious individuals. Evaluation of TST-positive household contacts for the presence of pulmonary TB, followed by prophylactic or supervised therapy as appropriate, may contribute to the prevention of further spread of M. tuberculosis infection. We recommend an awareness programme for household

contacts about the possibility of acquiring M. tuberculosis infection from AFB sputum smear-positive pulmonary TB cases. Future research may be focused on the evaluation of intervention programmes aimed to improve the knowledge and awareness of TB patients and their contacts about the disease and its complications in this and other similar settings.

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Is there a value of Mantoux test and erythrocyte sedimentation rate in pre-employment screening of health care workers for tuberculosis in a high prevalence country?

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Abstract

Setting: Pre-employment screening of health care workers (HCWs) is practiced widely. Research needs to be carried out to evaluate the screening procedure in developing countries.

Objective: To evaluate the efficacy of Mantoux test and erythrocyte sedimentation rate (ESR) for the diagnosis of active tuberculosis (TB), in pre-employment screening of HCWs, in a high prevalence country.

Design: Pre-employment screening of all new employees was reviewed from June to September 2000. The screening consisted of history, physical examination, blood and urine tests, Mantoux test and a chest radiograph. Patients with clinical, laboratory or radiological features suggestive of active TB were referred to a specialist.

Results: Out of 207 employees, a Mantoux reaction of >10 mm and ESR of >25 mm/first hour was noted in 90 (43.5%) and 21 (10.1%), respectively. One person had symptoms suggestive of TB and was already on anti-tuberculosis therapy at the time of screening. All other employees were asymptomatic. Based on radiographic findings, four (2%) cases were referred and one was given anti-tuberculosis therapy. An additional 48 (23.1%) employees were referred on the basis of positive Mantoux or elevated ESR; none were found to have active TB.

Conclusion: In high prevalence countries use of Mantoux test and ESR in pre-employment screening of HCWs is not recommended for detection of active TB.

Introduction

The last decade has seen an upsurge in the global prevalence of tuberculosis (TB), including multidrug-resistant (MDR) strains. Health care workers (HCWs) are at high risk of acquiring the disease during the course of their occupation, and once infected they can spread it further to their patients.[1] The Centers for Disease Control and Prevention recommends regular skin testing and appropriate follow-up care for all HCWs.[2] Measures used in industrialized countries to screen HCWs and to control nosocomial TB transmission are beyond the resources of low-income countries. Research needs to be carried out to evaluate the feasibility and cost-effectiveness of measures aimed at preventing TB transmission among workers in high-risk settings.

Screening of HCWs at the time of employment is practiced widely in order to identify asymptomatic cases. Hospitals vary widely in their pre-employment screening practices depending on resources, risk of nosocomial transmission and prevalence of TB in the community. Third world countries, where the risks are highest, unfortunately have the least resources available to them. In a small study from British Columbia, HCWs were not found to be at increased risk of TB.[3] In Africa, on the other hand, 79% of 512 HCWs in Abidjan had a tuberculin reaction of ≥10 mm.[4] In Malawi, 3.6% of 3042 HCWs had active TB with a case fatality rate of 24%, and compared with the general population the relative risk (95% confidence interval [CI]) in HCWs of all types of TB was 11.9 (95%CI 9.8-14.4).[5] Similarly, in Asia, the HCWs had a high rate of TB infection.[6]

Pre-employment screening programmes for HCWs are mostly developed in western countries, often based on consensus among experts rather than clinical evaluation, expensive, and may lack local relevance. The aim of our study was to evaluate the efficacy of the Mantoux test and erythrocyte sedimentation rate (ESR) in pre-employment screening of HCWs for the diagnosis of active TB.

Study Population and Methods

The study was conducted at the Aga Khan University Hospital, a teaching hospital located in Karachi, Pakistan. All employees referred for pre-employment screening over a period of 4 months (June-September 2000) were evaluated. Pre-employment screening consisted of history and physical examination, blood hemoglobin and ESR levels, detailed urine report, Mantoux test and a chest radiograph. Patients with clinical or laboratory features suggestive of active TB were referred to a specialist (pulmonary physician). The outcome of the referral and details of further investigations were recorded. The medical records of all the screened employees were reviewed in November 2001, after a follow-up period of 14-18 months, to detect any new case of active TB that might have been missed on initial screening.

The Mantoux test was administered as an

intradermal injection of 0.1 ml of purified protein derivative (PPD) containing five tuberculin units. The injection was given with a hypodermic needle into the anterior aspect of the forearm to produce a bleb, and a circle was drawn around it. The test was read after 72 hours by measuring the induration and not the erythema. A result of 10 mm or more was taken as positive.

The data were double entered and verified using Epi-Info Version 6.04 (CDC, Atlanta, GA). The analysis was done using SPSS Version 10.0 (SPSS Inc, Chicago, IL). Frequencies of individual variables and crosstabulation between outcome variable and independent variables were also performed. The mean distribution of variables was also performed where appropriate.

Results

A total of 207 employees (52% males and 48% females) were screened (Table). A history of bacille

Table: Characteristics of health care workers at pre-employment screening visit (n = 207).

	Mean (range)
Age (years)	26.7 (18-54)
Height (cm)	163.7 (142-193)
Weight (kg)	60.8 (33.5-132.0)
Systolic blood pressure (mm Hg)	113.7 (90-170)
Diastolic blood pressure (mm Hg)	75.3 (50-100)
Hemoglobin (gm/dl)	13.2 (8.1-16.5)
Hematocrit (%)	40.3 (25.9-50.4)
Random blood sugar (mg/dl)	100.8 (80-160)
Erythrocyte sedimentation rate mm in first hour)	11 (0-46)
Mantoux test (mm induration)	7.6 (0-28)
	n (%)
Abnormal chest radiograph	5 (2.4%)
Mantoux test result	
10 mm or above	90 (43.5%)
15 mm or above	45 (21.7%)
20 mm or above	15 (7.2%)
Sputum smear/culture-positive	None

Calmette-Guérin (BCG) vaccination was obtained in only 54 (26%) cases. History of TB in the family or contact with a TB patient was denied in 204 (99%) cases, but three were unsure about it. One patient had been investigated for fever and pleural effusion 3 months before her pre-employment screening. She was diagnosed with TB pleural effusion and was receiving appropriate therapy. The remaining 206 employees were asymptomatic at the time of presentation and had a normal physical examination.

Mantoux, ESR and chest radiograph findings

A Mantoux skin reaction of ≥10 mm and blood ESR of ≥25 mm after the first hour was noted in 90 (43.5%) and 21 (10.1%) employees, respectively. Only four of the 90 cases with a ≥10 mm reaction had an abnormal chest radiograph and were referred for further evaluation. None of the HCWs with a Mantoux ≥20 or ESR of ≥25 had clinical or radiological evidence of active TB.

Chest radiograph was abnormal in five (2.4%) cases. One was receiving anti-tuberculosis therapy for previously diagnosed pleural effusion and had pleural thickening on radiograph. One had hilar prominence, two had minimal linear scarring and one had linear and nodular infiltrate and loss of volume of the right upper lobe. Of the five cases with an abnormal chest radiograph, four had a Mantoux result of ≥10 mm and one had a result of 0 mm.

Referral to chest physician

At pre-employment screening one employee was already on anti-tuberculosis therapy and was referred to a specialist. All of the other employees were asymptomatic, with a normal physical examination, and would have not needed referral on a clinical basis. Based on chest radiograph findings four (2%) asymptomatic cases were referred. One with hilar prominence was investigated with computed tomography (CT) scan and was found to have a bronchial cyst. One with infiltrates and loss of lung volume was started on tuberculosis treatment on radiographic grounds; sputum smears and cultures were negative. Further investigations were not recommended for two patients with minimal linear scarring.

Based on the results of positive Mantoux and/or elevated ESR, 48 (23.1%) additional employees were referred to a specialist. The vast majority (77%) were young females below the age of 30 years. All had normal physical examinations and chest radiographs. The specialist recommended no further investigation, and none were diagnosed with active TB.

Based on chest radiograph only five cases would have been referred for pulmonary opinion and the only case of suspected active TB would have been picked up. When Mantoux and ESR were added to the screening process a ten-fold increase in the number of referrals was seen (total 52), with no extra case of active TB being detected.

One-year follow-up

Medical records of all screened employees were reviewed after a 14-18 month period following pre-employment screening. The outcome of physician encounters, laboratory investigations and radiographic studies were recorded. None of the employees was diagnosed with active TB during the follow-up screening.

Discussion

Our study suggests that in a high TB prevalence country the Mantoux test is not a useful diagnostic tool for pre-employment screening of HCWs. Of the employees screened, 44% had a positive test of ≥10 mm and half of these (22%) had a reaction of ≥15 mm. Such high rates of positive skin reaction among HCWs have earlier been reported in other studies from the US (40%)[7] and Mexico (70%).[8] The only case of active disease in our study had symptoms and signs suggestive of TB. Based on the result of Mantoux testing, a large number of referrals were made to the chest clinic with no further detection of active cases. At the 1-year follow-up none of these HCWs had developed active disease. In Pakistan, the use of Mantoux testing for screening resulted in delays in the recruitment process and extra costs for consultation. Similarly, an elevated ESR of ≥25 mm/first hour was seen in 10% of the employees, and in the absence of symptoms none of these were found to have active TB.

Mantoux testing is used widely for identification of infected cases. In high prevalence countries a large proportion of the population is expected to have a positive reaction, which limits the specificity of the Mantoux test as a screening tool for active disease.[9] Furthermore, skin reaction may not correlate with disease severity, and has been shown to decrease with disease severity. Therefore, tuberculin response in a BCGvaccinated TB-endemic area cannot be used as a diagnostic marker for active tuberculosis, particularly in advanced disease.[10]

Due to epidemiological differences between the industrialised and the developing countries, strategies for the diagnosis of TB need to be developed that are cost effective and take account of local factors. An International Union Against Tuberculosis and Lung Disease (IUATLD) task force, with members from 10 countries, developed a scoring system for screening children for TB and for selecting suspects for further investigations.[11] In a low prevalence country heavy reliance was placed on history of close contact and on a positive skin test. In high prevalence countries case contact and skin test was found to be less important, with symptoms being more indicative of active TB. The results of our study would support the development of a scoring system that relies more on symptoms than on skin test to screen adults and to select those who need further investigation.

The effectiveness of occupational health screening and surveillance procedures was evaluated in a study from the west Midlands region of the UK.[12] Most cases of active TB presented with symptoms, and no occupational health unit knew of any extra case that was not notified by the registry. An emphasis on prompt reporting of suspicious symptoms both before and during employment was recommended. Another 9-year study from a regional pediatric hospital in Cincinnati, Ohio, had evaluated the mandatory employee tuberculin skin test programme.13 Despite intense active surveillance among thousands of hospital employees with >97% annual compliance, tuberculin conversion rates were low, and no cases of active TB were identified during the 9 years of follow-up. Rates of TB in that community were low, and the application of guidelines appeared excessive and costly. The results of our study also indicate that the current screening programmes should be evaluated regularly and made relevant to the needs of the region.

The ESR is a non-specific test used by many physicians for screening patients with active diseases like TB. A recent study in children found that one-third of cases with active TB had a normal ESR at the time of diagnosis, and that ESR was of little value as a diagnostic test.[14] Our study results show that ESR was elevated in 10% of apparently healthy individuals, and that despite living in a high prevalence country none of these developed active TB over a 1-year period.

Based on the result of our study, we have discontinued performing Mantoux testing and ESR for preemployment screening of HCWs. Clinical assessment and chest radiograph is performed on each individual, and no further test is performed for asymptomatic individuals with a normal chest radiograph. Those with clinical and/or radiological abnormalities have three sputum samples tested for acid-fast bacilli and are referred to a specialist. We recommend that for pre-employment TB screening of HCWs in high prevalence countries, the main emphasis should remain on history and physical examination. Chest radiograph should be performed, when available, to detect early or asymptomatic cases. Further studies are needed to assess whether chest radiograph can be avoided altogether in asymptomatic individuals. The sample size of our study was small for an endemic region, and the results need to be validated with larger studies.

Conclusions

In a high TB prevalence country such as Pakistan, the use of Mantoux testing and ESR for pre-employment screening of HCWs is not cost-effective. Greater emphasis should be placed on symptoms to detect active cases. Despite a positive tuberculin reaction in 44% and an elevated ESR in 10% on initial screening, none of the HCWs developed active TB over a one-year follow-up.

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Prevalence of pulmonary tuberculosis on the roof of the world

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Abstract

Setting: The Shimshal Valley, a remote village in Northern Pakistan, is one of the seven Pamirs of Central Asia, widely known as the roof of the world.

Objective: To investigate the prevalence of pulmonary tuberculosis (TB) in the Shimshal Valley.

Design: The Rapid Village Survey Method (RVS) was used to investigate the prevalence of pulmonary tuberculosis. The selection criteria were chronic cough, hemoptysis, past history of TB and close contact with a tuberculous patient. After clinical examination, a chest radiograph was done and a single spot sputum sample was obtained for smear examination.

Results: The total population of the village was 1077, of whom 231 cases were studied. Overcrowding affected 75% of the study population. The prevalence of smear positive pulmonary TB in the village studied was 554 per 100 000 population, and the prevalence of active smear-negative TB was estimated at 1949/100 000. The prevalence of active pulmonary TB increased with age and the only risk factor for active TB was age over 45 years. Of the 21 cases with a past history of pulmonary TB, only 38% had completed a full course of chemotherapy.

Conclusion: Pulmonary TB is a very serious health issue in the rural community (Shimshal Valley) of Pakistan. This study highlights the lack of efficacy of national tuberculosis control programs in the country.

Key Words: tuberculosis; prevalence; rapid village survey.

Introduction

There has been a global resurgence of tuberculosis (TB) in the last decade and the vast majority of these TB cases occur in the impoverished countries of Asia, Africa and South America.[1]

Pakistan is a developing country with a population of 130 million people. In this country 1.5 million people suffer from TB, and more than 210 000 new cases occur each year.[2] At present, only 1 per cent of central government expenditure is spent on health care, and over half the country has little or no access to health care. Until recently there were no official guidelines for tuberculosis control in Pakistan, and there is serious concern that drug resistance is likely to increase at an alarming rate.

Shimshal Valley is a remote village in the Northern Areas of Pakistan, situated in the neighborhood of the Peoples' Republic of China, the former USSR, India and Afghanistan. The eight great mountain ranges including Karakuram, Hindukush, Himalaya and Pamir converge on this land of rocks and glaciers. Shimshal Pamir is one of the seven Pamirs of Central Asia, well known as the roof of the world. It is at an elevation of 7800 feet above sea level and at a distance of 45 kilometers from Karakuram highway, which links Pakistan to the other Central Asian States. The hardship endured by the people of the region

can be illustrated by the fact that there is not a single road to Shimshal Valley that is traversible on horseback. One therefore has to walk for 36 hours through the rocky mountains to reach the valley. According to a survey in 1996, pulmonary TB was the leading cause of death among adults in this region, whereas pneumonia was the leading cause of infant mortality (School research group. Mortality, morbidity and birth rate in Shimshal Valley. Unpublished data).

The objective of our study was to investigate the prevalence of pulmonary TB in Shimshal Valley using the Rapid Village Survey method.

Material and Methods

Planning and organization

Before starting field activities, a series of meetings was held with members of the Aga Khan Health Services, Pakistan (AKHSP) and the Government Health Department, Northern Areas of Pakistan (GHDNAP), to assess feasibility of the survey and funding. The funding for X-ray films and laboratory supplies was provided by AKHSP, a portable X-ray machine by GHDNAP, and the Aga Khan Foundation provided transportation by helicopter between the nearest town (Gilgit) and Shimshal Valley. The fuel for the electric generator, food and accommodation was arranged by the village volunteer service.

The final study design was approved after discussion with an epidemiologist and a pulmonologist. The work was carried out by a team consisting of a general surgeon, a resident family physician, three laboratory technicians, two lady health visitors, two health workers and a group of dedicated volunteers.

Rapid Village Survey method (RVS)

The study design was based on the experience of RVS for case finding in the control of pulmonary tuberculosis and leprosy by Elink Schuurman[3] and Tumbelaka.[4] This method is cost-effective and the overall accuracy is similar to the total village survey (TVS) method. The RVS team reached the village on 26 June 1996, and a meeting was held with the village president, health workers and volunteer services. The survey was planned over a five-day period. The health workers performed a door-to-door visit in the village, identified the villagers who fulfilled the selection criteria (as defined below) and invited the villagers, via a standard message, to report to the RVS center. Information about the schedule of the study was also conveyed by the radio broadcasting services. There was no registered medical practitioner in the village, and thus the survey provided the villagers with a unique opportunity to see a qualified physician.

The basic demographic data were provided by the village school research group. Data about symptomatic and high risk populations were gathered from the records of health workers. The demographic data were recorded by the medical health workers and the history and physical examination were done by a general surgeon and a family medicine resident. A portable chest radiograph was performed and a single spot sputum sample was obtained in the clinic. Free medicines were distributed for common illnesses, and difficult cases were referred to tertiary care centers in other parts of the country. The RVS team departed on the sixth day of the visit.

Selection criteria

The selection criteria used in the survey included: history of chronic cough (more than three weeks' duration), history of hemoptysis, past history of pulmonary TB, and close contact with a TB patient.

All subjects who had one or more of the above selection criteria were identified during door-to-door visits by the health workers and invited to attend the RVS center. At the end of day four, the lists of suspected cases were checked and the volunteers visited the houses of those who had not yet presented voluntarily to the RVS center. In this remote village we were able to screen all the suspected cases identified by the health workers.

Definitions

Smear positive pulmonary TB: A person with a smear positive for acid-fast bacilli (AFB), on a single spot sputum examination.

Smear negative pulmonary TB: A person with upper lobe infiltrates and/or cavitation on chest radiograph, in the absence of a positive sputum smear

Healed pulmonary TB: A person with evidence of fibrosis and/or calcification on chest radiograph in the absence of the above criteria for active TB.

Adult: A person aged 15 or over.

Statistical analysis

The database was completed after the sputum AFB smears had been read by a consultant pathologist and the chest radiographs by a consultant pulmonologist. The data were coded and entered into a commercially available program, Excel 7.0. Statistical analysis was done with the help of an epidemiologist using a statistical software package (SPSS 4.0). The data were analyzed for evaluation of active and healed tuberculosis. Univariate analysis was done to assess the significance of risk factors for active pulmonary TB such as age, sex and overcrowding. The level of statistical significance was set at $P < 0.05$.

Results

The total population of the village was 1077, of whom 49.7% were male and 54.5% were adults. The overall literacy rate was 18.4%, 25.9% in males and 10.9% in females. The source of income was agricultural produce and livestock in 94%, and 6% were in service or business. The crude birth rate was 4.93% and crude mortality rate was 1.02% per annum.

The characteristics of the study population are summarized in Table 1. The majority of the population (75%) lived in overcrowded conditions (more than three persons per room). Chronic cough was present in 82% of the study population, of whom two-thirds had productive cough. A history of hemoptysis was obtained in 35% of cases. Physical examination revealed crepitations in 38 (17%), bronchial breath sound in 26 (11%), rhonchi in 17 (7%) and cervical lymphadenopathy in three (1%) cases. Of the 231 study subjects, a satisfactory chest radiograph was obtained in 212 (92%) and a single spot sputum sample in 109 (47%) cases.

Table 1: Characteristics of the study population in Shimshal Valley, 1996. (Total population = 1077)

Characteristic	n (%)
Population studied	231
Sex: Male	98 (42)
Female	133 (58)
Age: 15 years	18 (8)
15–45 years	134 (58)
45 years	79 (34)
Past history of TB	21 (9)
Close contact with TB patient	159 (69)
Chest radiograph	
Normal	40 (17)
Active infiltrates/cavitation	23 (10)
Fibrosis/calcification	149 (65)
Poor quality/not obtained	19 (8)
Single sputum smear examination	
Smear positive	6 (2.5)
Smear negative	103 (44.5)
Sputum not obtained	122 (53)

Six sputum samples were smear positive and the prevalence of smear positive pulmonary TB in the village studied was 557/100 000. A further 21 cases had features of active TB based on radiological appearance, and the prevalence of smear negative active pulmonary TB was estimated at 1949/100 000 (Table 2). Based on radiological findings of pulmonary fibrosis and/ or calcification compatible with TB, the prevalence of healed TB was estimated at 13 835/100 000 population. The prevalence of active pulmonary TB increased with age: the only significant risk factor for active pulmonary TB was age > 45 years. Only 8% of the study population were in the pediatric age group, and no case of active pulmonary TB was found among them. In this village, 82% of children had received BCG vaccination.

Table 2: Characteristics of patients with active TB.

	Smear positive	Smear negative
Total number	6	21
Sex: Male	1	9
Female	5	12
Age: 15 years	0	0
15–45 years	3	5
45 years	3	16
Close contact with a TB patient	5	12
Past history of TB	3	3
Chest radiograph		
Active infiltrates/cavitation	3	21
Fibrosis/calcification	3	0

Of the 21 subjects with a previous history of pulmonary TB, three (14%) were still sputum AFB positive on a single smear and 28% were symptomatic with active infiltrates and/or cavitation on chest radiograph. Only eight (38%) cases had completed a full course of anti-TB treatment.

Discussion

The results of our survey confirm that in this remote village, where 75% of the population lives in overcrowded conditions, pulmonary TB is a major health problem. The prevalence of smear positive pulmonary TB (557/100 000) and smear negative TB (1949/ 100 000) is considerably higher than in other developing countries.[5-7] These smear positive patients continue to be a source of infection in the village, and when no treatment is provided each patient is expected to survive for about 2 years and to infect 10 to 15 further individuals each year.[8] During the period 1994 to 1996, 70% of the 24 adult deaths in the village were related to diagnosed or suspected cases of pulmonary TB. There was increased prevalence of pulmonary TB with increasing age, consistent with other studies from Asia.[9]

Our study also highlights the problem of poor compliance with treatment among patients known to have pulmonary TB. Only 38% completed a full course of anti-TB treatment. The reasons for poor compliance were unavailability of anti-TB medications, lack of a surveillance program for tuberculosis control, poor socio-economic conditions and low literacy rate. These partially treated patients remain a continuous source of TB infection, and could potentially promote the emergence of multidrug-resistant strains. In addition, as suggested by the Bangalore study, each year 10% to 15% of smear negative patients would be expected to progress to become smear positive.[10] The overcrowding observed in the study population would also be a strong risk factor for the spread of TB bacilli in the community.

Our study design using the RVS method has been

validated for case finding in the control of pulmonary TB.[3] Shimshal Valley was considered a suitable site for RVS, and the local factors that contributed to the validity and success of the survey were: 1) a village isolated from the rest of the country where all the people lived closely together; 2) a preliminary survey was available about the suspected and high risk population; 3) a strong village organization, dedicated health workers and volunteer service ensured a successful survey, and health workers were able to visit each house in the village to invite people to participate in the survey; 4) in the absence of a qualified medical practitioner in the village, the RVS was a rare opportunity for people to be examined by a qualified doctor and obtain free medicine for common medical ailments.

Our study differed from that of Elink Schuurman et al.[3] in some aspects. We did not have the facilities to perform cultures on the sputum samples obtained. Instead we depended on radiographic findings to detect smear-negative active cases. The sensitivity of chest radiograph in detecting active and healed cases of TB has been described to be low in mass radiography.[11] Of interest is a follow-up study of nearly 300 Chinese subjects who were considered to have active TB on clinical and radiological features but were sputum AFB negative on five smear examinations. Over the next 30 months, 71% had active disease confirmed and another 15% had evidence of changing lesions on serial chest radiographs, indicative of active disease.[12]

Secondly, compared to only 5% in their study, we screened nearly 20% of the entire village population, and believe that the chance of missing further symptomatic patients was small. Our study was, however, not followed by a total village survey. The prevalence of smear-positive cases among suspected individuals was similar in both studies, but the overall prevalence of smear-positive TB in the village was much higher in our study.

Our study has certain limitations. A single spot sputum sample was used for smear examination, potentially leading to an underestimation of disease prevalence. Ideally, three early morning sputum samples should have been collected, and this might have resulted in an even higher prevalence rate. However, in a study of smear-positive patients, 90% were found to be positive on their initial smear.[13]

Secondly, TB culture was not performed on the sputum samples obtained. Had resources been available, this would have helped us to define more accurately the prevalence of smear-negative, culture-positive cases, and to identify drug resistance patterns.

Thirdly, radiological features were used to define active and healed TB. We accept that a number of infectious, inflammatory, neoplastic and occupational diseases can mimic TB. Furthermore, patients with TB may have atypical presentations, and differentiation between active and healed TB may be difficult on radiological features alone. However, in a high prevalence region such as the Shimshal Valley, the commonest feature of reactivation TB is upper lobe infiltrates/ cavitation,[14] and pleural/pulmonary fibrosis and calcification in the upper zones is usually secondary to remote TB infection.

Fourth, very few children were included in the study and this, coupled with difficulties in the interpretation of radiograph and smear examinations in children, may have resulted in a failure to identify any cases with active TB. The prevalence of active TB in children in the village remains unknown. Similarly, the prevalence of extra-pulmonary TB was not studied.

Finally, our study may have underestimated the prevalence of active TB due to sample selection (exclusion of asymptomatic cases, failure of some symptomatic cases to report to the RVS center).

In order to prevent the spread of disease and to decrease TB related mortality, we made the following recommendations to the AKHSP. 1) Urgent treatment of smear positive and treatment failure cases. The success of treatment should be monitored carefully according to WHO recommendations,[15] and the target of successful treatment should be 80-90% compliance. 2) Treatment should be fully supervised by the health care workers. 3) Health care workers from the same village should be trained to monitor short course chemotherapy, to record patient data and to perform sputum AFB smears. 4) Treatment failure and relapses should be screened for multidrug-resistant bacilli. 5) Smear-negative cases with radiological features of active TB should also be treated. 6) New cases of pulmonary TB should be detected by a regular screening program, and all persons with productive cough should have three sputum smears for AFB examination. 7) BCG vaccination should be continued and its efficacy evaluated. 8) Chemoprophylaxis should be given to high risk cases who do not have active TB.

The successful implementation of a pulmonary tuberculosis control program in Shimshal Valley is possible through close collaboration between AKHSP and GHDNAP, but community participation will be the key to success. Implementation of our recommendations for control of pulmonary tuberculosis in Shimshal Valley was started in May 1997, and the program will strictly follow the WHO guidelines with emphasis on directly observed treatment and short course chemotherapy.

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Do private doctors follow national guidelines for managing pulmonary tuberculosis in Pakistan?

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Abstract

As private medical practitioners play a major role of in providing care to pulmonary tuberculosis (TB) patients, a survey was made of knowledge and practice in 2 cities in Pakistan. Only 1 of the 245 physicians was aware that cough > 3 weeks alone is the main symptom suggesting pulmonary TB. The majority diagnosed (80%) and treated (83%) cases themselves without referral. Less than 1% relied on sputum microscopy alone for diagnosis. None of the practitioners were following National TB Control guidelines for prescribing drugs and none ensured compliance with anti-TB treatment under supervision of a doctor/health worker. Only 3% kept records of pulmonary TB patients. None of the physicians assessed the effectiveness of treatment with sputum microscopy alone; the majority (76%) used only clinical assessment.

Introduction

Tuberculosis (TB) is the largest single infectious cause of death among young people and adults in the world, accounting for nearly 2 million deaths a year; about a third of the world's population harbours the infection.[1] This large pool of infected people means that TB will continue to be a major problem in the foreseeable future.[2] While they belong to all socioeconomic strata, the great majority of TB patients are poor.[3] Due to these and many other relevant factors, the TB epidemic was declared a global emergency by the World Health Organization (WHO) in 1993.[4]

TB remains one of the major public health problems in Pakistan. Moreover, WHO has identified Pakistan as among the countries with a high burden of disease.[5] According to the Pakistan national TB survey in 1987-88[6] the prevalence of sputum- positive or open cases of pulmonary TB was estimated to be 0.17 per 1000 population. These open cases form a reservoir of infection in the community and are the source of person-to-person transmission.

In Pakistan where only 36% of the population is literate and 28% is living below the absolute poverty line,[7] the private sector makes a major contribution to providing health care for all kinds of health problems including the management of TB cases.[8] Private medical practitioners in Pakistan, as in other developing countries, comprise a wide range of health care providers, ranging from unqualified and unskilled practitioners to highly qualified medical postgraduates. However, a large number are in the former category, who are readily available and accessible especially in the rural settings where 70% of Pakistan's population lives. The absence of any effective regulatory mechanism further

worsens the situation. In India it has also been noted that the private health sector in developing countries tends to be a relatively amorphous, unorganized and dynamic entity comprising various provider types of different sizes and characteristics.[9]

There is increasing interest in many countries about the role of the private health sector in TB care.[7] In a study of health-seeking behaviour in Pakistan,[10] it was found that 90% of TB patients had initially contacted a private practitioner before visiting a TB centre. Similarly, another study in a different setting also established that 80% of hospitalized TB patients had first consulted private practitioners.[11] Moreover, a study in India observed that 86% of TB patients had first consulted a private practitioner.[12] Yet TB patients attending the private sector may not be receiving the correct treatment according to the National Tuberculosis Control Programme guidelines.

The present study was carried out to determine the knowledge and practices of private general medical practitioners towards diagnosis, treatment and follow-up of pulmonary TB patients in 2 cities of Pakistan. In addition, we intended to collect baseline information to plan future interventions to involve the private sector in the National TB Programme.

Methods

The study design was a descriptive crosssectional survey. The study participants were selected from all formally qualified medical graduates who were practising medicine on a full- or part-time basis outside the government (public) sector in the 2 largest cities of Pakistan: Rawalpindi and Lahore. The basic criterion for inclusion in the study was that the private medical practitioners had managed at least 1 pulmonary TB patient during the previous year.

Out of a total population of 884 private general medical practitioners, 245 were randomly selected to be included in the study. This sample size was estimated at a confidence level of 95%, at 20% expected frequency of consistency with National TB Programme guidelines, and a power of 80%.

A standardized questionnaire on the relevant themes and issues was used in this study. Questions were mostly dichotomous choice with some rating scale questions. Questions were asked about diagnosis (knowledge about symptoms suggestive of TB, diagnostic and referral practices, diagnostic facilities), treatment (usual prescribing practices, knowledge about how to categorize patients for treatment, frequency of dispensing treatment), follow-up (ensuring compliance, record-keeping, assessing effectiveness of treatment, defaulter tracing and family contact tracing), and awareness of National TB Control Programme guidelines.

The responses were analysed by city and by qualification status of the general practitioner, i.e. medical graduate only or postgraduate qualification. A 95% confidence interval was calculated where relevant. The responses were compared for significant differences using Pearson chisquared. Data were analysed using Epi- Info, version 6.04c and SPSS, version 10.0.5. Frequency tables were prepared for most of the variables.

Table 1 Knowledge of private practitioners about duration of cough before suspecting tuberculosis by city and by qualification

Duration of cough	Graduates		Postgraduates		Total		P-value[a]
	No.	%	No.	%	No.	%	
Rawalpindi	(n = 83)		(n = 17)		(n = 100)		
2 weeks	14	17	2	12	16	16	0.923
3 weeks	21	25	4	24	25	25	
4–6 weeks	45	54	10	59	55	55	
7–9 weeks	3	4	1	6	4	4	
Lahore	(n = 125)		(n = 20)		(n = 145)		
2 weeks	15	12	2	10	17	12	0.945
3 weeks	23	18	3	15	26	18	
4–6 weeks	45	36	9	45	54	37	
7–9 weeks	42	34	6	30	48	33	

n = total number of respondents.
aGraduates versus postgraduates.

Results

The mean age of the 245 private practitioners was 38 years, ranging from 23 to 70 years. A total of 232 of them (95%) were below the age of 60 years; female practitioners comprised 20% (48). All of the sample were medical graduates; the year of graduation ranged from before 1960 to 2001. A postgraduate degree or diploma was held by 37 (15%): 6 (2%) had a postgraduate qualification in medicine and 31 (13%) had other qualifications (none of them had a postgraduate diploma or degree in chest diseases). There were 100 practitioners in Rawalpindi and 145 in Lahore. The proportion holding a postgraduate degree or diploma was 17% and 14% in Rawalpindi and Lahore respectively.

Of the respondents, 58% from Rawalpindi and 41% from Lahore had provided care to 1-5 pulmonary TB patients during the previous 3 months, compared with 34% and 41% respectively who had seen 6-10 patients.

Diagnosis

Knowledge about symptoms

In response to the question "In your opinion, what are the main symptoms that suggest pulmonary TB in adults?", only 1 out of 245 private practitioners mentioned cough for more than 3 weeks. Nearly half (45%) of the physicians described a combination of cough, haemoptysis, weight loss, night-sweating and lymph node enlargement, whereas 30% considered cough and weight loss as the main symptoms

suggestive of pulmonary TB.

The knowledge of physicians in the 2 cities about the main symptoms suggestive of pulmonary TB was significantly different (P = 0.010). More practitioners in Lahore considered cough and weight loss as the main symptom, whereas in Rawalpindi it was cough, haemoptysis and weight loss. There was no significance difference between graduates and postgraduates in Rawalpindi (P = 0.529) or in Lahore (P = 0.335) about knowledge of symptoms. None of the postgraduates mentioned cough more than 3 weeks as the main symptom suggestive of pulmonary TB.

On prompting for the duration of cough before suspecting pulmonary TB, only 21% of doctors (25% in Rawalpindi and 18% in Lahore) mentioned cough of 3 weeks in suspecting TB. Of the 37 postgraduates, only 7 stated that cough for 3 weeks is suggestive of TB. However, 45% of respondents overall stated that cough for 4-6 weeks and 14% that cough for 2 weeks is suggestive of TB. In both the cities, like graduates, the majority of postgraduates were also of the opinion that a cough for 4-6 weeks should be suspected for pulmonary TB. There was no difference in knowledge about duration of cough between graduates and postgraduates in Rawalpindi (P = 0.923) and Lahore (P = 0.945).

Diagnostic practices

Questions about their practices when they suspected a patient is suffering from pulmonary TB showed that 80% of respondents diagnosed the patient themselves, 11% diagnosed the patients themselves and then referred them to a TB centre or consultant and 8% referred the patient straight away. However, a significant difference (P < 0.0001) was noted between the 2 cities in relation to patient referral. In Lahore the majority of practitioners (90%) diagnosed cases themselves, whereas in Rawalpindi 66% relied on their own diagnosis and 24% initially diagnosed themselves and then referred the patients. In Rawalpindi 82% of postgraduates compared with 95% in Lahore diagnosed the patients themselves (Table 2). Graduates referred more patients than the postgraduates in Rawalpindi (P = 0.013), whereas in Lahore no difference (P = 0.923) was observed between graduate and postgraduate referral practices.

For diagnosis of pulmonary TB only 1 private medical practitioner (a graduate) out of 245 relied on sputum microscopy alone. In response to the question, "While diagnosing a suspected case of pulmonary TB, what actions do you usually take?" the majority of respondents (45%) reported using a combination of tests, i.e. clinical examination, tuberculin test, sputum microscopy, blood erythrocyte sedimentation rate (ESR), and chest X-ray. Table 3 summarizes the responses by city and by qualification. In Rawalpindi, the difference among graduates and postgraduates was significant (P = 0.044), since more graduates preferred clinical examination and chest X-ray, but the difference was not significant in Lahore (P = 0.717).

Table 2 Practices of private practitioners for action taken on suspecting pulmonary tuberculosis by city and by qualification.

Action taken	Graduates		Postgraduates		Total		P-value[a]
	No.	%	No.	%	No.	%	
Rawalpindi	(n = 83)		(n = 17)		(n = 100)		
Diagnose themselves	52	63	14	82	66	66	0.013
Diagnose themselves then refer	22	27	2	12	24	24	
Refer immediately	9	11	1	6	10	10	
Lahore	(n = 125)		(n = 20)		(n = 145)		
Diagnose themselves	112	90	19	95	131	90	0.923
Diagnose themselves then refer	4	3	1	5	5	3	
Refer immediately	9	7	0	–	9	6	

n = total number of respondents.
aGraduates versus postgraduates.

Table 3 Practices of private practitioners for actions taken to diagnose a suspected case of pulmonary tuberculosis by city.

Diagnostic method	Rawalpindi (n = 100)		Lahore (n = 145)		Total (n = 245)		P-value[a]
	No.	%	No.	%	No.	%	
Sputum	1	1	0	–	1	0.4	0.009
Clinical	3	3	2	1.4	5	2	
Clinical + sputum	0	–	1	0.7	1	0.4	
Clinical + X-ray	11	11	6	4	17	7	
X-ray + ESR	11	11	38	26	49	20	
Clinical + sputum + X-ray + ESR	26	26	22	15	48	20	
Clinical + sputum + X-ray + ESR + TT	45	45	64	44	109	45	
Others[b]	3	3	12	9	15	6	

Sputum = sputum microscopy, clinical = clinical examination, TT = tuberculin test, ESR = erythrocyte sedimentation rate.
[a]Rawalpindi versus Lahore.
[b]Serology, polymerase chain reaction, urine or blood tests.
n = total number of respondents.

Diagnostic facilities

Only 5 out of 245 private medical practitioners had facilities for sputum examination. Responding to the question, "Which facilities do you have for diagnosing pulmonary TB patients at your clinic?" 92% of doctors in Rawalpindi and 86% in Lahore stated that they did not have any facility at their clinics. Only 8% had the facility to perform ESR. Similarly, 1 respondent in Rawalpindi and 3 in Lahore had X-ray facilities. Among the 5 who had sputum examination facilities, only 2 had used sputum microscopy in the process of diagnosis. Among the postgraduates, only 1 had a facility for blood ESR in Lahore and 1 had a chest X-ray facility in Rawalpindi.

In response to the question, "If none, where do you usually send your patients for laboratory investigations?" 61% of private medical practitioners in Rawalpindi and 76% in

Lahore referred their patients to private laboratories. Respectively, 13% and 19% stated that they sent their patients to a public laboratory, whereas 26% and 5% did not recommend any specific laboratory. Among the postgraduates, 53% in Rawalpindi and 90% in Lahore referred their suspected TB patients to a private laboratory for investigations. A small proportion of them (18% and 10% respectively) sent their patients to public facilities. In both the cities, the difference between graduates and postgraduates was not significant (Rawalpindi P = 0.723, Lahore P = 0.250).

Treatment

Referral practices

After the diagnosis was established, 83% of the private medical practitioners treated the pulmonary TB patients themselves; only 17% referred the patients (10% to a TB centre, 7% to a consultant or other non- specified referral). However, a significant difference between physicians in the 2 cities was found regarding referral to a TB centre or consultant (14% in Rawalpindi and 10% in Lahore) (P < 0.0001). When comparing the responses by qualification, it was observed that significantly more graduates and postgraduates in Rawalpindi (75% and 88%, P = 0.014) than in Lahore (89% and 90%, P = 0.758) treated patients themselves.

Information gathering

In response to the question "If you have to treat a new case of pulmonary TB, what information would you like to have before prescribing treatment?", none of the doctors mentioned inquiring about the history of any previous anti-TB treatment. A total of 28% of private practitioners in each of the cites admitted that they did not know what to do. Information on family history and socioeconomic status was considered important in Rawalpindi, whereas liver function tests and patient's weight was believed to be essential in Lahore. These responses were significantly different between the cities (P < 0.0001). Among the postgraduates, 12% in Rawalpindi and 20% in Lahore admitted that they did not know what information was required. However, 35% of postgraduates in each of the cities considered family history and socioeconomic status to be of importance. The difference by qualification was significant in Lahore (P = 0.043) but not in Rawalpindi (P = 0.156).

Knowledge about categorization

In response to the question, "If you have to treat a new case of pulmonary TB, how do you categorize a patient based upon history and results of sputum microscopy, to select a treatment regimen?" most practitioners (97%) admitted that they did not know about the system of categorizing pulmonary TB patients (98% in Rawalpindi and 96% in Lahore). Among the postgraduates, 82% in Rawalpindi and 95% in Lahore were unaware of how to categorize pulmonary TB patients for treatment. In Rawalpindi, more postgraduates were aware of categorization than were graduates (P = 0.040), whereas in Lahore being a postgraduate did not have any effect on knowledge about categorization (P = 0.835).

Practice of national treatment guidelines

None of the private practitioners in either of the cities were following the National TB Control Programme guidelines for prescribing treatment. For the initial phase, the majority (68%) prescribed a fixed-dose combination of 4 drugs, whereas 12% prescribed combinations of 4 separate drugs and 15% 3 separate drugs. About 2% of practitioners also prescribed separate combinations of 5 drugs. These practices were significantly different in the 2 cities (P = 0.001).

When asked about the duration of the initial phase, 87% of respondents said they did not divide treatment into initial and continuation phases and kept the patients on continuous treatment with the same drugs until considered cured. Only 6% overall used an initial phase of 2 months duration (9% in Rawalpindi and 3% in Lahore, P = 0.27) (Table 4).

During the continuation phase, 42% of practitioners reported prescribing a fixed- dose combination of 4 drugs and 29% a fixed-dose combination of 3 drugs, whereas 15% and 10% prescribed a combination of 4 and 3 separate drugs respectively. The difference was significant (P < 0.0001) between the 2 cities: in Lahore 58% of respondents preferred a fixed-dose combination of 4 drugs whereas in Rawalpindi 53%

Table 4 Practices of private practitioners in initial and continuation phases of anti-tuberculosis treatment by city.

Treatment duration	Rawalpindi (n = 100)		Lahore (n = 145)		Total (n = 245)		P-value[a]
	No.	%	No.	%	No.	%	
Initial phase							
2 months	9	9	5	3	14	6	0.27
3 months	5	5	1	0.7	6	2	
5 months	0	–	1	0.7	1	0.4	
6 months	0	–	3	2	3	1	
Continuous (until cured)	81	81	132	91	213	87	
Don't know	5	5	3	2	8	3	
Continuation phase							
< 5 months	0	–	2	1.4	2	1	0.27
6 months	5	5	1	0.7	6	2	
7 months	6	6	2	1.4	8	3	
8 months	0	–	1	0.7	1	0.4	
9 months	1	1	0	–	1	0.4	
Continuous (until cured)	83	83	136	94	219	89	
Don't know	5	5	3	2	8	3	

[a]Rawalpindi versus Lahore.
n = total number of respondents.

prescribed a fixed-dose combination of 3 drugs. Even some of those who recognized the initial phase of treatment did not follow any fixed duration of continuation treatment and thus 89% overall continued the treatment until the patient was considered cured (Table 4). Only 6 physicians (2.4%) prescribed anti-TB drugs for 6 months. It was noted that, irrespective of drug combinations used, all the private practitioners prescribed rifampicin during the continuation phase of treatment.

Dispensing treatment

In response to the question "How do you give anti-TB medicines to patients?" 97% of respondents (96% in Rawalpindi and 98% Lahore, P = 0.305) revealed that they only prescribed the medicines and did not dispense them at their clinics. Only 2 out of 245 physicians called their patients daily to dispense medicines.

When asked "How often do you dispense/ prescribe anti-TB medicines to the patients?" 62% revealed that they prescribed medicines on a fortnightly basis whereas 30% did it on a monthly basis. These practices were significantly different between the 2 cities (P = 0.003); in Rawalpindi more doctors prescribed on a fortnightly basis than did those in Lahore where a monthly system was more common (Table 5).

Table 5 Practices of private practitioners in frequency of prescribing anti-tuberculosis drugs by qualification and by city.

Treatment frequency	Graduates %	Graduates 95% CI	Postgraduates %	Postgraduates 95% CI	Total %	Total 95% CI
Rawalpindi	(n = 83)		(n = 17)		(n = 100)	
Daily	1	–1 to 3	0	–	1	–1 to 3
Weekly	7	2 to 12	6	–5 to 17	7	2 to 12
Fortnightly	72	62 to 82	53	29 to 77	69	60 to 78
Monthly	16	8 to 25	35	12 to 58	19	11 to 27
Other	4	0 to 8	6	–5 to 17	4	0 to 8
Lahore	(n = 125)		(n = 20)		(n = 145)	
Daily	1	–1 to 3	0	–	1	–1 to 3
Weekly	4	1 to 7	0	–	3	0 to 6
Fortnightly	55	46 to 64	70	50 to 90	57	49 to 65
Monthly	40	31 to 49	30	10 to 50	39	31 to 47

n = total number of respondents.

None of the postgraduates and only 1 graduate in each city ensured they dispensed the medicines on a daily basis. The practices regarding frequency of prescribing/dispensing medicines between graduates and postgraduates were similar in Rawalpindi (P = 0.399) and Lahore (P = 0.599).

Follow-up

Ensuring compliance

None of the medical practitioners in either city ensured the intake of anti-TB medicines under the supervision of a doctor or a health worker, i.e. none of the private medical practitioners observed the DOTS strategy [directly observed treatment, short course].

In responding to the question, "Do you ensure that the patients take all the prescribed/ dispensed anti-TB medicines regularly?" 15% of private medical practitioners in both the cities admitted that they did not do anything about ensuring the intake of medicines, whereas 85% in both the cities simply stated that they ensured it. While answering the question, "How do you ensure that the patients take medicines?" 38% of respondents in Rawalpindi and 31% in Lahore stated that they ensured it through relatives of the patients (Table 6). The other means employed were clinical assessment (17%) and personal counselling (31%).

Table 6 Practices of private practitioners in ensuring compliance with anti-tuberculosis drugs by qualification and city.

Method of ensuring compliance	Overall responses %	95% CI
Rawalpindi		***(n = 85)***
Personal counselling	33	24 to 43
Clinical assessment	9	3 to 15
Relatives	38	28 to 48
Others	20	12 to 28
Lahore		***(n = 123)***
Personal counselling	30	23 to 37
Clinical assessment	22	15 to 29
Relatives	31	23 to 39
Others	17	11 to 23

n = total number of respondents.

Assessing treatment effectiveness

None of the private medical practitioners assessed the effectiveness of anti-TB treatment through sputum microscopy alone. Responding to the question, "How do you assess the effectiveness of your treatment?" 76% stated that it was through clinical assessment, followed by those who preferred X-ray and laboratory investigations. The difference between the cities was highly significant (P < 0.0001); 88% in Rawalpindi compared with 65% in Lahore said that they assessed it clinically. Ways of assessing treatment effectiveness were similar comparing graduates and postgraduates in Rawalpindi (P = 0.210) and in Lahore (P = 0.726).

Most of the private medical practitioners in Rawalpindi (48%) and Lahore (55%) assessed treatment effectiveness on a fortnightly basis, while 25% in Rawalpindi and 37% in Lahore assessed it quarterly. The majority of postgraduates in Rawalpindi (53%) assessed treatment monthly and in Lahore (60%) fortnightly, followed by 29% and 40% respectively on a quarterly basis. The difference between graduates and postgraduates for frequency of assessment was significant in Rawalpindi (P = 0.010) but not in Lahore (P = 0.350).

Record keeping

In response to the question, "Do you keep records of TB patients at your clinic?" most of the private medical practitioners (97%) did not maintain records for pulmonary TB patients; only 3% (n = 7) said they kept records. Practices in the 2 cities were the same (P = 0.373). Among the postgraduates, only 1 in Rawalpindi and 2 in Lahore had any records for the TB patients.

Patient tracing

Only 2% of private medical practitioners traced defaulters. In response to the question, "What action do you take if the pulmonary TB patient on treatment does not come back for the next appointment?" a majority (98%) in both the cities admitted that they did not take any action. Similarly, 94% postgraduates in Rawalpindi and 100% in Lahore admitted that they did not take any actions if a patient defaulted on treatment.

In response to the question "In case of a new pulmonary TB patient, do you take any action towards his/her close family contacts?" 41% of private medical practitioners in both the cities admitted that they did not take any action. Of those who said that they do take an action, 98% in both the cities would enquire about the symptoms of pulmonary TB and 2% relied on either sputum tests or chest X-ray. Similar patterns were observed comparing graduates and postgraduates.

Awareness of national guidelines

When asked "Are you aware of the National TB Control guidelines?", 96% of private medical practitioners in Rawalpindi and 99% in Lahore admitted that they did not know about the guidelines. Among the postgraduates, only 1 in Rawalpindi was aware of these guidelines. The status of awareness regarding the guidelines was the same for graduates and postgraduates in Rawalpindi (P = 0.664) and Lahore (P = 0.668).

In response to the offer, "Would you like to attend any training on National TB Control Guidelines?" a majority (94%) of physicians in both the cities showed a willingness to participate in such activities. Similarly, among the postgraduates, 88% in Rawalpindi and 95% in Lahore desired to participate in training.

Discussion

TB remains a major public health problem in Pakistan with a high prevalence of open cases who are the main source of personto- person transmission. In Pakistan, the private sector makes a major contribution to providing health care for all kinds of health problems including TB.

The present study showed that the knowledge and practices of formally qualified private medical practitioners were not in line with the National TB Control Programme guidelines. A majority of respondents (79%) incorrectly stated the duration of cough that is suspicious for pulmonary TB, giving a duration of either 4 to 9 weeks or 2 weeks. There was no significance difference between graduates and postgraduates in the 2 cities, Rawalpindi and Lahore.

For diagnosing a suspected case of pulmonary TB, none of the practitioners perform sputum microscopy alone. This finding is similar to a study conducted in India, which found that treatment practices of private practitioners were inadequate and only a small proportion of private medical practitioners suggested sputum examination.[12] Contrary to the findings of Marsh,[13] this study found that more than 90% of the private medical practitioners perform one or multiple laboratory tests in the process of diagnosis.

After private medical practitioners establish the diagnosis, 83% of them would start treatment themselves and only 10% would refer the patient to a TB centre. None of them take the history of any previous anti-TB treatment and most of them prefer to rely on family history and socioeconomic status to help them prescribe medication. A small percentage also perform liver function tests and record the weight of the patient. However, a significant difference was noted in relation to patient referral practices in the 2 cities. Graduates in Rawalpindi refer more patients than do postgraduates, whereas in Lahore no difference was observed between graduates and postgraduates.

Overall, 97% of the practitioners admitted that they had no knowledge of the categorization system for TB patients to select a treatment regimen. Even the postgraduates in Rawalpindi (82%) and in Lahore (95%) were unaware of the categories. It is therefore unlikely that a patient will receive appropriate treatment based upon categorization of his/her illness.

None of the private medical practitioners followed National TB Control Guidelines in prescribing medicines. The majority prescribe a fixed-dose combination of 4 drugs (a famous brand in Pakistan) or 3 drugs. A significant difference was observed between the preferences of practitioners for 4- or 3-drug fixed-dose combinations in the 2 cities. However, more important is the fact that there was no concept of initial and continuation phases of treatment and the majority of practitioners prescribe fixed or separate combination of drugs until the patient is considered cured. Interestingly, rifampicin is very popular and 100% of practitioners continue with it during the entire course of treatment. The practices regarding frequency of prescribing/ dispensing medicines were similar between physicians in the 2 cities and those who were graduates or postgraduates.

A majority (85%) of respondents said that they ensure

the intake of anti-TB medicine; however, none of them had a system for ensuring compliance under the supervision of a doctor or a health worker. Instead, the majority relied on personal counselling or on relatives to help with ensuring compliance. Graduates and postgraduates had similar practices in both cities. Almost all the private practitioners (98%) said they did not take any action if a patient on anti-TB medication does not return (defaults on treatment).

While the majority of practitioners prefer to continue the treatment until the patient is cured, none of them performed sputum examination alone to assess the effectiveness of anti-TB treatment. Most (76%) assessed the treatment effectiveness only clinically and the remainder depended on X-ray chest and laboratory investigations such as ESR, etc. The frequency of assessing the treatment effectiveness also varied. Most of them assess treatment on a fortnightly, quarterly or monthly basis.

In new cases of pulmonary TB, only 59% of the doctors would take action with the patients' close contacts and most of these (98%) would simply enquire about symptoms.

The facilities to investigate a suspected case of pulmonary TB were also rare at the private practitioners' clinics. Only 5 respondents had a facility to perform sputum examination. Interestingly, only 2 out of those 5 practitioners performed sputum microscopy in order to establish the diagnosis. Thus it is not only laboratory facilities that are scarce, there is also a lack of awareness among all cadres of private medical practitioners.

Only 3% of all the private medical practitioners were maintaining records for their TB patients.

Among all the respondents, 98% admitted that they had not heard of the National TB Control Programme guidelines and the other findings of the study suggest that even the 2% of practitioners who claimed to be aware of them do not follow the guidelines in practice.

It is concluded that, while a few of the private medical practitioners in 2 major cities in Pakistan are following some isolated components of the national guidelines, none of them (graduates or postgraduates in either city) are comprehensively following the guidelines in establishing a diagnosis, treating or following-up pulmonary TB patients.

Recommendations

The findings of this study strongly suggest the following:

◆ Private general medical practitioners throughout Pakistan, both those with graduate and postgraduate qualifications, should be trained in the National TB Control Programme guidelines.

◆ A functional collaboration needs to be established between private medical practitioners and the National TB Control Programme to provide quality TB care services.

◆ Mass public awareness should be raised to identify the main symptoms of pulmonary TB.

◆ Further studies are needed to assess the baseline knowledge of newly qualified doctors/ final year students, and of practitioners holding postgraduate qualification in chest diseases, and to determine the curriculum needs of medical colleges.

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Gender perspectives on knowledge and practices regarding tuberculosis in urban and rural areas in Pakistan

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Abstract

We investigated gender differences in knowledge of and attitude towards tuberculosis (TB) in urban and rural communities in Sindh province, Pakistan. Knowledge of symptoms was generally deficient, particularly in rural females. Regarding TB prevention, 22.4% of rural and 14.4% of urban males said completing treatment was important; only 9.8% of rural and 7.1% of urban females agreed. Doctors were an important source of information in rural areas and 60.9% of rural males said they would only stop treatment on a doctor's advice. In contrast, > 65% of respondents in urban areas said they would stop treatment when symptoms ended. Our study highlights the need to increase population awareness about TB in Sindh.

Introduction

Tuberculosis (TB) is one of the most important infectious causes of mortality in the developing world. Estimated annual global incidence is 8 million cases and there are 2 million deaths yearly.[1,2] The total number of TB cases is predicted to increase in all regions up to 2005, with the expected increase 3% per year on average. Pakistan has the 6th highest TB burden globally and accounts for 44% of the TB burden in the WHO Eastern Mediterranean Region [2]. It is currently estimated that there are around 1.5 million TB patients in Pakistan, while every year 250 000 people develop the disease.[3] In Sindh province, 88 000 persons get this disease every year, including 44 000 smear-positive cases.[3,4]

Tuberculosis kills more women than all causes of maternal mortality combined.[5] In 1998, about three-quarters of a million women died from TB and over 3 million contracted the disease, accounting for about 17 million disability adjusted life years.[6] A number of studies have shown that in high prevalence countries women in their reproductive years (15-40 years) have higher rates of progression to disease than men of the same age. This may be related to the physiological changes associated with reproduction.[7-9] As TB affects women mainly in their economically and reproductively active years, the disease has a severe impact on their children and families.[10] Women also face obstacles to gaining access to diagnostic facilities, investigation of the disease and completing treatment. In addition, the added burden of housework, childcare and employment allows them very little time to access health care and TB care for themselves.[10-12]

Gender, culture and personal experience are generally said to influence healthseeking behaviour. Several authors agree that the human element in TB control has often been overlooked and suggest that there would be significantly better control if more attention were given to the health culture of the population.[13-15] Local surveys on knowledge and attitude towards TB greatly benefit the planning, health education and implementation of TB control programmes. Research has shown that several health interventions have failed because they were designed without ascertaining any knowledge of the health behaviour of the target population.[16] For successful TB control, it is important to target women and to elicit the beliefs and knowledge of women regarding TB as well as their health-seeking behaviour.

To help in the baseline assessment of the differences in knowledge about TB in males and females, we conducted a study in urban and rural areas of Sindh province in Pakistan with the following objectives: to study the differences in knowledge of cause, spread and treatment of TB; to compare male and female health-seeking behaviours; and to compare urban and rural perspectives regarding knowledge of and attitude towards TB.

Methods

This was a cross-sectional, descriptive study. The study was conducted in 1 urban site in Karachi known as Baldia Town and 1 rural site in Hyderabad division known as Tando Jam. Two hundred households (100 urban and 100 rural) were selected from the data-base of voters using a table of random numbers. All family members 20-45 years were included in the study. The questionnaire was given to every adult male and female between 20 and 45 years of age living permanently in these households. Anyone who had been staying for less than 6 months was not interviewed. In the urban area, 455 individuals (229 males and 226 females) were interviewed, while in the rural area 299 individuals (156 males and 143 females) were interviewed, giving a total of 754. The mean number of persons per household in the urban area was 9.6, while in the rural area it was 8.4. Consent was obtained from the respondents before administering the questionnaire and there were no refusals.

Data were collected using semistructured questionnaires having both closed and open-ended questions. Questionnaires were translated into the national language, Urdu, and the local language, Sindhi. The household questionnaire included questions on age, sex, literacy and

socioeconomic status of the respondents. The individual questionnaires contained questions regarding knowledge of TB, including causes and factors responsible for its spread, signs and symptoms of TB, parts of the body affected, investigations needed in such cases, reasons for stopping treatment and sources of information. Health-seeking behaviour was also determined for both males and females.

Open-ended questions were asked concerning the individual's attitude towards TB and the sociocultural stigmas associated with the disease. The community's attitude towards females who develop TB was also elicited. The questionnaire was administered by interviewers who underwent a 2-day training on questionnaire administration techniques. In the case of male respondents, a male interviewer was used and for females, a female interviewer. The entire questionnaire was completed in 40 minutes. The raw data from open-ended questions was categorized into open codes. These open codes were applied by 2 independent researchers and the results were discussed with the whole team. P-values were calculated using chi-squared.

Results

Of the 754 people interviewed, 385 were male, 62% of them married, and 369 were female, 74.3% of whom were married. The greatest proportion of the households (42% in urban and 43% in rural areas) had an income of 2000-5000 Pakistan rupees per month (US$ 33-83). Radio and television ownership varied from 50% to 70% in urban areas and 45% to 65% in rural areas. Nearly 78% of women in rural areas were illiterate compared with 51% in urban areas. Male literacy was higher, urban 88% and rural 45%.

Observations were made regarding the symptoms of TB as perceived by males and females. In the urban area, cough was the most commonly cited symptom for both males (67.2%) and females (76.5%). Blood in sputum was again cited by both males (17.9%) and females (18.6%). Prolonged fever was most commonly reported by females (29.6%). Anorexia and night sweats were not reported by either males or females. In the rural area, a significant difference was seen between male and female perceptions of symptoms; 57.7% of males cited cough as a predominant symptom compared to 21% of females. Again, 25.6% of males gave blood in sputum as an important symptom compared with only 5.6% of females. Prolonged fever was cited by 19.2% of males but only 4.9% of females. Neither males nor females reported night sweats, anorexia or weight loss as symptoms before probing (Table 1).

Very few people were aware of the causative agent of TB, especially rural females. In the urban area 30% of males and 35% of females cited "germs" as causing TB, while in the rural areas 18.6% of males and 9.8% of females mentioned "germs". X-ray as a diagnostic test for TB was indicated by

Table 1 Male and female (urban and rural) perceptions regarding symptoms of TB.

Symptom	Urban			Rural		
	Male %	Female %	P-value	Male %	Female %	P-value
Cough	67.2	76.5	> 0.05	57.7	21	<0.001
Blood in sputum	17.9	18.6	> 0.05	25.6	5.6	<0.001
Weight loss	7.9	8.8	> 0.05	4.5	1.4	>0.05
Prolonged fever	7.4	29.6	< 0.01	19.2	4.9	<0.0001
Persistent cough	7.0	0.4	< 0.05	1.3	0	<0.0004
Anorexia	0.4	1.3	> 0.05	3.8	1.4	>0.05
Night sweats	0	0	–	0	0	–
Other	1.3	8.0	> 0.05	1.3	0	–

nearly 51% of males and females in the urban area, 69% of males in the rural area and 30% of rural females. Sputum testing, however, was not well known, with only 24% of urban males, 28.8% urban females, 23.1% of rural males and only 6.3% of rural females being aware of it.

We investigated the knowledge of the participants regarding spread of TB (Table 2). In the rural area, 37.2% of

Table 2 Male and female (urban and rural) perceptions on how TB is spread.

Spread of TB	Urban		Rural	
	Male %	Female %	Male %	Female %
Droplet	38.9	28.8	37.2	24.5
Spitting	9.2	11.5	29.5	4.2
Utensils	0.9	0.9	22.4	6.3
Dirty water	2.6	4.9	3.2	0.7
Sexual relations	3.1	14.2	1.3	0.7
Syringes	0.4	0	7.7	2.1

males and 24.5% of females said that TB is spread by droplets while in the urban area this was cited by 38.9% of males and 28.8% of females. Spitting as a means of spreading TB was given by 29.5% of males and only 4.2% of females in the rural area. In the urban area, only 9.2% of males and 11.5% of females said that TB is spread by spitting. More rural males (22.4%) than females (6.3%) said that using the same eating utensils as a TB patient can facilitate the spread of TB. In the urban area, 14.2% of females and 3.1% of males felt the same. Other reasons for the spread of TB included drinking dirty water, reusing syringes and sexual relations (Table 2).

Regarding protective measures against TB, there were significance differences between urban and rural groups (Table 3). In the urban area knowledge about bacille Calmette-Guérin (BCG) was negligible in males, 1.7% compared to 32.7% in rural males. About a quarter of all respondents said that staying away from a TB patient was the best protective measure; while in men the difference between the urban and rural areas was significant (P = 0.002), it was not so for

women (P = 0.6). Only 7.1% of the urban females said that completion of treatment at home was the best protective measure. This figure was 22.4% for rural males (Table 3).

Table 3 Male and female (urban and rural) perceptions on protective measures against tuberculosis (TB).

Measures to protect against TB	Male			Female		
	Urban %	Rural %	P-value	Urban %	Rural %	P-value
Stay away from patient	27.9	22.4	0.002	23.9	25.2	0.6
Complete treatment at home	14.4	22.4	< 0.0001	7.1	9.8	< 0.0001
Use anti-TB drugs	6.1	4.5	< 0.0001	10.6	0.7	< 0.0001
Have separate utensils for TB patient	5.7	8.3	< 0.0001	13.7	2.1	< 0.0001
Use boiled water	3.5	3.2	< 0.0001	3.5	0	< 0.0001
bacille Calmette-Guérin	1.7	32.7	< 0.0001	4.9	8.4	0.0002
Other	0.4	0.6	–	1.6	0.7	–

Table 4 Male and female (urban and rural) perceptions regarding which part of the body tuberculosis affects

Body part affected	Male		Female	
	Urban %	Rural %	Urban %	Rural %
Chest	59.8	45.5	41.2	19.6
Lungs	39.9	26.9	47.8	13.3
Kidney	10.5	0	12.8	3.5
Digestive system	2.6	2.6	8.8	2.1
Anywhere	2.6	6.4	31.7	4.2
Neck	1.3	0.6	0	2.1
Bones	0.4	0	3.1	2.1
Skin	0.4	10.9	0	3.5
Ribs	0.4	1.3	2.1	11.9
Reproductive organs	0	0	0	0
Liver	0	0.6	0	1.4

Urban-rural disparity was evident in gauging knowledge as to which part of the body TB affects (Table 4). More urban males (39.9%) than rural males (26.9%) said the lungs were involved. Some men, 59.8% urban and 45.5% rural, said that TB affects the chest. Urban females were more knowledgeable than rural; 47.8% said that lungs were involved compared with only 13.3% of rural females. Around 41.2% of females in the urban area said the chest was involved compared with 19.6% in the rural area (P < 0.05). In both areas, neither males nor females were aware that kidneys, bones, the digestive system and the reproductive system could also be affected.

In the urban area, 81.4% of females preferred to go to a private clinic for treatment of minor illnesses compared to 21.7% of rural females. The majority of the rural females (62.9%) preferred to visit the tertiary care hospital compared to only 13.3% of urban females (P < 0.05). In males, a similar pattern was seen with 84.7% of urban males preferring to go to a private clinic compared with only 39.7% of rural males. The most favoured type of health facility for rural males was the tertiary care hospital (50.6%). Rural males also went to the hakim (traditional healer) and homeopath more often than women (rural and urban) and urban males (Table 5).

Table 5 Male and female (urban and rural) health-seeking behaviour.

Health facility	Urban areas		Rural areas	
	Male %	Female %	Male %	Female %
Private clinic	84.7	81.4	39.7	21.7
Tertiary hospital	7.9	13.3	50.6	62.9
Government dispensary	3.9	4.0	10.9	21.0
Hakima	2.6	0	5.1	1.4
Homeopathic	0.9	0.4	0.6	0.7
NGO clinic	0	0.9	0.6	0

[a]Traditional healer.
NGO = nongovernmental organization.

When asked about stopping treatment, the majority of urban respondents (> 65%), males and females, said that they would stop treatment when the symptoms ended. This view was also expressed by 43.4% of rural females but only 32.1% of rural males. In rural males, 60.9% said they would follow the advice of the doctor on when to stop the treatment but in the urban areas < 25% of the respondents emphasized the role of the doctor in this respect. A very small percentage said they would stop treatment if they could not afford it (Table 6).

Table 6 Male and female perceptions (urban and rural) about when to stop antituberculosis treatment.

When to stop treatment	Male		Female	
	Urban %	Rural %	Urban %	Rural %
When symptoms end	65.5	32.1	66.8	43.4
When doctor advises	23.6	60.9	23.0	21.0
Cannot afford it	0	1.9	1.3	0.7

When asked with whom they would visit the health facility, only 28.7% of rural females said they would go alone while 53.0% said they would go with their husband or a family member (35.0%). The majority (72.0%) of rural males said they would go alone. In the urban area, only 35.8% of females were willing to go alone but 33.6% said that they would need to be with their husband while 55% said they could be accompanied by any family member. A majority of the urban males (77%) also said that they would go to the health facility alone.

To ascertain if it would be possible to get to hospital to get treatment for TB on a regular basis, nearly 30.5% of urban females said that they would not be able to go to the hospital, while 90% of males said they would go. In the rural areas,

65% of males said that they would be willing to go to the hospital to get treatment, while 70% of females did not agree to go to the hospital to get treatment. Only 27% of males and 38% of females in the urban area said that they would allow an outsider to come and give the medicine to a TB patient. Of these, half said that only a doctor could come, while nearly a quarter said that only a female could come. In contrast, in the rural area nearly 63% of males and 86% of females said that an outsider could come and provide the TB medicines. However, 80% of them said it should be a doctor or a woman.

Only 12%-14% of the respondents (except rural males, 34.8%) had received information about TB from either the radio or television (Table 7). About 15% of men, both urban and rural, had received information from newspapers. Very few rural women (3.5%) received any knowledge about TB from newspapers. However, 66.0% of rural men acquired knowledge about TB from their local doctor, compared with 31.0% of urban men. Friends were also an important source of information in urban areas (Table 7).

Table 7 Sources of information on tuberculosis (TB) stated by males and females in urban and rural areas.

Source of information	Male		Female	
	Urban %	Rural %	Urban %	Rural %
Doctor	31.0	66.0	12.8	25.9
Friends	27.5	3.8	16.8	1.4
Newspaper	15.3	14.7	12.8	3.5
Radio/television	14.8	34.6	14.6	11.9
TB patient	6.1	1.3	15.9	1.4
School	1.7	0	0.9	0
Leader/religious man	0	0	0	0.7

Discussion

Overall knowledge regarding TB has been found to be extremely deficient in both sexes, but especially in rural females. The respondents' perceptions about the disease indicate the sociocultural trends prevalent in society as well as lack of correct information on the disease. Several important trends regarding basic knowledge as well as the social perceptions pertaining to gender differences and urban-rural disparity have been highlighted through this study.

The perceived causes of TB varied from "germs" to dirty water, many respondents, however, also associated TB with drug addiction, which is an interesting observation. Smoking and alcohol consumption have also be cited in several other studies conducted in Kenya, Philippines and Bombay.[17-19] Rural males were more concerned about the sharing of utensils than rural females. Most respondents were aware that TB is a contagious disease and "sharing with a TB" patient was considered a major factor in its spread. This finding is supported in studies from Kenya and India.[17-19]

Knowledge about BCG vaccination as a preventive measure was very limited, except in rural men (32.7%). Again, a substantial proportion of rural men (22.4%) and some urban men (14.4%) said that completing the treatment helped in preventing others from developing TB. Rural females generally had less knowledge on means of protection against TB than the other 3 groups.

The disparity in health-seeking behaviour between the urban and rural population was quite apparent in this study; the urban respondents generally frequented private clinics while the rural respondents, especially males, visited government public hospitals more frequently. Females were found to be more likely to discuss their medical problems with their husbands or other family members while the males were found to chiefly discuss these issues with their doctors. It was seen that rural males followed the advice of the doctor regarding when anti-TB treatment should be stopped. This health-seeking behaviour explains the better knowledge level of the rural males. Doctors appear to play a limited role in providing health education in urban areas. In the urban area, males and females frequently visit private practitioners and in slum areas, many private practitioners are unqualified health care providers. Even if qualified, they do not participate in continuing medical education programmes and are unaware of the recent trends in disease and they do not have time to give health education messages to their patients. Since public health programmes such as directly observed treatment short-course (DOTS) are not implemented through the private system, many are not even aware of these strategies. Hence, in the urban areas, knowledge of males as well as females was limited.

In the rural areas, most public health strategies are implemented at the public health facilities, where the doctors are well versed in the public health programmes and provide health education messages to all patients. Since rural males visit these public health facilities, they have a better perception of the disease and are more knowledgeable about various issues pertaining to TB. Rural females are not allowed to venture out of the house freely, hence their exposure is limited, and not only do they have a narrow vision of the disease implications, their understanding and perception of the disease are also very limited. They tend to view TB as a "punishment from God" and strongly stigmatize the disease. These observations are further strengthened by the finding that the media (radio, television, newspapers) were not an important source of information on TB except for rural males. This is a manifestation of groups of rural men watching television in hotels in villages. In the case of rural males (66%), the doctor plays an important part in imparting knowledge. Hence, contrary

to the general belief, it was the rural males who were more aware of the disease implications of TB.

The DOTS strategy is the recommended treatment for TB in Pakistan. This strategy involves supervised administration of TB drugs and may require daily visits of the TB patient to a health facility for administration of the drug or supervised drug administration at home in the presence of the health worker. We found that both rural and urban females were generally reluctant to visit health facilities alone, more so rural females. Rural women would not be allowed to visit the health facility unless accompanied by husbands or other family members. Rural respondents were, however, more open to allowing outsiders to come to the house to provide medicines.

Health-related beliefs and practices play a very important role in the success of any health intervention strategy. For the success of DOTS in Pakistan, it is important ascertain the willingness of the patients to take the TB medicines in the presence of health personnel. Our study outlines the constraints that females, especially rural females, may face in regular visits to the health facility. The urban restraint, i.e. unwillingness to allow outsiders into the house, should also be taken into consideration. Female health workers, either lady health workers or female community workers, could be employed in this capacity. However, this would need to be strengthened by forceful motivation from the Government.

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Prevalence of pulmonary tuberculosis in Karachi juvenile jail, Pakistan

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Abstract

Jail inmates may be at increased risk of contracting tuberculosis (TB). We studied 386 detainees (mean age 17.7 years) in Karachi juvenile jail to determine the prevalence of TB and possible risk factors for contracting TB. We found a 3.9% prevalence of TB among the inmates, significantly higher than the estimated 1.1% prevalence in the general population of Pakistan. Positive family history of TB was a significant risk factor for TB. Poor adherence of previously diagnosed patients to anti-TB treatment was found. Our study highlights the vulnerability of inmates to TB owing to the presence of highly infectious cases, along with environmental conditions such as overcrowding and poor ventilation. This study strongly indicates the need for an effective treatment programme in the jails as well in the general community.

Introduction

Available data around the globe suggest that jail inmates are at increased risk of contracting pulmonary tuberculosis (TB).[1-3] Factors such as overcrowding, malnutrition and limited access to health care services put prison inmates at high risk. Children and adolescents are even more vulnerable. There is increasing recognition that the high risk of TB in settings such as prisons, remand centres, police stations, detention centres for asylum seekers, penal colonies, and prisoner-of-war camps poses a problem for those imprisoned and for the wider society.[2] A study conducted in Mwanza, Tanzania, revealed that 40.7% of the prisoners studied had smear-positive TB.[3]

Pakistan contributes 43% of the disease burden in the Eastern Mediterranean Region of the World Health Organization, and thus ranks sixth among the countries with the highest burden of disease for TB,[4] but unfortunately there are limited data available regarding prevalence of TB among jail inmates in general, and juvenile detainees in particular. Through this study we proposed to determine the prevalence of pulmonary TB and the associated risk factors among juvenile detainees in Karachi in order to complement national and international efforts to control TB in the community in general and in prisoners in particular. The city of Karachi was selected for the study because it is the most populous city of the country, with a population of more than 10 million, and has residents from all parts of the country. The juvenile prison in Karachi reflects the same characteristics as the city, housing prisoners from all parts of the country and even from neighbouring countries.

The proposal for this study was approved by the Ethical Research Committee of Sindh AIDS control programme, Karachi, Pakistan. Study participants were recruited after obtaining informed written consent and all study participants diagnosed with TB were provided with free treatment through the government of Sindh directly observed treatment short course (DOTS) programme.

Methods

A cross-sectional study was conducted in the juvenile prison in Karachi during the calendar year 2002. The medical officer of the prison and technicians were trained in laboratory techniques, clinical diagnosis and management of TB with the DOTS strategy at Ojha Institute of Chest Diseases, Karachi, for 2 weeks. The technician and the prison dispenser also received training in sputum microscopy at the Institute of Chest Diseases.

All participants were interviewed using a structured questionnaire which included questions on sociodemographic characteristics, past and family history of TB, and other risk factors. They were then clinically examined by the medical officer.

Prisoners were suspected of having TB on the grounds of clinical findings, past history of diagnosis of TB infection and family history of the illness.

Individuals identified as suspected TB cases were investigated for acid-fast bacilli (AFB) in their sputum. A TB suspect was defined as any person who presented with symptoms or signs suggestive of TB, in particular cough of long duration (more than 2 weeks).[5]

Three specimens of sputum were then collected form the suspects and examined by microscopy using the Ziehl-Neelson method of staining. The first specimen from a suspected inmate was obtained on the first day of examination after coughing and clearing the back of throat (1st spot). The inmates were given a container to bring the second (overnight) specimen next day. The third and final specimen was collected on the second day (2nd spot).

Individuals with at least 2 positive smear results were diagnosed as sputum smear-positive active pulmonary TB cases, and were registered for the DOTS programme with Sindh TB control programme.

Diagnostic criteria for sputum smearnegative pulmonary TB cases were: at least 3 sputum specimens negative for AFB, no response to a course of broad-spectrum antibiotics and a decision by a clinician to treat with a full course of anti-TB chemotherapy.

Neither X-ray nor culture facilities were available in the jail and were therefore not included in the case definition.

This programme was carried out under the auspices of the government of Sindh with the assistance of the World Health Organization. Efforts were also made to transfer patients to the nearest DOTS programme after their release from prison.

Risk factors for contracting TB infection in prison were studied by random selection of 60 controls among non-suspect individuals and comparing them to the 15 cases.

The Z-test was used to compare the prevalence of TB in prisoners and in the general population. Univariate and multivariate analyses of risk factors for contracting TB in prisons was performed by calculating the odds ratio and 95% confidence interval. Data management was carried out using Epi-Info, version 6.04 and SPSS, version 10.0 statistical packages.

Results

We enrolled 386 single male juvenile detainees in the study. Mean age ± SE was 17.7 ± 1.3 years (range 15-23 years) though the official age limit for juvenile jail inmates is 18 years. Pakistanis accounted for 357 (92.5%) detainees. The rest were from India or Myanmar (Table 1). Most (87.9) were residents of Karachi. The average family size for the detainees was 8 (range 1-25). They were all imprisoned in 10 barracks, averaging 35.0 ± 11.7 prisoners per barrack (range 10-59 prisoners).

In 14.7% (53) of cases, the father of the inmate was dead. In the rest of the cases 25.4% (98) of the fathers were labourers, 18.9% (73) self-employed, 12.7% (49) in public or private service, 24.4% (94) had other professions and 4.9% (19) were unemployed. Of the inmates themselves, 1.0% (4) were unemployed, 47.7% (184) were labourers, 17.1% (66) were selfemployed, 13.2% (51) were in service, and the remaining 21.0% (81) had other professions. About 60% (228) of participants were illiterate, and none had higher secondary school or above education (Table 1).

The period of imprisonment was 1-6 months for 52.3% (202) of jail inmates, 6- 12 months for 20.2% (78), more than 1 year for 16.3% (63) and less than 1 month for 11.1% (43). In addition, 12.7% (49) of inmates had a previous record of imprisonment. We found that 42.6% (164) of jail inmates were smokers and 21.5% (83) were drug users. Among the drug users, 83.6% were inhaling the drugs and only 1.4% had a history of injecting (Table 2).

Table 1: Sociodemographic characteristics of juvenile jail detainees (n = 386).

Characteristic	No.	%
Age		
15–16 years	58	15.0
17–18 years	239	61.9
18 + years	89	23.1
Education		
Uneducated	228	59.1
Primary	79	20.5
Secondary	79	20.5
Nationality		
Pakistania	357	92.5
Non-Pakistani	29	7.5
Residence		
Karachi	320	82.9
Outside Karachi	66	17.1
Father's occupation		
Died	53	13.7
Unemployed	19	4.9
Labourer	98	25.4
Government service	23	6.0
Private service	26	6.7
Self employed/business	73	18.9
Driver	29	7.5
Farmer	26	6.7
Fisherman	31	8.0
Other	8	2.2
Detainee's occupation		
Unemployed	4	1.0
Labourer	184	47.7
Service	51	13.2
Self employed/business	66	17.1
Fisherman	38	9.8
Student	30	7.8
Other	13	3.4
Family members in the household		
1–4	50	13.0
5–8	187	48.4
9–12	123	31.9
> 12	26	6.7

aArea of origin: Karachi (82.9%); interior Sindh (1.3%); Punjab (4.1%); North-West Frontier province (2.6%); Balochistan (1.3%); northern areas (0.3%).
s = standard deviation.

Nine jail inmates had previously been diagnosed with TB; 3 had received the full 6 months treatment, 2 did not receive any treatment, and 4 received irregular treatment, but all of them were symptomatic on clinical examination during our study (Table 3). One of the 3 cases who had received 6 months treatment was also positive for AFB. All had been symptomatic for TB for more than a month. Among the 6 patients who received no or irregular treatment, 3 complained of cough, fever, weight loss and haemoptysis. One had a history of fever and cough while the other 2 were suffering from chronic cough.

Table 2: Risk factors for tuberculosis (TB) among juvenile jail detainees (n = 386).

Characteristic	No.	%
Duration of stay in jail		
< 1 month	43	11.1
1–6 months	202	52.3
> 6–12 months	78	20.2
> 1 year	63	16.3
Past history of imprisonment		
Yes	49	12.7
No	337	87.3
Family history of TB		
Yes	29	7.5
No	347	89.9
Don't know	10	2.6
Smoking history		
Smoker	164	42.6
Non-smoker	222	57.5
History of drug use		
Drug user	83	21.5
Non-drug user	303	78.5
Method of drug use		
Inhalation	61	15.8
Ingestion	9	2.3
Inhalation + ingestion	2	0.5
Inhalation + ingestion + injection	1	0.3
Didn't reply	10	2.6

Table 3: Aspects of previous treatment for tuberculosis (TB) among juvenile jail detainees (n = 386).

Characteristic	No.	%
History of TB		
Yes	9	2.3
No	377	97.7
History of treatment for TB		
Yes	7	1.8
No	2	0.5
Course of treatment		
Completed	3	0.8
Not completed	4	1.0
Duration of incomplete treatment (months)		
3	2	0.5
3.5	1	0.3
5	1	0.3
Duration of interruption to treatment (months)		
< 1	1	0.3
≥ 1	3	0.8

Forty-eight (12.4%) prisoners had been suffering from 1 or more symptoms (cough, fever, weight loss and haemoptysis) for more than 1 month (Table 4).

Seventy-three jail inmates (18.9%) were initially suspected for TB on the basis of clinical symptoms, family history and past diagnosis of TB. Of these, 48 had clinical signs and symptoms suggestive of TB, 33 had a family history of TB, while 8 had symptoms suggestive of TB in addition to family history of the disease.

Table 4: Rates and clinical features of tuberculosis (TB) infection among juvenile jail detainees (n = 386).

Characteristic	No.	%
Registered for DOTS	15	3.9
Symptoms suggestive of TB		
Cough > 4 weeks	20	5.2
Cough + fever > 4 weeks	10	2.6
Cough + fever > 4 weeks + weight loss	1	0.3
Cough + fever > 4 weeks + weight loss + haemoptysis	4	1.0
Cough + fever > 4 weeks + haemoptysis	1	0.3
Cough > 4 weeks + haemoptysis	2	0.5
Fever > 4 weeks	4	1.0
Weight loss + haemoptysis	1	0.3
Haemoptysis	5	1.3
Sputum smear microscopy		
Specimen 1		
Positive sputum	1	0.3
Negative sputum	17	4.4
Fresh blood	5	1.3
Saliva	50	13.0
Specimen 2		
Positive sputum	3	0.8
Negative sputum	16	4.1
Fresh blood	4	1.0
Saliva	50	13.0
Specimen 3		
Positive sputum	3	0.8
Negative sputum	16	4.1
Fresh blood	4	1.0
Saliva	50	13.0

For the AFB smear test, of 73 suspected cases, in 19 (26.0%) cases we were able to obtain sputum while the rest had saliva and blood in their specimen but no sputum. Of the 19 whose sputum was tested, 5 (26.3%) showed AFB on microscopy.

On the basis of the AFB smear results, previous diagnosis of the disease and signs and symptoms strongly suggestive of TB, 15 (3.9%) jail inmates were identified as suffering from TB and selected for the DOTS regimen. Inmates who had tested negative for AFB and had no history of earlier diagnosis were selected for the DOTS regimen mainly on the clinical judgement of the treating physician.

Table 5 shows the risk factors for contracting TB. There was elevated risk among patients who were illiterate, Karachi residents, those whose father was unemployed, smokers or drug users; the results were not, however, statistically significant. However, there was a 7-fold increased risk among those reporting a family history of TB, and this was statistically significant.

Table 5 Risk factors for contracting tuberculosis (TB) infection in prison.

Risk factor	Cases (n = 15)		Controls (n = 60)		Crude OR	95% CI	Adjusted OR	95% CI
	No.	%	No.	%				
Education								
Uneducated	10	66.7	36	60.0	1.33	0.35–5.24	1.33	0.36–5.60
Educated	5	33.3	24	40.0				
Nationality								
Pakistani	15	100	57	95.0	ND		ND	
Non-Pakistani	0	0	3	5.0				
Residence								
Karachi	14	93.3	52	86.7	2.15	0.23–50.6	2.14	0.25–102.3
Outside Karachi	1	6.7	8	13.3				
Father's occupation								
Died or unemployed	3	20.0	7	11.7	1.89	0.23–10.20	1.87	0.27–9.84
Employed	12	80.0	53	88.3				
Number of family members in household								
> 6	9	60.0	45	75.0	0.50	0.13–1.94	0.51	0.13–2.03
6 or less	6	40.0	15	25.0				
Duration of stay in jail (months)								
> 6	5	3.3	18	30.0	1.17	0.29–4.53	1.16	0.27–4.42
≤ 6	10	66.7	42	70.0				
Past history of imprisonment								
Yes	0	0	11	18.3	ND		ND	
No	15	100	49	81.7				
Family history of TB								
Yes	4	30.8	3	5.2	8.15	1.22–58.59	7.78	1.12–62.48[a]
No or don't know	9	69.2	55	94.8				
Smoking history								
Yes	9	60.0	29	48.3	1.60	0.44–5.96	1.59	0.44–5.37
No	6	40.0	31	51.7				
History of drug use								
Yes	7	46.7	20	33.3	1.75	0.48–6.42	1.74	0.43–6.40
No	8	53.3	40	66.7				

OR = odds ratio.
CI = confidence interval.

[a]Yates corrected chi-squared = 5.21; Fisher exact P-value = 0.018.
ND = not determined.

Discussion

We found a 3.9% (15/386) prevalence of TB among the prisoners in Karachi juvenile jail. This high prevalence of the disease in the inmate population may be related to overcrowding, poor ventilation and malnutrition in the jail environment. Furthermore, poor health care facilities jeopardize adequate treatment of the infection and could possibly result in the development of resistant strains in prisons.

Our study highlights one of the important aspects of M. tuberculosis infection in the community-a high rate of poor compliance and the possible emergence of multidrug resistant strains. Of 9 cases diagnosed with TB, 4 had received partial treatment and only 3 had completed their treatment. But all these cases, irrespective of whether they received treatment or not, were symptomatic. The detection of 5 AFB positive cases during our study suggests a high vulnerability of jail inmates to TB. The presence of AFB in the sputum suggests a high level of infectivity. Coughing, overcrowding and poor ventilation produce conditions which allow the bacteria which cause TB to remain viable for a long time, thus exposing everyone who comes into the barracks, whether a prisoner, member of staff, visitor or an investigator, to infection.

Family history was identified as a major risk factor for TB, with 33 (8.5%) prisoners reporting history of TB in the family. Of these, 8 (24%) were initially suspected of having TB on the basis of signs and symptoms. Later, 4 (50%) were selected for the DOTS programme; 2 of them were AFBpositive and 2 had a history of cough, fever, and haemoptysis for more than 1 month.

Poverty was stated as a major reason for not receiving treatment following diagnosis in 14% (17) of previously diagnosed, but not treated, prisoners. Similarly, in 14% (17) ignorance of the consequences of the disease may have been the reason, as those prisoners failed to give any explanation for not receiving treatment. Poor compliance to the anti-TB regimen appeared to be

responsible for treatment failure in 42% (37) of cases, circumstances which may favour the emergence of multidrug resistance.

Our study identified a limitation in using the AFB test as the sole criterion for diagnosing TB infection. It certainly improves the specificity of the diagnosis, but at the cost of poor sensitivity. No AFB-positive prisoner was found asymptomatic, suggesting no false positive diagnosis, using this criterion. Many patients suffering from TB infection were, nevertheless, AFB-negative, suggesting the possibility of some false negative results, perhaps due to undetectable levels of AFB in the smears, or poor quality of specimen collection, staining and microscopy. This may be related to indiscriminate use of antibiotics, including antimycobacterial drugs.

Another limitation noted in the study was the language barrier. There were prisoners from the whole of south-east Asia, speaking different languages and dialects. This may be the reason that compliance of the prisoners with regard to sputum collection was poor, even among the prisoners who were complaining of a productive cough. Difficulty was also noted in taking the clinical history of the patients. It was also noted that 2 weeks training of technicians with regard to AFB staining and microscopy may not be sufficient to carry out these procedures independently.

In our study, owing to the absence of radiological support and culture facilities in the jail environment, the treating physician was left with no option but to use his clinical judgement and start the DOTS regimen for 7 previously diagnosed patients who had symptoms and for 3 clinically suspect cases who tested negative for AFB and had no history of the disease. For the effective and rational use of DOTS in prisons, it may be appropriate to have facilities for radiography and microbial culture in clinically suspected but AFB smear-negative cases before making any judgement regarding treatment.

The finding of this study that jail inmates are at increased risk for TB infection is in line with earlier studies conducted in prisons in other parts of the world.[1-3]

It is suggested that a TB control programme be introduced in the jail environment, ensuring regular screening of prisoners for TB infection and the early and effective management of cases. Special attention should be given to those reporting a positive family history of TB as they have proved to be more likely to be infected. There is also a need to ensure that all prisoners who were receiving DOTS during their prison term continue to do so after their release until the course of treatment is completed. Overcrowding and poor sanitation and ventilation provide M. tuberculosis an opportunity to persist for long periods and infect others. There is a need to improve ventilation, sanitation and overall living conditions in the jail environment.

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Differences in Clinical Presentation of Pulmonary Tuberculosis in association with Age

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Abstract

Objectives: To study the differences in presentation of pulmonary tuberculosis in young adult and elderly patients.

Design: A prospective study was conducted between December 1999 to May 2000, which included all the patients presenting with pulmonary tuberculosis at the Department of Thoracic Medicine, Jinnah Postgraduate Medical Centre (JPMC), Karachi.

Patients and Methods: here were 67 young adult (mean age 30.63 yrs) and 36 elderly patients (mean age 65.92 yrs) with pulmonary tuberculosis. The difference in presentation of two groups were analyzed for statistical difference. Chi-square test was used for testing difference of percentage. The students t-test was used for testing difference of mean. The $P < 0.05$ level of significance was adopted.

Results: he elderly patients were more likely to have dyspnoea (73% vs 23.9% P<0.001) and non-specific symptoms (62.2% vs 17.9% P<0.001) but less haemoptysis (21.6% vs 46.3% P<0.01). The chest radiograph in elderly patients more commonly had extensive bilateral infiltration (32.4% vs 14.9% P<0.03) and lower zone infiltration (37.8% vs 3% P<0.001).

Conclusion: he result of our study suggests that elderly patients with pulmonary tuberculosis were more likely to present with dyspnoea, non-specific symptoms and atypical radiographic appearance (JPMA 53:321;2003).

Introduction

Tuberculosis is one of the important communicable diseases world wide.[1] The incidence of tuberculosis has been increasing globally, almost 2 billion people (one third of the world's population) around the globe are infected with M. tuberculosis.[2] It is the world's biggest killer by a single pathogen causing the death of three million people every year, which is equal to approximately 6% of all the deaths worldwide.[3] Some studies have shown that the diagnosis of TB in elderly is frequently delayed or found at autopsy.[4-11] However others suggested that the pattern of TB in the elderly is so characteristic, that it should be given a separate classification.[12] In this prospective study we tried to evaluate, whether there is any difference in presentation of young and elderly patients with pulmonary tuberculosis, as the incidence of tuberculosis in our population is very high.

Patients and Methods

This study was conducted between Dec, 1999 to May, 2000 in newly diagnosed patients of pulmonary tuberculosis, at the Department of Thoracic Medicine, JPMC, Karachi. Demographic data, presenting symptoms, radiographic appearance, weight of the patients, AFB smear either sputum of gastric lavage (those who failed to produce sputum) were collected. The patients were divided into two groups (1) younger (<60 years) and elderly (>60 years) age groups. The difference in presentation of the two groups were analyzed for statistical differences, chi-square test was used for testing difference of percentage and student's t-test was used for testing difference of means. The P<0.05 level of significance was adopted.

Results

Demographic data for the patients are presented in Table 1, consisting of 67 young and 36 elderly patients with pulmonary tuberculosis. The diagnosis was made by positive AFB smear. The mean age in the younger group was 30.63 years and in the elderly group 65.92 years. The mean body weight of elderly patients was greater than that of younger patients (47.83kg vs 45.69kg P not significant). There were greater number of smokers amongst elderly patients (38.88% vs 23.9, P not significant) (Table 1).

The presenting symptoms are listed in table-2 patients with younger age group were more likely to have night sweats (56.7% vs 8.1% P<0.001), fever (98.3% vs 83.8% P<0.01). haemoptysis (46.3% vs 21.6% P<0.01) and weight loss (74.6% vs 51.4% P<0.02). However the elderly patients were more likely to have dyspnoea (73.0% vs 23.9% P<0.001), chest pain (40.5% vs 14.9% P<0.002) and non-specific symptoms (62.2% vs 17.91% P<0.001) such as dizziness, body aches and abdominal pain. The symptoms of cough, sputum, anorexia and malaise were not significantly different between the two groups (Table 2).

Radiographic finding are given in Table 3. The patients in the younger age group had a greater frequency

Table 1: Demographic data of patients with pulmonary tuberculosis.

Patient Charecterstics	Young (n=67)	Elderly (n=36)	P Value
Age			
Mean	30-36	65-92	P<0.001
Range	18-55	61-80	
Sex			
Male	35 (54%)	20 (52.2%)	NS P>0.92
Female	32 (43.2%)	16 (47.8%)	NS P>0.70
Body weight (kg)	45.69	47.83	NS P>0.25
Sputum AFB smear	64	33	NS P>0.25
Gastic lavage AFB smear	3	3	NS P>0.25
Smoker	16 (23.9%)	14 (38.88%)	NS P>0.11

NS = not significant

Table 2: Presenting symptoms in patients with pulmonary tuberculosis.

Presenting symptoms	Young (n=67)	Elderly (n=36)	P Value
Night sweats	38 (56.7%)	3 (8.1%)	P<0.001
Cough	66 (98.3%)	34 (94.4%)	P<0.56*
Sputum	57 (85.1%)	37 (73.0%)	P<0.11*
Fever	66 (98.3%)	31 (83.8%)	P<0.01
Haemoptysis	31 (46.3%)	8 (21.6%)	P<0.01
Weight Loss	50 (74.5%)	19 (52.4%)	P<0.02
Anorexia	49 (73.11%)	23 (62.2%)	P<0.21*
Malaise	23 (34.3%)	11(29.7%)	P<0.69*
Chest Pain	10 (14.9%)	15(40.5%)	P<0.002
Non-Specific	12 (17.91%)	23 (62.2%)	P<0.001

* Not-significant

of upper zone infiltration only (31.3% vs 5.4% P<0.002). The as elderly age group patients tended to have more extensive lesion of both lungs (32.4% vs 14.9% P<0.03). The lower zone infiltration was also seen more frequently in elderly group patients (37.8% vs 3% P<0.001) (Table 3).

Associated medical problems are listed in Table 4.

They were more commonly seen in elderly patients (80.55% vs 25.37% P<0.001).

Table 3: Major radiographic finding in patients with pulmonary tuberculosis.

Presenting symptoms	Young (n=67)	Elderly (n=36)	P Value
Upper Zone inflatration Only	21 (31.3%)	2 (5.4%)	P<0.002
Middle Zone inflatration Only	7 (10.4%)	-	-
Lower Zone inflatration Only	3 (4.5%)	2 (5.4%)	P<0.81*
Wide Spread infilatration of one lung	21 (31.3%)	5 (13.5%)	P<0.05
Wide Spread nflatration of both lung	10 (14.9%)	12 (32.4%)	P<0.03
Cavitation	12(17.9%)	2 (5.4%)	P<0.011*
Miliary shawoding	2 (3%)	2(5.4%)	P<0.80*

*NS = not significant

Table 4: Associated medical problems in patients with pulmonary tuberculosis.

Medical problems	Young (n=67)	Elderly (n=36)	P Value
COPD	2 (3%)	9 (24.3%)	P<0.001
Asthma	-	2(5.4%)	-
Pneumonia	3 (4.5%)	2 (5.4%)	P<0.81*
Malignancy	-	-	-
Bronchiectasis	1 (1.5%)	-	-
Diabetics	6(9%)	4 (10.8%)	P<0.082*
Cirrhosis	1 (1.5%)	-	-
Peptic Ulcer	-	2 (5.4%)	-
Hypertension	1 (1.5%)	6(16.2%)	P>0.01
Psychiatric	2 (3%)	-	-
Others	1 (1.5%)	4 (10.8%)	P>0.08*
Total	17 (23.37%)	29 (80.55%)	P<0.001

* Not-significant

Discussion

The diagnosis of tuberculosis in elderly is frequently made only at autopsy.[4-11] The delay in diagnosis has often been attributed to atypical clinical and radiological presentation.[13] Many studies have compared the clinical presentation of pulmonary tuberculosis in young adults versus the elderly.[8,16-20] Morris went on to state that elderly patients with pulmonary tuberculosis had a different disease.[12]

In the present study we have found that non-specific symptoms are more commonly present in elderly patients. They may therefore be treated for other medical illness initially. There may be a considerable delay before the diagnosis of TB is finally made.

Dyspnoea is more common in patients in the elderly age group, and could be due to the higher incidence of smoking, COPD and more extensive lesions.

Haemoptysis is more common in patients with younger age group and is probably related to a higher incidence of cavitation.

Cough was a common presenting symptom in both groups. Although many elderly patients have other associated medical problems which may give rise to cough, such as chronic bronchitis, emphysema, asthma and malignancy, this symptom should be evaluated seriously particularly if it prolonged and not responding to treatment.

With respect to the difference in radiological findings between the two groups, Some studies found there was no difference.[16] Teale C, et al suggested that in the elderly there is a shift toward less common presentations such as lower zone and miliary shadowing.[21] In our study lower zone infiltration only,

occurred more frequents in elderly patients.

The findings of our study are consistent with most of international studies.

Conclusion

Our study showed that elderly patients with pulmonary tuberculosis were more likely to present with dyspnoea and non-specific symptoms. Similarly radiographic appearance were atypical viz lower zone infiltration and bilateral extensive lesions were more common in this age group.

On the other hand younger patients presented with classical symptoms of TB, and also had greater frequency of upper zone infiltration on chest radiograph. A knowledge of these differences should help make an earlier diagnosis of pulmonary TB, especially in the elderly in whom it may be often delayed.

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Cost of DOTS for Tuberculous Patients

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Abstract

Objective: To determine the cost of DOTS (directly observed therapy short course) incurred by the patients.

Methods: A hospital based cross-sectional study was conducted at Nazimabad Chest Clinic and Ojha Center for Chest Diseases from January 2005 to July 2005. Two hundred and twenty tuberculous patients with acid-fast bacilli positive in their sputum were analyzed. Variables for cost were assessed with respect to money and time.

Results: Most of the tuberculous patients (68%) registered during the data collection period were females. Thirty seven percent of the patients belonged to families with 8-10 family members living under one roof. The expense of direct cost for two months treatment was Rs. 3060-3600 (if patient was not buying the anti-tuberculous drugs). Most of the patients who were on DOTS spent more than 4 hours per day in obtaining the therapy. The disease was found to be common in poor families (75% of patients had total monthly income less than Rs. 2000).

Conclusion: Tuberculosis was common in poor and large-sized families. Time consumption on travel for DOTS was a deterrent for compliance. DOTS coverage should be modified to reduce time and financial cost for the patients.

Introduction

Tuberculosis is a disease that has a major impact on a global scale.[1] Tuberculosis causes death of nearly 3 million people every year.[2] Tuberculosis eradication has become a matter of greater concern among the national, international and local health authorities. Contributing 85% to the total global burden, 22 countries have been identified and labeled as highly endemic countries by W.H.O.[3] Due to the emergence of H.I.V., increased migration and the deterioration of the health services in many countries, the incidence has risen so drastically in recent years, that T.B. was declared a global emergency by W.H.O. in 1993.[4] Without increased investment in intervention strategies, the global tuberculosis situation is expected to worsen in the near future.[5]

There is little reliable epidemiological data available for Pakistan, although TB is considered to be a major cause of ill health.[6] According to World Health Organization (W.H.O.) report of the year 2000, Pakistan stands at number " 6" behind China, India, Bangladesh and Indonesia in the list of 22 highest burden TB countries of the world.[7]. There are estimated 268,000 new cases and 64,000 deaths from TB each year in Pakistan; which bears 44% burden of TB cases in the W.H.O. Eastern Mediterranean Region (E.M.R.O.).[8] The annual incidence of infectious T.B. cases is estimated to be between 85-100 / 100,000 persons. Annually around 120,000 new TB cases are being added to the existing number of infectious individuals. Based on burden of disease estimates, TB represents 5% of the total DALYs (disability adjusted life years); which indicates that the burden of tuberculosis in Pakistan, is substantially higher than the world's average of 3%.[9]

Tuberculosis is especially prevalent in the population undergoing stresses of poor nutrition, overcrowding, inadequate health and displacement.[10] Government of Pakistan endorsed DOTS strategy and in 1994, in collaboration with W.H.O., revised the TB control policy and technical guidelines.[11]

In DOTS patient swallows the medicines under the watchful eye of the doctor, a health worker, community volunteer, mohalla molvi, pharmacist, or even any entrusted family member.[12] The TB patient is almost always cured if these medicines are taken regularly for the entire period of time. The anti-tuberculous drugs in this short-course chemotherapy are Isoniazid, Rifampicin, Pyrazinamide and Ethambutol or Streptomycin.

DOTS stops TB bacteria at the source. Curing a contagious patient is the best way to prevent TB bacteria from spreading to others.[13]

In Pakistan low treatment adherence prevails.[14] In the sixties Sloan and Sloan observed dropout rates of 66% in Sindh[15], similar reports were found in the recent Rawalpindi cohort study.[16] Several studies have shown financial factors contributing to non-adherence to treatment. Research has shown irregularity of attendance during the initial phase to be a major determinant for treatment adherence not only in the initial phase but also in the continuation phase.[17] This study was conducted at Karachi Medical and Dental College on tuberculous patients to identify the barriers in the implementation of DOTS.

The other objective of the study was to determine the cost on DOTS incurred by the patients and the factors responsible for non-compliance.

Patients and Methods

A cross-sectional study was conducted at Iqbal Yad Chest Clinic (O.P.D.) of Ojha Center and Nazimabad Chest Clinic. A sample of 220 was estimated assuring compliance of 50% with a level of significance of 5%. All the consenting patients attending the TB O.P.D. between 9:00 a.m. till 1:30 p.m. were registered between January and June 2005. Non-probability convenience sampling technique was used.

A questionnaire was prepared keeping in mind the information needed regarding DOTS with respect to money and time. The variables for money were in terms of direct cost spent in traveling and buying the O.P.D. slip. The cost on buying anti-tuberculous drugs was not included as those were given free at the centers. Indirect cost on DOTS was the time spent in traveling and waiting in O.P.D. Cause of previous incomplete treatment was also asked from the re-treatment cases.

The questionnaire consisted of twenty close-ended questions. For each question a code was assigned and data was collected by face-to-face interaction through verbal communication. Sputum was tested for acid-fast bacilli. Pre-testing was carried out three days before the actual study in O.P.D.

Results

Most of the patients registered in the TB center (82%)(180/220) were the new cases. Nine percent were relapses and 9% were defaulters (Figure 1). Sixty eight percent (150/220) patients registered in the T.B. O.P.D. were females, among them 40% (87/220) were in the age group of 11 to 20 years and 21% of the males (45/220) were in the age group of 31 to 40 years (Table 1).

Thirty seven percent (81/220) of the T.B. patients belonged to those families where total family members

Table 1: Association of sex with the age of the TB patients.

Age in years	Male No.	Patient %	Female No.	Patient %	Total No.	Total %	p-value
11-20	3	1	87	40	90	41	
21-30	15	7	30	13	45	20	
31-40	45	21	15	6	60	27	0.000
41-50	3	1	15	6	20	9	
> 50	4	2	3	1	5	3	
Total	70	32	150	68	220	100	

Table 2: Relationship of reasons for previous incomplete treatment with the total monthly income of the patients.

CAUSES N=220	INCOME IN RUPEES								p-value
	<2000 n=170		2000-4000 n=31		4000-6000 n=10		>6000 n=9		
	No.	%	No.	%	No.	%	No.	%	
1. Expensive medicine n=5	2	40	1	20	1	20	1	20	0.0001
2. Prolonged treatment not necessary n=5	1	20	2	40	1	20	1	20	0.001
3. Long distance n=30	20	67	5	17	3	10	2	6	0.006
4. No cause as new cases n=180	147	82	23	12	5	3	5	3	0.0003

** Expensive drugs was the cause of discontinuation of treatment when tuberculosis was first diagnosed.

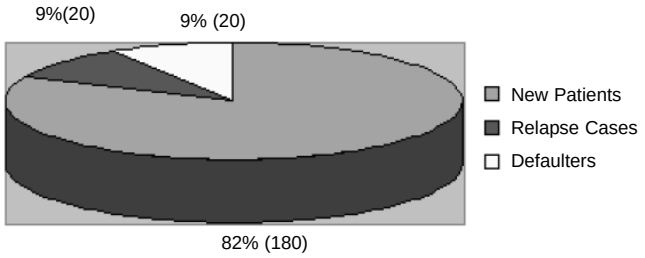

Figure : Distribution of the categories of the TB patients

were between 8 to 10 living under one roof. Sixty one percent (135/220) patients spent Rupees 41 to 60 on traveling. The mean daily expense was Rupees 42 and for two months intensive therapy it was Rs.2520. Forty four percent (96/220) patients stated that more than 4 hours were spent (including traveling both ways and waiting in the O.P.D.) on DOTS practice, mean time spent was 3 hours and 15 minutes.

Table 2 shows the causes of previous incomplete treatment compared with the total monthly income of the T.B. patients. Eleven percent (25/220) of the patients were those who stopped treatment as it was expensive. Seventy five percent (167/220) of the patients belonged to the families where total monthly income was less than Rs. 2000. The relationship between the total monthly income and the causes of previous incomplete treatment was statistically significant (p=0.001).

The distance in kilometers traveled by the patients compared with the categories of the patients, revealed that 57% (124/220) patients came from a distance more than 15

kilometers and among them most were new cases i.e., 43% (95/220) The relationship between the categories of the T.B. patients with the distance was statistically significant (p= 0.0038).

Discussion

Various studies in U.K. have established overcrowding and socioeconomic deprivation as major factors for the rise in tuberculous cases.[18] A study in Lahore, Pakistan showed that majority (71%) of the tuberculous patients were members of the poor, deprived and lower social class [19]. In our study also majority of the patients were from lower socioeconomic group (monthly income less than Rs.2000) and having large families. Overcrowding in small enclosed spaces with close and prolonged contact with other family members provides an opportunity of infection to spread from one individual to the other through droplets or coughing.[20] Most of the patients spent Rupees 51- 60 daily and for two months intensive therapy amounts to Rs. 3060-3600, which the poor patients could not afford. With poverty also comes malnutrition leading to weakening of body defences. With the expense of treatment and the lengthy therapy involved for tuberculosis, majority of the patients could not afford to buy medicines and bear traveling expenses when their basic needs are not being met. Most of the male patients in our study group were found to be in the age group when their families were dependent on them for earning and providing financial support. This would simply perpetuate the vicious cycle of poverty leading to lower defences. Females from illiterate families in general have a lower status in the family, and are deprived of better quality of food leading to poor nutritional status. In addition early marriages and multiple pregnancies put extra burden on their defence system leaving them more vulnerable to tuberculosis.

From our study it appears unlikely that medical advances alone can control tuberculosis. As the powerful tools for treatment and prevention which are currently available have made little impact, so any new methods would have little impact unless there is global political willingness to address gross inequalities of wealth and health care provision in society.[21]

While tuberculosis can affect anyone, the greater burden of disease falls on the poor.[22] The director of W.H.O. Global TB Program has stated, "epidemic is no longer an emergency only for those who care about health, but for those who care about justice".[23]

Conclusions

Tuberculosis continues to affect the poor deprived communities and despite increased coverage of DOTS the disease continues to increase in younger females and males in their prime productive ages. DOTS coverage should reach TB patients at home as time and travel cost are major deterrents to compliance.

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Knowledge, Attitude and Misconceptions regarding Tuberculosis in Pakistani Patients

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Abstract

Objective: To assess knowledge of patients with tuberculosis; about their disease and misconceptions regarding TB.

Methods: A cross sectional study was conducted at Out-patient clinics of two teaching hospitals (private and public) in Karachi, Pakistan. A questionnaire was filled for the purpose.

Results: A total of 170 patients were interviewed, 112 from private and 58 from a public sector hospital. Cough, fever, bloody sputum and chest pain were recognized as the common symptoms of TB. Eleven (7%) patients thought TB was not an infectious disease and 18 (10.6%) did not consider it a preventable disease. Contaminated food was considered the source of infection by 81 (47.6%) and 96 (57%) considered emotional trauma/stress the causative agent of TB. No counseling about preventing spread was received by 81 (50%) patients and 97 (57%) considered separating dishes as an important means of preventing spread. Thirty one (18%) patients would have discontinued their medications following relief of symptoms. Thirty nine (23%) of the respondents thought that TB could lead to infertility and 66 (38.8%) believed that there were reduced chances of getting married following infection.

Conclusion: Misconceptions concerning TB are common in Pakistani patients. Lack of knowledge on Tuberculosis is alarming.

Introduction

Tuberculosis (TB) has reached epidemic proportions in many developing countries, with a third of world population being infected. Every year there are 8 million new TB cases that results in 2-3 million deaths worldwide, making TB the leading killer amongst all infectious diseases. Pakistan ranks 6th in the world among countries with the highest prevalence of TB. It has an annual incidence of around 300,000 new TB cases.[1]

Deficiencies in National TB Control Program are compounded with widespread misconceptions and false beliefs among TB patients. These myths have turned TB into a social stigma. This stigmatization can play an important role in reluctance of patients in seeking treatment.[2] Very few studies have been conducted in Pakistan regarding awareness of TB among patients. No programme for TB control can be effective unless erroneous beliefs amongst the masses are identified and removed. Future education has to be based on existing scientific knowledge and presented in a manner that can be easily comprehended and accepted by the patients. Social and cultural factors have to be taken into account as they play an important role in compliance of TB patients.[3]

The objectives of this study were to assess knowledge of TB patients about their disease, and to identify their misconceptions and social stigmas associated with TB.

Methods

A cross sectional study was conducted at the out-patient pulmonary clinics in two teaching hospitals of Karachi, which has a population of about 14 million. Aga Khan University Hospital (AKUH) is a private sector hospital, while the Jinnah Postgraduate Medical Centre (JPMC) is a government sector health facility.

A total of 170 patients were interviewed. Unselected adult patients (aged above 16 years) who were suffering from TB or had suffered from TB in the past were included in the study. Convenience Sampling was used to recruit participants. They were questioned about knowledge, attitudes and misconceptions concerning TB.

A multiple choice questionnaire comprising a total of 36 questions was designed in English. The questionnaire was first pilot tested. After a few modifications the questionnaire was implemented. The questionnaire was translated in Urdu (the national language of Pakistan) and administered to the patients by trained research officers.

The questionnaire data was entered and analyzed using SPSS version 11.0.

Results

A total of 170 patients were interviewed at two tertiary care hospitals in Karachi. The demographic

variables are presented in the Table. Forty one (24%) respondents had not received formal education of any kind, whereas seventy nine (46.5%) were either unemployed or earned less than Rupees 5000 ($85) a month.

Table: Patient characteristic of TB cases from the Aga Khan University Hospital (AKUH) and Jinnah Post Graduate Medical Centre (JPMC), Karachi.

Variables	AKUH	JPMC	Total
Total number of patients	112	58	170
Gender: Males	72	20	92
Females	40	38	78
Level of education			
None	17	24	41
Below matriculation	24	23	47
Past matriculation	54	11	65
Graduate	14	-	14
Post Graduate	3	-	3
Monthly income (in Pak. Rupees)			
< 5000	30	49	79
5000-10,000	25	10	35
10,000-15,000	15	2	17
15,000-20,000	19	-	19
> 20,000	20	-	20

Forty seven (27.6%) had not heard of TB before they were diagnosed themselves and 16 (9.4%) thought that it was a rare disease in Pakistan. Eleven (7%) did not consider TB as an infectious disease. Inhaled droplets were recognized as the common source of infection but eating contaminated food (47.6%), use of blood products (32.9%) and inheritance (27%) were also considered important modes of transmission. Lung was considered as the only organ affected by TB by 39 (23%) patients and 96 (57%) thought that stress and emotional trauma could lead to tuberculosis.

The four most commonly recognized symptoms of tuberculosis were thought to be cough (83.5%), fever (54.7%), chest pain (24.7%) and bloody sputum (24.7%). Twenty eight (17%) responders thought that TB occurred only once in a life-time and did not recur for a second time after treatment. Thirty one (19%) patients believed that the total duration of treatment was less than 6 months; while 31(18%) were of the view that treatment should be stopped following control of symptoms.

TB was not considered a preventable disease by 18 (10.6%) patients and 97 (57%) considered separating dishes as the most commonly used method for preventing the spread of TB. Thirty seven (22%) were not aware of availability of vaccine against tuberculosis.

Fifty six (33%) patients were not concerned about spreading TB infection to their family members. Eighteen (10.6%) patients sought treatment approximately six months after onset of symptoms. In the first instance, 94 (55.3%) patients first consulted their general practitioners in private sector for treatment. In 18 (10.6%) patients it took over 6 months from the time they first consulted a doctor and were diagnosed with tuberculosis.

Diagnosis of TB was kept hidden from family and friends by 70 (41%) patients and 66 (39%) thought that there were less chances of getting married if one was ever infected with tuberculosis. Thirty nine (23%) patients believed that pulmonary tuberculosis could lead to infertility.

Health care workers were the main source of information about tuberculosis in 127 (75%) cases but 81 (50%) patients claimed to have received no counseling by their physicians about how to prevent spread of infection.

Discussion

This study showed that misconceptions regarding tuberculosis were widespread in Pakistani patients. Poor knowledge of TB patients concerning their disease may contribute to the high burden of TB disease in the country.[2] The level of knowledge and awareness about TB is known to correlate with seeking health care and time of presentation.[4,5] By educating the patients and removing their misconceptions, patient compliance with therapy and spread of disease is likely to improve.[6]

Diagnosis of TB was associated with anxiety and sense of isolation. TB patients are exposed to a great deal of ostracism from the community.[7,8] Those infected have fear of social aversion.[2] Such stigmatization of TB patients in the society can lead to reluctance in seeking treatment. In this study, nearly 40% patients did not reveal their disease to their relatives and friends. A majority of patients and their relatives feel that the dishes of TB patients should be kept separate from rest of the family members thus isolating them further from their families. These misconceptions were compounded by the fact that the patients received inadequate education from their physicians; half of patients received no information about ways to prevent the spread of disease. Majority were unaware that TB was not infectious after few weeks of treatment. Many patients felt that preventive measures should be practiced for an indefinite or long period of time.

Despite the fact that these patients were visiting a pulmonary clinic in teaching hospitals, and were on treatment or had received treatment for TB, it could not be assumed that they had received enough insight into their disease. This study has highlighted serious deficiencies in the knowledge of TB patients about their disease. In a similar study from India Singh et al. reported that only 2.3% of their respondents knew that TB was caused by a germ.[8] More than half of the patients in our study were of the opinion that TB may result from stress and emotional trauma and 20% were of the view that treatment can be stopped after control of symptoms. Clinical improvement, unavailability of drugs or cost of drugs were reported to be the main reasons for defaulting treatment in earlier studies.[9,10] Poor drug compliance could contribute multi-drug resistance (MDR) TB in the country.

Another important aspect noted in this study was that more than half of TB patients in Pakistan first presented to their general practitioners in private sector and up to 10% delayed seeking treatment for more than six months after the onset of illness. A person suffering from TB infects an average of 10-15 people in a year and therefore the community should be made aware of TB symptoms and the need for early treatment. Early diagnosis, prompt treatment with compliance are necessary to control the incidence of TB.

Coupled with poor patient knowledge, general practitioners in high burden countries like Pakistan do not have sufficient knowledge on TB therapy. Low compliance with WHO guidelines makes the situation worse.[11,12] The physicians themselves were also prone to myths and misconceptions concerning tuberculosis.[13] It has been shown that the method of diagnosis, treatment and monitoring of treatment carried out by general physicians was not satisfactory.[14] Health care workers face the challenge of changing behaviours in the community to ensure that people with symptoms present early for screening and that people diagnosed as having tuberculosis comply with treatment.[15] Health care workers must also learn about local beliefs that may influence presentation and adherence of patients.[16] Therefore in order to make the TB control programmes effective, not only the communities but also health care providers must be educated.

Diagnosis of tuberculosis is associated with social stigma in many countries. Almost half of the TB patients in our study were of the view that being infected with TB reduced their chances of getting married. Even though 95% knew that TB was treatable, almost 40% claimed they would not marry their children to someone who was currently diseased, or had been infected in the past and has now been cured of tuberculosis. In Ethiopia evil spirit and sexual intercourse have been found to be incriminated as a cause for TB. Their community also exhibits a great deal of ostracism towards TB patients.[7] "Cold" has been cited as a cause of TB in Ethiopia.[9] Belief in an association between HIV and TB has been found in Zambia and Ethiopia.[7,17] Alienation of TB patients has also been found in relatively developed countries like South Africa.[15] In the different communities, different cultural beliefs like tuberculosis resulting from sex after the death of a family member and after a woman has a spontaneous abortion are prevalent. People also believe that the resulting disease can only be treated by traditional healers. There is also a belief in a 'western' type TB that can spread from sufferers or is due to environmental pollution or to smoking or alcohol excesses.[16]

To remove misconceptions about TB community based awareness strategies should be designed, information and education on TB must be disseminated out.[7,8] Studies conducted in Bangladesh, which faces similar social and cultural background, have shown that well conducted community health education campaigns can affect level of knowledge and produce favorable attitudes towards tuberculosis.[18]

In conclusion, poor knowledge and misconceptions concerning tuberculosis are rampant in Pakistani patients. Public awareness programs using the electronic media and literature are crucial in educating the masses and removing misconceptions. TB control program will remain ineffective unless myths and fears of TB patients are addressed simultaneously.

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Is Ministry of Health fully prepared to implement an effective DOTS program in Pakistan? An Operations Research on TB Control Program in the Public Health Sector in Sindh

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Abstract

Purpose of the Study: Pakistan is among the high-burden countries for tuberculosis. One of the fundamental problems in TB control is a high defaulter rate among the registered TB cases in the public sector. In 1999, a cross-sectional study was designed to identify the determinants of low compliance for the TB treatment in two rural districts in Sindh.

Methods: Before the actual data collection, a pilot testing was planned in a secondary level care hospital. Fourteen defaulters for TB treatment were identified but none could be contacted due to incomplete addresses. Other alternatives were explored with the health facility team to reach them including a field-based search through Lady Health Workers of the National Health Program but all endeavors went into vain. The pilot testing propelled us to postpone the cross-sectional study but we continued scrutinizing the follow up problem for TB patients in other health facilities. Not surprisingly, more or less a similar picture was found in those health facilities.

Principal Conclusions: The study concludes that the public health care system in Pakistan lacks even the basic requirements for an effective TB control program, that is, a viable information system and the functional integration of program with rest of the health care delivery system. A DOTS strategy to control TB was initiated in the public sector in Pakistan just one year prior to this study. The Ministry of Health requires re-visiting the program to ensure that the lacunae identified in this study are being taken care of in the current DOTS strategy.

Introduction

Pulmonary Tuberculosis is among the major killer diseases. About one third of the world's population is infected with the disease, 95% of which are in the developing countries and 98% of all TB related deaths occur in these regions. The burden of TB is greater in adults, more than three-quarters of cases occur in the 15-59 age groups.[1] Situation in Pakistan is not different from that in other developing countries. In Pakistan, an estimated 260,000 new cases occur annually and more than 50,000 individuals die due to TB.[2] With a very high defaulter rate for the completion of TB treatment, the incompletely cured patients return to the community to further infect 10-14 people in the course of a year. R. Liefooghe[3] et al. cited results of a follow up of 3950 TB patients, registered in Bethania Hospital Sialkot, Pakistan between January 1988 and December 1990. The study revealed that 72% of the patients did not complete their prescribed treatment course. Tuberculosis is a disease which requires not only uninterrupted long-term treatment but also, continuous monitoring of the patients in order to ensure treatment compliance. Non-availability of drugs, financial and physical accessibility to the health centers and a lack of awareness regarding consequences of incomplete treatment are the known causes for low compliance for the TB treatment. Inconsistent treatment policy with poorly managed, under funded and incorrectly conceptualized TB control programs are the added factors.[4] Non-compliance of a course can lead to relapse, possibly

with drug-resistant bacilli.[5] A larger part of the resources within developing countries is likely to be used in near future for diagnosis and treatment of TB, thus rendering it a growing economic and financial burden.[6]

Control of tuberculosis is often given as a classical example of a public health activity that is important for the whole society and in which it is appropriate for the state to play a dominant role.[7] WHO recommends that each country should analyze treatment results through cohort studies based on a national recording and reporting system? Data obtained from the Department of Health (DoH), Sindh (Table 1)[8] depicts the seriousness of the problem in the public sector, showing a very high percentage of defaulters of all diagnosed registered TB cases, ranging from 45% in 1999 to 79% in 1997. It is better to understand the dynamics involved in this dismal situation. A descriptive study was therefore planned in 1999, in order to: 1) identify and contact defaulters for TB treatment, registered at the government health facilities. 2) find out the reasons for low compliance for the treatment and, 3) determine the present status of treatment and the disease among the identified defaulters.

Table 1: Summary of treatment outcome for TB patients in Sindh, during 1995-99.

	1995	1997	1998	1999
Registered Patients	524545	41959	27470	76408
Regular Patients	167727	8911	12185	42241
Defaulters	356818	33040	15285	34167
	(68%)	(79%)	(56%)	(45%)
Cured	9386	4213	5469	8470
Deaths	48	122	72	151

Source: Directorate Tuberculosis Control, Department of Health, Sindh, Hyderabad, 1999.

A provincial directorate of TB control manages the National TB Control Program (NTP) in Sindh. The office of the directorate is situated at Hyderabad. A district TB Coordinator oversees the program in each district. The program is part of an overall provincial and district health system but operates as a vertical program, parallel to the existing health services through their TB clinics and microscopy centers. There are 161 TB clinics and 108 microscopy centers in Sindh.[9] The program has its own information system. The information gathered at the facility level is sent to the District TB Coordinator who compiles the report and forward it to the Director, TB control.

Methods and Results

Study design and study population

A descriptive study was designed to evaluate defaulters for the TB treatment at the government health facilities in Sindh. Districts Mirpurkhas and Khairpur, reporting the highest number of defaulters in 1998 (637 and 3116 respectively),[8] were selected for the study. Based on the TB defaulter rates for 1999, a sample size of 400 was calculated.

In order to obtain the concurrence of the Directorate TB Control and also to involve them in the study, several meetings were held with the program director and his team at Hyderabad. A pilot testing was planned to enhance the internal validity of the data collection tools and also to examine logistical requirements and the feasibility in the field. Taluka Hospital at Tando Allahyar in Hyderabad district was chosen for this purpose to make it convenient for the Director TB control and his team to participate in the study.

Data collection

The study data was planned to collect identified defaulters using a structured questionnaire. Besides socio-economic and demographic variables, the questionnaire included specific variables such as: history of TB treatment at the government health facility, method of diagnosis, type and duration of treatment and reasons for discontinuation of treatment. To assess the current status of the disease, collection of three consecutive sputum smears according to the WHO guidelines, was also planned.

Pilot Testing

The pilot testing was planned to identify the defaulters for TB treatment who were registered at the Taluka Hospital Tando Allahyar in Hyderabad district from June 1998 to June 1999. Initial visits were paid to the health facility to develop rapport with the health facility team and also to give them an orientation about the study. The Director of the TB control program and his assistant also accompanied the principal investigator.

Available records were reviewed to identify TB treatment defaulters. Fourteen defaulters were identified through the TB register during the period June 1998 to June 1999. They could not be treated due to their incomplete addresses. Other alternatives were explored with the health facility team to reach the defaulters. Lady Health Workers (LHWs) of Prime Minister's Program, now called as National Program for Primary Health Care and Family Planning, were considered to be the best option to reach them*. Around 40 LHWs were contacted and requested to find the reported defaulters. Again with the incomplete addresses none of the 14 defaulters could be identified. With this frustrating situation, another compromising strategy was applied. All 40 LHWs were asked to provide addresses of all TB cases known to them in their catchment area, in a

hope to find defaulters for the government health facilities from their lists. Of 110 TB patients identified by the LHWs, 16 were reported to have discontinued their treatment before the completion of the advised course. Among those, 12 were available for the interview and the collection of their sputum smear. None of them had ever registered or received any treatment for tuberculosis in a government health facility. Mean age of the identified defaulters was 39.4 with a range between 25 and 54 years. Six were males and 6 females. Sputum specimens were sent to the collection point of Aga Khan Hospital's laboratory at Hyderabad, and the final examination was done at AKUH's main laboratory at Karachi. No sputum was reported positive for acid-fast bacilli.

Further exploration after the pilot testing

The whole exercise appeared a futile one. It was concluded that further efforts to pursue with the same strategies would produce no results in the proposed study sites viz. Mirpurkhas and Khairpur. This pilot testing however brought up some very important operational issues and problems attached with the health care delivery system in the public sector. The most apparent and important finding was an inefficient health management information system for the TB control program. In a seminar, held in Cotonou, Benin, organized by the International Union Against Tuberculosis and Lung Diseases, it was stressed that a good notification system is a key element for the success of National Tuberculosis Programs (NTPs).[10] A valid and credible information system is a pre-requisite for instituting an effective decision-making process. Owing to the importance of this area for TB management, we shifted the focus of our study to further explore the issue of proper registration of TB cases in other health facilities in the province.

Pursuing further, we visited five more health care facilities in Hyderabad, Dadu and Badin districts (Table 2) to assess the TB management information system and its role in the follow-up of registered TB cases. Of five health facilities visited, one had discontinued its TB clinic due to non-availability of a medical officer and irregular supply of anti-TB drugs. Rest of the health facilities had the same problem of inadequate addresses of the registered TB patients. One medical officer explained that he had good relationships with two local General Practitioners (GPs) and that they always helped him find the TB cases whenever needed for follow up. He further explained that since there was no formal setting of households in the rural areas with proper addresses, one has to find and live with such kind of alternate arrangements. However, on request to demonstrate such mechanism, he regretted that two GPs were only available in the evening time at their clinics. In one health facility, we did not find a single defaulter for the TB treatment during the whole calendar year, an unexpected and startling finding despite incomplete addresses in the TB register. The TB medical officer explained that this was made possible only due to his personal efforts. He further claimed that being a local doctor he knew the whole catchments population of his health facility. He, however, clarified that patients who came from areas outside the catchment area of his health facility, were not labeled as defaulters if they were lost during the course of treatment. The other two health facilities also portrayed a similar picture with inadequate addresses, no follow-up mechanism, shortage of anti-TB drugs, and non-availability of properly trained personnel for TB management.

Table 2: List of health facilities in three districts visited after the pilot study.

Location of health facilities	Type of health facility	District
Kotri	Taluka Headquarter hospital	Dadu
Talher	Rural health center	Badin
Nassar Pur	Rural health center	Hyderabad
Tando Jam	Rural health center	Hyderabad
Chumber	Rural health center	Hyderabad

Conclusion and Recommendations

A flawed assumption of tracing TB treatment defaulters using the existing information system led to premature cessation of the study during the pilot phase. However, this pilot testing followed by a brief operations research has identified certain important operational problems that render the delivery of TB control program less effective. The most striking discovery was the lack of any meaningful management information system, which can facilitate any follow up of patients. Moreover, there was a serious lack of integration of the TB control Program with the rest of the available health care services, particularly with the field-based Lady Health Workers' National Health Program. These findings indicate that the public sector health care delivery system in Pakistan lacks even the most fundamental elements of an effective health care system.

A DOTS strategy is being implemented in Pakistan under the revised National Tuberculosis Control Program (NTP). DOTS expansion began in earnest after 2000 when the government rehabilitated provincial TB programs through World Bank's Social Action Program Project II.[11] This small-scale operations research was conducted just one year prior to the country-wide launching of DOTS program. The findings thus have several implications for an effective DOTS strategy in the country. The ambitious target of achieving 100% DOTS coverage by the year 2003 requires the Ministry of Health to revisit current DOTS strategy in order to assess the role of Lady Health Workers, the local

communities and the General Practitioners in TB case finding, and the use of information system for monitoring the program activities. The existing Health Management Information System in the public sector has tremendous potential to deliver health services more effectively. Its proper utilization in decision-making can improve the quality of collected data. Just recording the complete address of the registered TB patient would greatly facilitate follow-up to ensure completion of the prescribed treatment regimen.

In conclusion, we take this unfinished study as an opportunity to highlight the basic requirements for rendering the TB control program more effective in Pakistan. A reliable health management information system and the functional integration of DOTS program are the important prerequisites to promote an effective decision-making and implementation process. A very good infrastructure is available in the public health system in Pakistan that requires some in-depth inquiry to identify under-lying factors and the means to further strengthen its functional structure.

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New drugs in resistant tuberculosis

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Abstract

The World Health Organization estimates that up to 50 million persons worldwide may be infected with drug resistant strains of TB. The fatality rate of MDR-TB is 20-80%.

Drug resistant tuberculosis cases are on the rise in Pakistan. The reasons for this menace are multiple including improper prescription, compliance and over the counter sale of anti-TB drugs. The treatment cost of drug-resistant TB is high, both to the individual patient and society.

This article is written to create awareness about the available second line drugs and those in the pipeline. Considering the fact that resistant tuberculosis is difficult to manage, it is suggested that these drugs should only be used after consultation with a physician experienced in the treatment of drug resistant TB. The most frequent mistake made by treating physicians is addition of one drug in the failing regimen.

At present, 27 potential anti-TB drugs are at various stages of development. The aim is that by 2010 at least one of these molecules completes the journey and should come in the market.

Introduction

Tuberculosis infects one third of world population and every 15 second one patient dies of TB. Tuberculosis takes global economic burden of $12 billion a year. During the last thirty years no new anti-tuberculosis drug has been introduced for clinical use. Now research is on going for developing new drugs in this field. There is a great need to

win the war against tuberculosis. Some of the drugs have been very effective against Mycobacterium Tuberculosis like Rifamycin derivatives, combination of betalactum inhibitor and betalactum agents and fluoroquinolones. The purpose of this article is to discuss new emerging drugs and their efficacy in the treatment of tuberculosis.

New Anti-Tuberculosis Drugs

Rifamycin derivatives: The rifamycins are a group of antibiotics, which are synthesized either naturally by the bacterium Amycolatopsis mediterranei, or artificially. Rifamycin acts by binding specifically to the ß-subunit of bacterial DNA-dependent RNA-Polymerase, RpoB.[1] Rifamycins are particularly effective against mycobacteria, and are therefore used to treat tuberculosis, leprosy and mycobacterium avium complex (MAC) infections.

The rifamycin group includes the following drugs:

* Rifamycin A, B, C, D, etc. (the "classic" rifamycin drug)
* Rifampicin
* Rifabutin: an orally active, semi synthetic antibiotic which is derived from Rifamycin S. It is used for the prevention of disseminated Mycobacterium avium complex.
* Rifamide: a derivative of Rifamycin B is used against gram-positive cocci causing respiratory tract infections and against gram-negative and gram-positive organisms in biliary tract infections.
* Rifapentine: has a longer half-life than Rifampin and is similar to it.

Rifabutin

Rifabutin is a semisynthetic spiropiperidyl derivative. Rifabutin inhibit mycobacterial RNA polymerase like Rifampicin. Its activity is better against Mycobacterium Avium Complex (MAC). This lipophilic drug after absorption from the GI tract is eliminated in the urine and bile. In patients with renal impairment dose adjustment is not needed. It has been shown that Rifampicin sensitive M. tuberculosis strains were also sensitive against Rifabutin and about one third Rifampicin resistant strains still sensitive to Rifabutin.[2]

Therapeutic uses: It is effective for the prevention of MAC infection in HIV-infected individuals. At 300 mg/day, it decreases the frequency of MAC bacteremia by 50%. Rifabutin is commonly substituted for Rifampicin in the treatment of tuberculosis in HIV-infected patients due to its less profound interaction with indinavir and nelfinavir.[3] In combination with clarithromycin and ethambutol, it is also used in the treatment of MAC disease.

Side effects: Rifabutin is generally well tolerated. Reported side effects when used in HIV patients are rash (4%), GI upset (3%), and neutropenia (2%).

There is a need to evaluate Rifabutin in randomized controlled trials for the treatment of new smear positive pulmonary tuberculosis and MAC pulmonary disease. Its long half-life suggests that it would be useful in intermittent therapy. It is suggested that before such trials are initiated, it is important to determine the optimal dose, lest failure to show effect be attributed to a sub therapeutic dose. It is imperative that controlled studies of various drug regimens that contain higher doses of Rifabutin be undertaken for the treatment of patients with disseminated MAC disease and AIDS.

Rifapentine

Rifapentine is a semi synthetic Ansamycin antibiotic similar in structure to Rifampin. The in vitro activity of Rifapentine is 2-4 times that of Rifampicin against a variety of clinical mycobacterial isolates. Rifapentine is bactericidal against actively growing bacilli, with a rate of killing similar to that documented for Rifampicin. Rifapentine half-life is ~4-fold greater in humans than Rifampicin. The prolonged elimination half-life of Rifapentine is likely due to its higher lipophilicity, which facilitates tissue penetration of the drug and lack of biotransformation to antimicrobially inactive metabolites.[4] Absorption is enhanced when the drug is taken after a meal.

Mode of action: Rifapentine inhibits DNA-dependent RNA polymerase activity in susceptible microorganisms. Specifically, these antibiotics interact with bacterial RNA polymerase interfering with initiation of biosynthesis but not elongation. The mammalian enzyme is unaffected by the Rifamycins.

Uses: Rifapentine is approved for the treatment of pulmonary tuberculosis in combination with other effective antituberculosis drugs. Initial results of a study[5] of Rifapentine in tubercular patients, indicated comparable efficacy with Rifampin in producing negative sputum cultures for M. tuberculosis. Higher relapse rates were reported in the Rifapentine-treated group (10%) than the Rifampin-treated group (5%) during follow-up.

In a TRC study[6], of 103 strains of M. tuberculosis tested, 52 strains were sensitive to both. The remaining 51 strains resistant to Rifampicin were also resistant to Rifapentine, indicating complete cross- resistance. It was interesting to note that among sensitive strains Rifapentine has a 2 to 16 fold higher activity than Rifampicin.

The results of Rifapentine in pulmonary TB with HIV are disappointing. A randomized trial[4] compared Isoniazid / Rifapentine (600mg once a week) with Isoniazid

/ Rifampicin (600mg twice weekly) in 71 HIV-positive people with TB. Four people on Rifapentine developed drug resistance compared with none of the Rifampicin group. The author was of the opinion that the once weekly Rifapentine / Isoniazid should not be used among people with HIV.

Adverse Reactions: The adverse reaction profile of Rifapentine is similar to that of other Rifamycin antibiotics. Rifapentine is an inducer of cytochromes P450 3A4 and P450 2C8/9 isoforms and may increase the metabolism of other drugs that are metabolized by these enzymes.

Dosage/administration: During intensive phase 600 mg with an interval of not less than three days between doses is continued for two months. Rifapentine may be given with food if stomach upset, nausea or vomiting occurs. During continuation phase, treatment is continued once weekly for four months in combination with Isoniazid or an appropriate agent for susceptible organisms.

Fluoroquinolones

Fluoroquinolones(FRQs) have bactericidal activity against M. tuberculosis.

FRQs inhibit the gyrase, an enzyme involved in DNA replication.[7] There is no cross resistance between these agents and other antituberculosis drugs. Ofloxacin, Ciprofloxacin, Lomifloxacin, levofloxacin, sparfloxacin and Moxifloxacin have shown activity against M. tuberculosis.

Ofloxacin

Ofloxacin is a bactericidal drug. It is active in vitro against M.tuberculosis as well as against M. kansasii, M. xenopi, M. fortuitutum, and M. marinum. Mycobacterium avium and most strains of M. chelonei are resistant to ofloxacin.

Natural resistance to Ofloxacin appeared to occur in about 1 in 105 organisms, a proportion similar to that for other drugs.[8]

The MIC for Ofloxacin is less than 4 mg/l and after normal oral dose of Ofloxacin peak serum level attained is 10.7 mg/l, which is quite high.

Uses: Ofloxacin has an excellent activity against M. tuberculosis in clinical investigations. In a recently reported study from Hong Kong[9], use of Ofloxacin in MDR TB patients was associated with favorable outcome. The author concluded that the presence of cavitation, resistance to Ofloxacin in vitro and poor adherence emerged as variables significantly associated with adverse outcomes.

Levofloxacin

It is less neurotoxic than Ofloxacin.[10] Its efficacy against M. tuberculosis is proven in clinical trials. One of the studies concluded that levofloxacin-containing regimen resulted in a similar rate of adverse events compared with conventional first-line regimens when used for treatment of active tuberculosis.[11]

Ciprofloxacin

Ciprofloxacin[12] is active against all strains of M. tuberculosis sensitive to Streptomycin, INH, Rifampicin, and Ethambutol and inhibited almost all strains showing intermediate sensitivity or resistance to one or more of the above agents. Nearly all isolates, including atypical one were inhibited at a concentration of 3.2 mg/1. Efficacy of Ciprofloxacin is proven in clinical trials.[13] Other fluoroquinolones like Lomifloxacin and Sparfloxacin have also shown efficacy in appropriate clinical settings.

Moxifloxacin

ATS guidelines[14] stress that among the new fluoroquinolones, Moxifloxacin appears to be the most promising in the treatment of resistant tuberculosis. In an experimental study, Lounis[15] proved that addition of Moxifloxacin as a companion drug provide better protection against development of drug resistance.

The most potent of the currently available FQNs in descending order of in vitro activity against M. tuberculosis are moxifloxacin, gatifloxacin, levofloxacin, ofloxacin, and ciprofloxacin.[16]

Co-amoxyclav

Amoxicillin is a semi synthetic beta-lactam antibiotic, with a broad spectrum of bactericidal activity against many gram-positive and gram-negative microorganisms. The addition of a beta-lactamase inhibitor to amoxicillin greatly improves its in vitro activity against M. tuberculosis.[17] The beta-lactam inhibitors (i.e., clavulanic acid) possess no intrinsic antimycobacterial activity, but they are able to inhibit the enzyme in part responsible for the resistance of M. tuberculosis to beta-lactam antibiotics. There are no in-vivo studies using this drug combination against M. tuberculosis. Beta-lactam antibiotics penetrate poorly into mammalian cells, and this characteristic may limit the effectiveness of these agents in therapy for tuberculosis.

Tuberactinomycin

Tuberactinomycin[18] (Enviomycin) resembles Viomycin structurally as well as in its mode of action. It acts by inhibiting protein synthesis.

Tuberactinomycin containing regimens have shown good clinical response.[19] Negative sputum culture at six

months ranged from 73% to 80% in the Tuberactinomycin containing regimens compared to 63% in a similar Viomycin containing regimen. In advanced cases, this ranged from 67% to 76% in the Tuberactinomycin containing regimens compared to 59% in the Viomycin containing regimen. Thus Tuberactinomycin was better than Viomycin.

Clarithromycin

The second generation macrolide, Clarithromycin, is effective against Mycobacterium avium-complex, and other NTM (Non-tubercular mycobacteria) including M. paratuberculosis.[12] It is also recommended in the treatment of infections caused by Mycobacterium marinum and Mycobacterium fortuitum complex. It has been shown to cause a reduction in the bacillary load and clinical improvement of M. avium disease in AIDS patients.[20]

Amikacin

Amikacin[21], an aminoglycoside, is highly bactericidal against M. tuberculosis. It is given five days a week in a dose of 15 mg/kg/day as a single dose, usually by intramuscular injection. The major side effect of Amikacin is nephrotoxicity and vestibular damage. Hearing loss, hypocalcaemia, hypokalaemia and hypomagnesaemia are other side effects. In comparison to kanamycin, it is less ototoxic and less painful.

Capreomycin

Capreomycin[21] is an aminoglycoside which is bactericidal against M. tuberculosis. It is given in a dose of 15 mg/kg/day intramuscularly with maximum of 1 Gram. It is toxic to the eighth cranial nerve, causing high frequency hearing loss in 3.2 to 9.4% of patients before vestibular dysfunction occurs. Renal toxicity is somewhat more common with Capreomycin than with streptomycin, and it may be associated with electrolyte disturbances secondary to tubular damage. It is suggested that in elderly patients when there is similar susceptibility to Capreomycin and Amikacin, Capreomycin should be used since older patients seem to experience more renal and ototoxic effects with Amikacin than with Capreomycin.

Clofazimine

Clofazimine[21] is a substituted iminophenazine bright-red dye that inhibits mycobacterial growth and binds preferentially to mycobacterial DNA causing inhibition of transcription. The MlCs of clofazimine against M. tuberculosis have not been published.

Adverse reactions include discolouration of the skin, gastrointestinal upset, severe and life-threatening abdominal pain and organ damage caused by clofazimine crystal deposition, and asymptomatic discolouration of the eye.

Potential compounds of the future

Nitroimidazopyran

A series of new compounds containing a nitroimidazopyran nucleus that possess antitubercular activity has been reported.[22] This compound is related to metronidazole. It seems that it will be available in future for clinical evaluation. After activation by a mechanism dependent on M. tuberculosis F420 cofactor, nitroimidazopyran inhibited the synthesis of protein and cell wall lipid. In contrast to current antitubercular drugs, nitroimidazopyrans exhibited bactericidal activity against both replicating and static M. tuberculosis. Lead compound PA-824 showed potent bactericidal activity against multi-drug resistant M. tuberculosis and promising oral activity in animal infection models.

The nitroimidazopyran compound PA-824 has bactericidal activity comparable to that of INH. However, additional preclinical evaluation of PA-824 is needed before clinical studies could begin.

Oxazolidinones

Oxazolidinones (eperezolid and linezolid) are an appealing class of antimicrobials due to their unique bacteriostatic mechanism of action, lack of cross-resistance with other agents, good oral bioavailability, potential for structural manipulation, and broad spectrum of activity. The mechanism of action appears to be the ability to inhibit protein synthesis by binding to the 50S subunit and preventing the 30S complex from forming the 70S complex, resulting in inhibition of translation.[23] Eperezolid and linezolid were shown to have activity against a wide variety of organisms, including gram-positive cocci, gram-negative anaerobes, and mycobacteria. Due to their predominantly gram-positive activity, these agents were compared to vancomycin, penicillins, macrolides, minocycline, and similar antibiotics.[23] Linezolid have shown activity against M. tuberculosis in a murine model.[24]

Linezolid appear to be well tolerated when given both orally and parenterally. Drug related adverse events[25] occurred in 32.7% of patients, which were mild to moderate in severity and which resolve on discontinuation of therapy. They were nausea (5.4%), diarrhoea (5.2%), tongue discolouration (2.5%), oral thrush (2.3%), taste perversion (2.3%) and headache (2.3%). Thrombocytopenia (2.4%) is related to duration of therapy.

Role of surgery: Recently few studies on the role of surgery emerged as a light of hope in the management of difficult to treat pulmonary tuberculosis. Pomerantz BJ[26] reported in his patients with severe drug resistance (about 5 drugs) benefited from the resection of cavitary or badly damaged lung tissue when compared with historical control.

A recent study[27] concluded that the use of resection lung surgery was associated with overall improved outcome in patients with highly resistant MDR-TB, with a trend toward improvement for those taking fluoroquinolone antibiotics.

It is hoped that in future we will have more data on the role of surgery but it is a disease, which can be managed medically, and surgery is the last hope as an adjuvant not as sole mode of treatment.

Immunotherapy for tuberculosis

Mycobacterium vaccae

M. Vaccae is found in the soil, first described in a study from Uganda. It was found that prior sensitization of animals with M. vaccae could optimize the protective effect of subsequently administered BCG vaccine.[28] A single intradermal injection of 0.1 ml suspension of dead M. vaccae containing 109 bacilli is administered a week or more after starting effective chemotherapy. Following effects have been noted: weight gain, rapid clearance of tubercular bacilli from sputum and decrease ESR.[29]

Further work is needed to evaluate the role of M. vaccae in the management of tuberculosis.

Interleukin-2

It is believed that immunity against M. tuberculosis is mediated by T-lymphocytes that produce the type 1 (Th1) helper T cell cytokines IFN and interleukin (IL)-2.[30] In TB patients, Th1 cytokines predominate at the site of disease, but the systemic immune response in peripheral blood is characterized by enhanced production of the type 2 (Th2) helper T cell cytokine IL-4, and by reduced secretion of IFN and IL-2 by peripheral blood T cells.[31] The systemic Th1 response in TB patient is low which inclined researchers to use IL-2 as an immunotherapeutic adjunct to treat tuberculosis. IL-2 strongly induces IFN and is a potent growth factor for CD4+ and CD8+ T cells, both of which contribute to immunity against tuberculosis.[30]. Furthermore, IL-2 stimulates expansion and enhanced functional capacity of natural killer cells, which can eliminate intracellular M. tuberculosis.[32]

Rapid sputum conversion was noted in a pilot study from Bangladesh and South Africa, in which intradermal IL-2 (225, 000 IU) twice daily was used during the first month of TB therapy as an adjuvant.[33] A later randomized trial in South Africa comparing daily and pulsed IL-2 with placebo in MDR TB found improved sputum clearance with daily treatment.[34] A recent study[35] concluded that IL-2 did not enhance bacillary clearance or improvement in symptoms in human immunodeficiency virus-seronegative adults with drug-susceptible tuberculosis.

It seems that we have again gone into an era similar to that of early forties when no cure for tuberculosis was available and only hope was fresh air, rest, good diet and sunlight. The present era when anti-TB drugs are available, is more dangerous because of the development of MDR tuberculosis due to irregular use of ATT, problems in implementation of effective TB control programme in many countries, over the counter sale of ATT and others. It is hoped that effective implementation of TB control programme under DOTS strategy, awareness of the mass as well as the health care providers about tuberculosis, judicious use of presently available medication, and control over the counter sale of ATT would have an impact on the control of MDR menace of tuberculosis.

Recently WHO published current drugs in pipeline for the resistant tuberculosis.[36] Diarylquinoline TMC207 is bactericidal, and is currently in phase-IIa clinical trial. Pyrrole LL-3858 is active against drug sensitive mycobacteria and currently in phase-I clinical trial. Other promising drugs are Pleuromutilins, Didiperidine SQ-609, ATP Synthetase Inhibitor FAS20013 (FASgene), Translocase I Inhibitor, InhA Inhibitors and Isocitrate Lyase Inhibitors.

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Adherence of Private Practitioners with the National Tuberculosis Treatment Guidelines in Pakistan: A survey report

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Abstract

Objective: In Pakistan, over 80% of the patients suffering from TB consult a private practitioner for the initial evaluation. A cross-sectional survey was conducted in seven thickly populated urban communities of Rawalpindi district to evaluate the adherence of private practitioners with TB treatment guidelines as laid down by National Tuberculosis Control Programme (NTP) in Pakistan. The data was collected over 30 days.

Methods: A young lean man was simulated to act as a TB patient and was provided with a chest X-ray suggestive of TB and two Acid-Fast Bacilli (AFB) positive sputum reports. Only those prescriptions were included for analysis which either had recognized the patient having TB or had any TB drug written in the prescription.

Results: A total of 77 practitioners were visited. Prescriptions of 53 general practitioners fulfilled the inclusion criteria and were analyzed. Only 2 (3.7%) prescriptions out of 53 met the required standard for TB patients as laid down by NTP. Eighty three percent (n = 44) favored a combination drug for the treatment while the rest preferred individual preparations.

Conclusion: The study reflects the lack of knowledge about standardized TB treatment protocols amongst the private practitioners in Pakistan. Public Private Partnerships between government public health departments and non-governmental organizations working in public health can be a valuable tool in generating mass awareness campaigns.

Introduction

Tuberculosis (TB) is a major public health problem and according to World Health Organization, (WHO) Pakistan ranks 6th in the countries having high disease burden.[1] It contributes 26% of avoidable deaths among adults and children in Pakistan.[2] The present annual incidence of open TB cases is between 85-100/100,000 persons and about 361,000 new cases of TB are added every year in Pakistan.[3]

The International Union against Tuberculosis and Lung Disease has estimated tuberculosis to be the cause of one death every 10 seconds worldwide.[4] Four out of 5 TB patients in Pakistan still remain undetected, untreated and inadequately managed.[5] Lack of proper diagnostic equipment and skills, irrational prescriptions and non-availability of essential anti TB drugs are among the major contributing factors of various complications including emerging resistance. Multi Drug Resistant (MDR) TB is a major cause of high costs, mortality and longer duration of treatment. A simple TB case management incurs a cost of 3600 rupees for the treatment of 9 months while a MDR TB case, which requires treatment for 2 years, costs about 250,000 rupees.[6]

Tuberculosis control in Pakistan is primarily the responsibility of the government sector, which has not been fulfilled for years. In Pakistan, over 80% of the patients suffering from TB consult a private practitioner for the initial evaluation.[7] it is important to know the prescribing habits of these doctors. Various national studies on the issue have shown poor knowledge and prescribing behavior in prescribers.[8-10]

In order to standardize the TB management in our country National TB control Program (NTP) introduced guidelines in 1995 which were revised in April 1999 containing diagnosis and treatment modalities for TB. This study was conducted to evaluate the adherence of private practitioners with TB treatment guidelines as laid down by NTP in Pakistan.[11,12]

Subjects and Methods

A cross-sectional survey was conducted in seven thickly populated urban communities of Rawalpindi district. The study population comprised of private practitioners in these areas and from each such area 10 practitioners were selected at random. A total of 77 practitioners were visited, over 30 days. A young lean man was trained to act as a TB patient and was provided with a chest X-ray suggestive of TB and two Acid-Fast Bacilli (AFB) positive sputum reports. These positive investigation reports were given to him so that he did not had to undergo investigations each

time to get prescriptions from the doctors. The patient was trained by anticipating the general questions which he could come across during his encounter with the doctor (Annexure I). Prescriptions generated as a result of the simulated encounters were analyzed for the purpose of the study. Only those prescriptions were included for analysis which either had recognized the patient having TB or had any TB drug written in the prescription. The practitioners who were not qualified MBBS doctors, who did not write any prescription or who prescribed treatment other than TB were excluded from the study.

A standard prescription from a specialist doctor was obtained for comparison, which followed national TB control program guidelines and was validated by the National Guidelines for Tuberculosis Control in Pakistan (NTP). The prescriptions of 53 General Practitioners fulfilled the criteria and were analyzed. Data collected was entered on computer software and simple analysis was carried out including percentages, means and averages.

Patient Presentation

A young lean man of 25 years age presents in front of the doctor with the case history of 2-3 months lethargy, low grade intermittent fever with spiking in the evening, loss of appetite, weight loss and 4 weeks cough with yellowish sputum usually, but brownish at times. The temperature if noted was always between 100-100.50 F. He feels that he is becoming weak. He is living with his 7 member family in a small flat in a poor sector of the city. He did not receive any TB treatment as yet. He is working as a sales man at a garments shop and on the suggestion of a regular customer (who was a doctor) he got his chest x-ray and sputum test done.

Results

The majority of doctors interviewed were males (92.5%). Four (7.5%) practitioners were also working in the government sector in addition to private practice. General practitioners constituted 85% (n=45) of the practitioners, whereas 3.7 (n=3) were specialists, 9.3% (n=5) did not mention their status.

The patient record on the prescriptions showed that age, weight and family history was recorded by 83% (n=44), 18.9% (n=10) and 5.7% (n=3) respectively. Signs and symptoms were described in only 13.2% (n=7) of prescriptions, 17% (n=9) demanded further laboratory investigations (Table 1). Only 24.5% (n=13) asked the patient to come for a follow-up and advised a date. Interestingly not a single prescriber mentioned any categorization of the disease as desired by NTP guidelines or kept patient records.

Only 2 (3.7%) of prescriptions out of 53 met the required standard for TB patients as laid down by NTP.

Table 1:

Any type of investigations requested	17.0% (n=9)
Blood CP	11.3% (n=6)
Liver function tests	5.7% (n=3)
X-ray chest	7.5% (n=4
Sputum smear for AFB	1.9% (n=1)
ESR	11.3% (n=6)

Eighty three percent (n = 44) favored a combination drug for the treatment while the rest preferred individual preparations. Pyridoxine, an important supplement of the treatment was correctly prescribed by only 2 doctors (3.8%) (Table 2). None of the doctors prescribing individual

Table 2:

Doctors prescribing Fixed dose combination	**83%**	**(n=44)**
Correct dose given	43.18%	(n=19/44)
Correct dose timing	59.09%	(n=26/44)
Correct duration of therapy	43.18%	(n=19/44)
Doctors prescribing Individual drugs	**17%**	**(n=9**
Correct dose given	0%	(n=0/9)
Correct dose timing	0%	(n=0/9)
Correct duration of therapy	0%	(n=0/9)
Doctors prescribing pyridoxine	**47.16%**	**(n=25/53)**
Correct dose given	3.8%	(n=2/53)
Correct dose timing	26.4%	(n=14/53)

preparations could prescribe correctly. Seventy percent of prescriptions also contained medicines other than those required for treating newly diagnosed TB case. These include brands of ciprofloxacin, doxycycline and clarithromycin.

Discussion

This study in Pakistan is the first ever study that has used a simulated subject as a patient. The advantage of a simulated patient was that same pathophysiological parameters were presented to every prescriber in the study. The rehearsal of anticipated questions to the patient also helped in presenting essentially same qualitative history to every prescriber, without having any obligation of treatment of the subject or any change of patient parameters during the study period.

This study reflects the situation in only one geographical area of the country however comparison of results with other studies on prescribing behaviors show similar situation and this can be used as an indicator of current situation with regards to National Tuberculosis Control Programme in Pakistan, that essentially is based on WHO guidelines.

The National TB Control Programme (NTP) in Pakistan was the result of WHO's emergency call to fight the onslaught of TB in 1993, years after previously formed National Tuberculosis Control Board was liquidated due to inadequate functioning. The NTP produced first set of national guidelines for treatment of tuberculosis in 1995 that were revised again in 1999. There has never been any mechanism for disseminating these guidelines to private practitioners, even to those working in government institutions. The NTP also adopted DOTS strategy to combat ever increasing disease burden in 1994, it has taken nine years for NTP to launch DOTS in 75% of districts of the country that too only in the government owned allopathic treatment centres, without any facilitative systems that could link up with private practitioners.

Private healthcare system in Pakistan consists of majority of General Practitioners (GPs) who work exclusively in their privately owned clinical or hospital setups, however a number of doctors working in government managed healthcare setups also practice privately in their off hours. A considerable number of public sector paramedics, although legally not entitled, work privately in parallel with registered physicians in their off hours. We studied a cross section of different settings of private practice in the seven most populated regions of Rawalpindi city. It was expected that we'll come across a few of these paramedics that were to be excluded from the study.

The prescribing patterns of doctors in this survey as well as in previous similar studies conducted show that inappropriate prescribing is common amongst GPs. Prescription analysis at a private teaching hospital in Karachi showed that on an average, 53% dosages were written correctly and not more than 79% doctors resorted to the recommended four drug regimen of RHZE.[13] Another KAP survey of family physicians done in Karachi revealed that of the 39% doctors resorting to four drug regimen, only 7.3% could write the correct dosages.[14] Similar findings could be quoted from studies done in Maharashtra India, where results of one study gave 71% wrong prescriptions amongst postgraduates[15] and another indicated 79 different prescriptions among 122 practitioners.[16]

Having 3% correct results reflects the quality of healthcare system in Pakistan in combating TB. These results also show the lack of effective collaboration between the private sector and the National TB Control Programme. The prescribing behaviour also indicates that the private practitioners are not receiving continuing education and training on TB case management guidelines. The effects of such prescribing behavior can be interpreted in terms of its negative effects of ineffective treatment, non-compliance and emergence of drug resistance.

It is suggested that NTP guidelines should be widely disseminated. Public private partnerships between

government health departments and non-governmental organisations working in public health can be a valuable tool in generating mass awareness campaigns, to fill the gaps and to effectively utilize the existing public health infrastructure.

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The Dynamics of Tuberculosis Treatment Adherence

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Abstract

Aims: To establish various factors that affect TB treatment adherence over time.

Design/Setting: Semi-structured questionnaire. All newly diagnosed cases of TB at Bethamia Hospital, Sialkot were interviewed at the beginning of treatment, one month of therapy and at the end of intensive phase.

Results: Perception of TB as a stigmatizing disease was found related to early defaulting and to a lesser degree to late defaulting. Knowledge of TB in itself did not have a clear impact on defaulting, but the attitude towards interruption of treatment did. The strongest risk factor is irregularity of drug intake and appointment keeping.

Conclusion: Strategies to improve treatment adherence should concentrate on methods to increase patients motivation for treatment.

Introduction

Low adherence to the treatment regimen has been of the recognized as a major threat for tuberculosis (TB) control program.[1] A successful treatment plan consist of the daily intake of a combination of drugs for a period of 6 to 9 months. TB patients obviously face many constraints in order to adhere to this treatment. To gain a better understanding of the process of treatment adherence it is necessary to identify its determination factors and especially those that are vulnerable to change.

The majority of studies have concentrated on socioeconomics factors such as age, gender, education, occupation, travel distance or knowledge of TB.[2-5] Other important behavioral factors described in more recent health behaviour models[6,7] such as intention to comply; perceived barriers to TB treatment; attitudes towards the treatment and social support, are often overlooked. TB is a major cause of ill health in Pakistan.[8] Several studies documented the problem of low treatment adherence.[9-11]

Others have shown that behavioral factors,[12] including social stigma,[13] contribute to non-adherence.

This study was carried out in Bethania Hospital (BH), Sialkot. Annually, approximately 1000 TB patients receive treatment in BH.[14] Newly diagnosed sputum positive cases receive daily four drugs during the intensive phase (2 months) followed by two drugs daily for the continuation phase (6 months).[1] To ensure treatment supervision during the intensive phase, hospitalization was recommended for all sputum positive cases. The study amide to understand the barriers and problem areas in TB treatment compliance. An attempt was made to identify the dynamics of the risk factors in the intensive and continuation phases of treatment.

Patients and Methods

Risk factors for defaulting were assessed through semi-structured interviews. For each patient information was collected at the start of the treatment (T0), after one- month (T1) and at the end of the intensive phase (T2)

Questions were based on previoud qualitative[13,15] and quantitative studies.[16] Questionnaires were pretested and adapted where necessary. All participants gave their informed oral consent voluntarily.

Variables Measured

Intention to comply was measured by the question "Are you confident you will finish the entire treatment" and recorded on a 1-5-point scale (T0-T1-T2)ii. Perceived barriers were measured at different points in time (T0-T1-T2). To assess the attitude towards the curability of TB, patients were asked to give their opinion on six statements on a 1-5-point scale (T0-T1-T2) Perceived stigmatization score was measured by the sum of patient's agreement on seven statements (T0-T2).

Subjective social control was measured through two questions on a 1-5-point scale. Patients were first asked to what extent they believed their family, relatives or friends were convinced that they should comply with the TB treatmand secondly how strongly this opinion would affect their own decision to comply (T0-T1-T2).

Social support was assessed by several questions concerning the financial and material support (bringing food to the hospital, looking after the children, helping in the fields) given to the patient (T1-T2). For OPD patients, regular drug intake was assessed twice (T1-T2) by the question "Did you ever forget to take your drugs?"

Regularity of the treatment: A regular patient was defined as a patient who was never more than 2 days late for a check-up appointment in the intensive or for more than 7 days in the continuation phase. Assessment of knowledge of TB consisted of questions concerning the transmission of TB (T0-T2) and the duration of treatment (T0-T1-T2). The attitude towards treatment adherence was measured by asking patients to indicate their agreement, on a 5 point scale, with the statement: "Do you believe that stopping your treatment before completing the full course will be harmless or harmful to your health?" (T1-T2).

Demographic profile included age, gender, tehsil of residence and marital status. Socio-economic status was measured by schooling (none, primary, or higher); #persons in the family; dependency ratio (#persons in the family / #persons economically active), occupation and whether the patient was the sole breadwinner).

The outcome parameter was defaulting. A defaulter was defined as a patient who interrupted treatment for more than two consecutive months. Patients who defaulted in the intensive treatment phase were defined as "early defaulters"; those who defaulted during the continuation treatment phase as "late defaulter".

Data Analysis

Data were analyzed by SPSS-plus software. Risk factors of patients' defaulting were assessed in two strata: the intensive phase and the continuation phase for those who had completed the intensive phase. The relative risk of defaulting was used as the parameter of association; the alpha error was put at a 0.05 level. Throughout the study, bilateral hypotheses were tested. The association were tested through t-test for equality of means, X2 test of association and X2 test of linear trend; 95% confidence intervals (CI) around the rate ratios (RR) are given.

Results

Study Population

Six hundred and fifty three sputum positive TB cases were diagnosed between September 1996 and October 1997 at BH. The criteria for eligibility was that the patients had to be 15 years or older, not critically ill and the follow-up to the treatment carried out in BH. Patients who died (47) or were transferred out (15) or failures (8) were eliminated from the study. Fourteen initial Interview were missed (2.5%) and 3 patients refused to be interviewed, the remaining 563 patients constitute the study population.

Of 563 patients 44% were females and 56% males. More than 70% of the patients were between 15-45 years. The educational level was very low; half of the patients had not received any form of education. This was even more so for women of whom only one third had had any schooling at all. The majority (73%) of patients were residents of Sialkot district. Almost all patients (90%) accepted hospital admission initially but only 54% completed the full two months of supervised treatment in the hospital. Overall 433 (77%) complied with the entire treatment course and 130 (23%) defaulted.

Defaulters in intensive treatment phase (Early defaulters)

Sixty patients defaulted during the intensive treatment phase. They were somewhat older (35.5 vs. 30.0 years median age) than compliant patients and contained 1.5 times more males than females. Patients living outside Sialkot district defaulted two times more than those living in the district did (RR=2.3; CI: 1.5; 3.7). Illiterate patients had a higher risk of defaulting (RR=l .8; CI: 1.1; 3.0) compared to literate patients. Single patients had half the defaulter rate (6.1%) than married

patients (12.6%) while those widowed, separated or divorced had the highest rate (14.3%). No significant differences were found for other socioeconomic indicators.

Table 1 summarizes factors significantly affecting early defaulting. At the start of treatment, three quarters of the patients felt very confident they would finish the entire treatment course. Those who expressed less confidence in their ability to conform to the treatment requirements had a higher risk of early defaulting. Low confidence was related to a lower belief in the curability of TB (P=0.024).

Early defaulter rates were three times higher in patients who rejected hospitalization. They perceived more constraints (mean score 15.5 ±5.0 vs 13.5 ±4.1; p=0.002) and had a more negative image of TB (stigmatization score 25.2 ±6.6 vs 23.4 ±5.5; p=0.02). Many patients perceived TB to be a stigmatizing disease. The majority agreed that "one should avoid talking to others about one's disease". They clearly felt that their friends and relatives should not know they had TB. Half of them believed "TB has life long consequences" and a quarter felt "it is difficult to earn a living after recovering from TB". Early defaulters felt stronger about the stigma. This was mainly because considerably more defaulters felt "TB in the family to be a disgrace" and "friends desert you when you have TB". Initial knowledge of TB and TB treatment did not differ significantly between defaulters and non-defaulters. Almost all patients were aware they had TB. Only one in three patients knew the correct duration of the treatment and only one out of four how TB is transmitted.

Defaulters anticipated more obstacles to the treatment than compliant patients did (Table 2). The regular visits to the doctor, long treatment and cost of the treatment were the most important constraints. A significantly negative correlation was observed between the motivation for the treatment and perceived barriers (rp=0.29; p<0.0001) iii.

Table 1: Cognitive and emotional factors affecting early defaulting (n=563).

Factor	Modalities	%defaulters (n)	RR (95%CI)	p-value
Confidence in finishing	- Low	28.6 6/21	3.3 1.6;7.0	0.0019*t
treatment	- Medium	14.3 18/126	1.7 1.0;2.8	
	- High	8.7 36/416	1	
Acceptance for DOT	- No	25.8 16/62	2.9 1.8;5.0	0.0000++
Hospitalization	- Yes	8.8 44/501	1	
Score	Stratum	Mean Score	-	-
Perceived stigma of TB	- Early defaulters	25.7 (±6.1)	-	0.0030**
	- Compliant pts.	23.4 (±5.6)	-	

* Mantel-Haenszel test for linear association
++ Peason chi-square
** T-test for equality of Means

Second month defaulters

Thirty early defaulters were interviewed at T1 three inter-views were missed. Six interviews of compliant patients were also missed. After one month of treatment, almost all patients felt their health had improved. The few, who did not, had a seven times higher risk of defaulting in the following month (RR=7.2; 95% CI: 3.0; 17.2). Low confidence in finishing the treatment quadrupled that risk (RR=4.0; 95% CIS: 2.0; 8.0). In addition, patients who were not convinced of the harmful effects of discontinuing treatment had twice the risk of defaulting in the following month.

The importance of social support became evident during the second interview (Table 3). Less encouragement from the family for the daily drug intake or for the continuation of treatment, resulted in a higher risk for

Table 2: Early defaulting in function of perceived constraints at onset of treatment (n=563).

Constraints for treatment	% of early defaulters in stratum (n)			p-value
	Strongly agrees	± agrees	Does not agree	
Long treatment is frightening	25.0%(7/28)	13.6% (9/66)	9.4% (44/469)	0.0086*
Regular visits to the doctor difficult	34.0% (17/50)	11.7% (11/94)	7.6% (32/419)	0.0000*
Daily intake medicine difficult	18.8% (24/128)	9.8% (16/164)	7.4% (20/271)	0.0011*
Daily life strongly affected	15.5% (29/187)	7.7% (16/208)	8.90% (15/168)	0.0321**
Cost of treatment insuperable	23.4% (15/64)	10.9% (19/175)	8.0% (26/324)	0.0010*

*Mantel-Haenszel test for linear association
**Pearson chi-square

Table 3: The role of family support in second month of treatment (n=527).

Family support	Modalities	%defaulters (n)	RR (95% CI)	p-value
Encouragement for treatment	- Low	33.3 (4/12)	8.3 (3.2; 21.4)	
compliance	- Medium	7.1 (12/168)	1.8(0.8; 3.7)	0.0012*
	- High	4.0 (14/347)	1	
Participation in family life OPD	- Seldom	17.6 (6/34)	3.7 (1.0; 13.7)	
patients (n=108)	- Regular	10.5 (2/19)	2.0 (0.4; 11.2)	0.0667*
	- Always	5.5 (3/55)	1	
Social network is informed	- Few	17.1 (7/41)	2.9 (0.9; 9.2)	0.0641**
patient has TB (OPD; n=108)	- Most/All	6.0 (4/67)		

**Mantel-Haenszel test for linear association
**Pearson chi-square

defaulting. For OPD patients, a link was observed between the degree of social isolation and defaulter rates. Not surprising, those who seldom participated in family life or whose friends ignored them, reported a higher stigma score (25.7±4.6 vs 23.4±5.6). Equally, OPD patients who concealed their disease from their environment had three times the risk of defaulting compared to those who did not. Again, concealing the disease was linked to a significant stronger perception of stigmatization (mean score 26.0±5.5 vs 22.7±5.4).

Defaulting during the continuation phase (Late defaulters)

Of the 503 patients who complied with the intensive treatment phase, 493 could be interviewed (T2). Seventy patients defaulted in the continuation phase, 63 of these were interviewed (90%). Only three interviews (0.7%) were missed out of the 433 compliant patients.

More late defaulters had no or only primary schooling; lived outside the coverage area and had a longer history of illness (Table 4). The relation between schooling and defaulting was stronger in women than in men:

Illiterate women had a 3-1/2 times greater risk of defaulting than literate women (RR=3.4; CI=1.6; 9.5); for men this was only 1-1/2 times (RR=I.6; CI: 0.9; 2.7). Remarkably, none of the higher educated females defaulted.

At this stage of the treatment, 99% of the patients were receiving strong encouragement from their family to comply with the full course. The financial support of the family became important in the continuation phase and patients who had no financial support had thrice the risk for defaulting (Table 5). Material assistance from the social network such as regular visits from family and friends, assistance with the care of children, in the home, with the job or studies, contributed to compliance. After two months of treatment, basic knowledge of TB improved substantially. The number of patients that correctly stated tile transmission mode of TB or the correct length of TB treatment doubled from 21% to 44% and from 35% to 74% respectively. The effect of knowledge on treatment adherence was rather negligible.

The perception on stigma related to TB had not drastically changed. Ninety percent of the TB patients still agreed that "you should not talk to others about your disease", 51% believed "TB to be a disgrace to the family". Late defaulters scored significantly higher on four statements. They feared that "even best friends might desert them because they had TB". More agreed that TB patients should hide their disease for their family or for friends and believed that "TB patients wilt experience the consequences of the disease for the rest of their life".

Correct drug intake and regularity of treatment strongly related to a better treatment adherence (Table 6). If during the first two months of treatment OPD patients forgot to take their medicine, they had twice the risk for defaulting. Those who were late for the scheduled appointment, even once, had 3-1/2 higher defaulter rates as those who attended regularly. The relationship became even stronger if

Table 4: Socio-economic factors related to defaulting in the continuation phase (n=503).

Factor	Modalities	%defaulters (n)	RR (95% CI)	p-value
Schooling	- No Schooling	17.8 (44/247)	2.7 (1.4; 5.6)	0.0022*
	- Primary	14.4 (18/125)	2.2 (1.0; 4.9)	
	- Higher	6.1 (8/123)		
Coverage area	- No	19.8 (25/126)	1.7 (1.1; 2.6)	0.0266**
	- Yes	11.9 (45/377)		
Duration of illness before	- ≥ 3 months	19.9 (40/201)	2.0(1.3; 3.1)	0.0002**
consulting BH	- < 3 months	9.9 (30/302)		

*Mantel-Haenszel test for linear association
**Pearson chi-square

Table 5: Risk factors of defaulting in the continuation phase, assessed at T2 (n=493).

Family support	Modalities	% Defaulters (n)	RR (95% CI)	p-value
Financial support from family	- No	32.1 (9/28)	2.8 (1.5; 4.9)	0.0016*
	- Yes	11.6 (54/465)		
Material assistance from social net work	- None	16.7 (11/66)	2.1 (1.0; 4.6)	
	- Low	14.7 (40/273)	1.9 (1.0; 3.5)	0.0329*
	- High	7.8 (12/154)	1	
Cognitive factors	Modality	% Defaulters (n)	RR (95% CI)	p-value
Correct knowledge of the cause of TB	- No	15.2 (42/277)	1.6 (1.0; 2.6)	0.07**
	- Yes	9.7 (21/216)		
Correct knowledge of treatment duration	- No	11.1 (13/117)	0.8 (0.5:15)	0.53**
	- Yes	13.3 (50/376)		
Emotional Factors	Modality	Mean Score (SD)	-	p-value
Perceived stigma	- Defaulters	15.1 (±3.9)	-	0.012#
(partial score)	- Compliant	13.9 (±3.6)	-	

*Mantel-Haenszel test for linear association
**Pearson chi-square
#T-test for equality of Means

Table 6: Appointment keeping regular drug intake and late defaulting (n=493).

Treatment regularity	Modalities	% Defaulters (n)	RR (95% CI)	p-value
Forgot to take medicine	- Yes	25.0 (6/24)	2.2 (1.0; 4.7)	0.06*
(OPD, intensive phase)	- No	11.6 (27/232)		
Appointments missed	- Yes	31.0 (9/29)	2.9 (1.5; 5.7)	0.0019**
(OPD, intensive phase)	- No	10.6 (24/227)		
Irregular appointment	- Yes	24.4 (58/238)	12.4 (5.1; 30.5)	0.0000**
Keeping (whole treatment)	- No	2.0 (5/255)		

*Mantel-Haenszel test for linear association
**Pearson chi-square

appointment keeping during the whole treatment course is considered. In such cases, a patient who missed a single appointment had more than twelve times the risk of defaulting compared to patients who kept the scheduled dates.

Discussion

Different mechanisms influence treatment adherence behaviour over time. Motivation at the start of treatment is an important predictor for early defaulting. Lack of confidence in the capability to finish the full treatment course increases the likelihood for defaulting in the early weeks of treatment. Motivation is easy to assess at the start of the treatment through a simple question like "How confident are you that you will be able to finish the treatment course?" However, motivation has to be understood in the context of the constraints patients' face in their ever day life. The greater the anticipated barriers at the start of treatment, the higher the risk for early defaulting. Early defaulters are also more reluctant to accept the supervised treatment in hospital.[17]

The findings show that the family's encouragement for the treatment is an essential element in the intensive phase. As treatment advances, financial support from the family becomes increasingly important. The financial burden of the TB treatment is difficult to overcome by the patient and his/her nuclear family alone. To be able to fulfill the treatment requirements patients often need practical assistance, such as help with the children, household, job or studies. Kinship institutions such as biraderi are central to the social life in Pakistan. They provide, through a network of kinship, a support mechanism. In case of illness, a person can count on the biraderi for moral, financial and practical support.[18] As found elsewhere,[19-21] for TB patients this support is extremely important and positively associated with an improved treatment adherence. Clearly, late defaulters receive less support from their social network. They also feel more stigmatized.

Stigmatization is reflected in the negative perceptions patients have about the disease.[13,22] Even after two months of treatment, the majority of patients still conceal their health problem from their environment. Neither the interaction with the health care providers nor improvements in the patients condition could after the preconceived ideas of the social stigma.

Knowledge about transmission of TB and regimen duration is low at the start of treatment but improves over time. The study confirms that better knowledge does not influence treatment adherence.[23] However, a careless attitude towards prematurely stopping the treatment dose. Apparently

imparting knowledge or an advice-giving approach is insufficient to motivate TB patients to adhere to the treatment. Efforts should rather focus on providing support and enabling patients to overcome treatment barriers.

One of the best predictors of adherence to the full treatment course is early compliance. Patients who forget to take their drugs or who are late for their appointments, even once, have a high risk of becoming defaulters. This corroborates the findings of a study carried out in Rawalpindi in which irregular appointment keeping was the strongest predictor for subsequent defaulting.[9] This factor is easy to assess and has a powerful operational value: patients who are from the start erratic in drug intake and appointment keeping will need extra support and guidance.

Socio-economic status is often mentioned as an important predictor for treatment adherence. We only found a slightly higher "early defaulter" rate in vulnerable groups such as widowed/separated patients. The predictive value of geographical accessibility is apparent. Regular treatment follow-up beyond a certain distance from the treatment centre seems to be very difficult. This problem can only be solved once a network of conveniently located TB treatment centers becomes available.

The relationship between education and treatment adherence has been established before.[2,24] For Pakistan, a country with a low female literacy rate,[25] it is important to report that in particular, female education has a strong positive impact on treatment adherence.

Classical economic factors such as occupation, dependency ratio or being the sole breadwinner are not related to treatment outcome. In the cultural context of the Pakistani "biraderi" support system, financial and material support from the network is probably a more meaningful socio-economic indicator.

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Pattern of Tuberculosis in General Practice

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Abstract

An audit of 690 cases of tuberculosis out of 46,276 patients seen during the last 25 years in a busy general practice is reported. Of the 690 cases, 67% were pulmonary, 33% extra-pulmonary TB. Modes of both types of tuberculosis are described and the reason for increased incidence of extra-pulmonary tuberculosis are discussed (JPMA 48:183, 1998).

Introduction

Tuberculosis is a common disease in Pakistan and World Health Organization in 1987-88, reported a sputum positive prevalence of 0. 17 per 1000 million.[1] Tuberculosis is more prevalent in urban low socio-economic conditions, chiefly due to malnutrition, over crowding and unhygienic conditions. With increased resistance to anti-tuberculosis drugs that is being reported from all parts of the world, the problem has become acute with AIDS compounding its incidence in developing countries, specially in Africa and South East Asia. Treatment with three or four drugs is being advocated, which makes it much more expensive; this further reduces the compliance, as not many patients can afford expensive drugs over a period of six to nine months. An audit of all the cases of tuberculosis seen in a busy general practice, in a middle to lower middle class populace during the past 25 years was conducted by adopting simple organizational measures of health care to see the pattern of diseases encountered and evaluate the final out come.

Patients and Methods

In the general practice, records of all patients seen over 20 years were maintained. Special sheets and reference registers with complete details of the patients were filled in. Reference cards had individual numbers for each patient which were used for all the future ailments, that helped in establishing a system for supervision and for operational management, treatment and follow- up.[2] In this retrospective analysis, case records of 813 suspected cases of tuberculosis seen during the study period were reviewed. In each case the patient had X-ray's, complete blood picture with ESR, Mantoux test and sputum for A.F.B. Other investigations i.e. FNAB, histopathology and specialized X-ray's i.e. small bowel enema, lumbar puncture, ultra sound guided aspiration of psoas abscess and thoracocentesis were also obtained when required. Based on the site of lesion, cases were divided into pulmonary and extra pulmonary cases.

Results

Of 813 suspected cases of tuberculosis, 123 were non-tubercular and hence excluded. Of the 690 remaining cases, 335(485%) were male and 355(51.4%) females.[3] Ages of the patients ranged from 2 to 60 years, 70% were between 10-39 years; of the total, 466 (68%) were pulmonary tuberculosis, 27 (4%) had both pulmonary and extra pulmonary tuberculosis and 224 (32.4%) were only extra pulmonary. The chief presenting symptoms among the pulmonary cases were cough with expectoration, fever, weight loss, malaise. Haemoptysis was present in 127 (18%) cases and night sweat in 10 cases, Infiltration was observed in 218 (47%) cases, of which 110 (59%) were bi-lateral. Infiltration plus cavitations was seen in 91(20%) and 27(6%) were pneumonic (Table I).

Table I: Pattern of Lung lesions (n=466).

	Total		Left		Right		Both	
	Nos.	%	Nos.	%	Nos.	%	Nos.	%
Infiltration	235	50	56	12	75	16	104	22
Infiltration with cavities	91	20	37	6	52	11	2	2
Pleurisy	29	6	14	3	15	3	0	0
Pneumothorax	28	6	9	2	15	3	4	1
Pneumonic	27	6	9	2	15	3	3	1
Fibrotic	56	12	18	4	24	5	14	3

Among extra pulmonary tuberculosis the chief presentation was swellings of glands. Very few complained of constitutional symptoms, except those with pleural and pericardial involvement and those suffering from abdominal, bone and joint disease. The pattern of extra-pulmonary lesion is presented in Table II. In this series, except one case of axillary and one of suprca cavicular lymph adenopathy, none required surgical intervention.

Table II: Pattern of extra pulmonary lesions (n=224).

Lesion	Nos.	%
Hilar lymph adenitis	80	36
Peripheral lymph adenitis	51	23
Pleural effusion	34	15
Primary abdominal tuberculosis	23	10
Spines	15	7
Bones and joints	8	4
Meningitis	4	2
Pericardial effusion	3	1
Paratrachial lymph adenitis	2	0.9
Others (Larynx, BCG vaccination etc.)	4	2

Discussion

The frequency of extra pulmonary tuberculosis is consistent with UK experience,[1] where 34% of the Asians compared to 18% of whites were seen with this lesion. In USA there has been a gradual increase of extra pulmonary disease over the years. It has always been suggested that in areas where bovine tuberculosis is common, lymphatic and abdominal tuberculosis is more frequent. In a study from Lahore no bovine bacilli were discovered in 100 cervical gland specimens[4] some a typical mycobacteria, mainly Scotochromnogenic were isolated. Similarly in Saudi Arabia, atypical Mycobacterium mainly Mycobacterium Fortuitum and Mycobacterium Chlonie were isolated. Asian and African variants were isolated from both Saudi and non Saudi patients.[5] The incidence was highest among young adults, and in females. In Karachi there is a gradual increase in extra pulmonary tuberculosis. It seems that altered immune status may be responsible for this change. Tubercular meningitis, a disease of childhood is now being reported amongst adults. Recently fifty consecutive cases of meningeal tuberculosis amongst adults aged 15-70 years were reported from tertiary treatment centers.[6] Diagnosis of extra pulmonary tuberculosis presents a problem specially in abdominal tuberculosis, which comprised 10% in these series. Fourteen (61%) of these had ileocaecal tuberculosis and 6 (26%) had peritonitis. In majority of cases modern technique of imaging i.e. small bowel enema, ultra sound, fine needle aspiration biopsy are of great help for diagnosis, subject to proper clinical assessment.

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Recent Trend in the Radiological Presentation of Pulmonary Tuberculosis in Pakistani Adults

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Abstract

Objective: To determine the radiological presentation of pulmonary tuberculosis in adults and to compare it with that of other national and international studies.

Method: This descriptive study was done on 150 newly diagnosed smear positive pulmonary tuberculosis patients. Two chest physicians reviewed the chest radiographs. Those x-rays were selected in which there were no difference of opinion.

Results: There were 77 male and 73 females. The average age was 34.52 years with range of 17 to 80 years. Out of 150 films, eighty-seven (58%) showed the typical pattern (infiltration and / or nodules with or without cavitations, involving upper zone). While sixty three (42%) showed the atypical pattern (pattern other than typical one).

Conclusion: Typical pattern of pulmonary tuberculosis is still the common mode of presentation in adults but there is a trend toward increase in atypical pattern.

Introduction

Pulmonary tuberculosis is generally classified into primary and post primary tuberculosis, both have distinct characteristic on radiology. Post primary tuberculosis is the commonest form in adults, in which the patients usually present with infiltration with or without cavitations involving the apical and posterior segment of upper lobe.[1-3] In some cases the apical basal segment of the lower lobe is the first to be involved. The other lobes may be involved but classically follow involvement of the upper lobe. Based on these

characteristics, pulmonary tuberculosis is divided into typical or usual pattern and atypical or unusual pattern.

In the typical pattern, there is upper zone involvement in the form of infiltration or nodules with or without cavitations. In the atypical pattern all other forms are included e.g. lower lung field tuberculosis, hilar lymphadenopathy. miliary tuberculosis, diffuse pulmonary tuberculosis, tuberculoma, atelectasis, pleural effusion, pnemothorax etc.

The object of the study was to determine the current radiological presentation of pulmonary tuberculosis and to compare it with that of other national and international studies.

Material and Method

This prospective study was done between August 2000 and November 2000, in patients attending Nazimabad and Malir Chest clinics of Ojha Institute of Chest Diseases, Karachi. We included those cases that were diagnosed as smear positive pulmonary tuberculosis and the fresh chest X-rays were available These Chest radiographs were reviewed by two chest physicians. Only those X-rays were selected in which there were no difference of opinion.

Results

A total of 150 patients were included in the study, seventy-five from each clinic. There were 77 male and 73 females. The average age was 34.52 years with range of 17 to 80 years.

Out of 150 films, eighty-seven (58%) showed the typical pattern and sixty three (42%) showed the atypical pattern. Among the typical, 65 films (74.71%) had unilateral and 22 films (25.28%) had bilateral disease. Table 1 shows the distribution of atypical radiological pattern.

Table 1: Atypical radiological presentation.

Diffuse pulmonary TB	32	21.33
Lower long field TB	14	9.33
Middle zone infiltration only	7	4.66
Hilar lymphadenopathy	6	4
a) Unilateral 5		
b) Bilateral 1		
Military TB	3	2
Atelectasis	1	0.66S

Discussion

Although the gold standard for the diagnosis of pulmonary tuberculosis is isolation of mycobacterium tuberculosis from respiratory secretions but chest X-ray is equally important in the diagnosis. There are a number of cases in which there is no expectoration or in which the disease is minimal or who cannot just bring their sputum up. In such cases we rely on clinical and radiological features.

It is well known that tuberculosis can be included in the differential diagnosis of almost any pulmonary case, so knowledge of radiological presentation of pulmonary tuberculosis is beneficial for the practicing physicians.

In this study 58% of the patients presented with typical radiological pattern, which mean still the majority of the patients present with typical pattern.

In 1993, Javaid K. et a1[4] reported the typical pattern in 76% of culture positive pulmonary tuberculosis cases. In 1997, Saulatullah et al[5] reported the typical pattern in 60% of Diabetic and 70.7% of non-diabetic patients. In our series only 10 patients were diabetic, out of which 3 (30%) presented with typical pattern and 7 (70%) with atypical pattern. Table 2 compare the pattern of lung involvement in patients presenting with typical chest X-ray. In this study unilateral disease was more common than other two locally reported studies.

Table 2: Typical pattern - Comparison with national studies.

	Rao, Sadiq	Javaid et al	Saulatullah K et al	
			Non-Diabetic	Diabetic
Unilateral disease	74.70%	35.00%	37.8%	33.4%
Bilateral disease	25.30%	65.00%	62.2%	66.4%
Infiltration / Nodule	78.00%	87.70%	60.4%	35.6%
Cavitation	25.30%	49.10%	39.6%	64.4%

Table 3 compares the atypical pattern. The higher presentation of diffuse pulmonary tuberculosis in this study i.e., 21.33%- is noteworthy, while Javaid K reported just 0.66%[4] The inclusion criteria of the patients reported by Javaid K was culture positive pulmonary tuberculosis, and their patients usually belong to higher socioeconomic group and they consult medical services earlier. Our patients belong to the poor community and for them daily earning is top priority than their health. So they seek medical advice late.

Table 3: Atypical pattern — Comparison with national studies.

	Rao NA et al	Javaid K. et al	Saulatullah K et al	
			Non-Diabetic	Diabetic
Lower lung field T.B.	9.33%	9.33%	8.00%	14.7%
Diffuse T.B.	21.33%	0.66%	6.70%	13.3%
Hilar lymphadenopathy	4.00%	3.33%	5.30%	6.7%
Miliary T.B.	2.00%	2.00%	-	-
Pleural effusion	-	8.66%	6.50%	4.0%
Middle zone infiltration only	4.66%	-	-	-
Pneumothorax	-	-	2.70%	2.7%
Atelecatasis	0.66%	-	-	-

Pleural effusion has not been reported in any case in this study because our cases were smear positive for pulmonary tuberculosis. Middle zone infiltration only was

noted in 4.66% cases, which most probably represents apical basal segment. Which is also the common site of post primary pulmonary tuberculosis.

One of the patients presented with atelectasis and was smear positive, which indicate endobronchial tuberculosis with or without lymph node enlargement. While comparing this study with international ones the typical pattern is reported from 68% to 86%[6-8] Among the atypical pattern, lower lung field pulmonary tuberculosis was from 5.31% to 7%,[6-8] hilar lymphadenopathy from 7.44% to 9.7%[7,9] and miliary tuberculosis 4.5%.[6]

In 1998, Vanden BP et al reported an increase in unusual presentation of tuberculosis from 24% in 1981-85 to 35% in I986-90[10] but this study was from Belgium where tuberculosis is well under control. We are observing the same phenomenon of increase in unusual presentation in this part of the world where tuberculosis is highly prevalent. In this regard it is suggested that radiological presentation of pulmonary tuberculosis must be stressed during undergraduate training. This is important because in post sanatorium era, emphasis on tuberculosis teaching has been declining. A study was carried out to determine the fact. In that study[11] 44% of the patients was undiagnosed on admission despite of the fact that majority of them had characteristic chest X-ray findings. This likelihood is greater when the patient present with atypical radiological pattern.

Conclusion

Typical pattern of pulmonary tuberculosis is still the common presentation in adults but there is a trend toward increase in atypical pattern. It is suggested that medical students and practicing physicians must also be aware of atypical presentation.

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Tuberculosis Control in Pakistan: Critical Analysis of its Implementation

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Introduction

Tuberculosis (TB) constitutes a major public health challenge. Due to the emergence of HIV, increased migration and the deterioration of the health services in many countries, the incidence has risen so drastically in recent years, that TB was declared a global emergency by WHO in 1993.[1] Without increased investment in intervention strategies, the global tuberculosis situation is expected to worsen in the near future.[2]

Epidemiology of TB in Pakistan

There is little reliable epidemiological data available for Pakistan, although TB is considered to be a major cause of ill health.[3] The annual incidence rate of infectious TB cases is estimated to be between 85-100/100,000 persons. Annually around 120,000 new TB cases are being added to the existing number of infectious individuals. Some areas in the country have much higher figures, such as Northern Pakistan where a prevalence figure of 554/100,000 cases was observed.[4]

As in other developing countries, young age groups are affected the most. Male patients outnumber females in most age groups, except in the adolescents. Based on Burden of Disease estimates, TB represents 5% of the total DALYs (disability adjusted life years); which indicates that the burden of tuberculosis in Pakistan, is substantially higher than the world average of 3%.[5]

Historical Review of TB control activities in Pakistan

The first survey was carried out in 1962. The results triggered a collaborative effort between MoH, WHO and

UNICEF for a twenty year TB control programme, that focused on establishing specialized TB centres and special TB wards at the DHQ Hospitals. In 1985 UNICEF withdrew its financial support. WHO declared TB a global emergency in 1993 and the GoP endorsed the DOTS strategy. In 1994 the MoH, in collaboration with WHO, revised the TB control policy. National policy and technical guidelines were drafted; however, to date there is no draft yet for operational guidelines. In 1995 the MoH decided on the location of 5 DOTS pilot sites, but only 1 site became operational. A highly centralized and vertical five-year development plan was prepared by the Federal NTP. Since the Provinces expressed certain reservations with regard to the plan, it was not approved. In 1996 the Directorate for TB Control of Pakistan was abolished and the MS of the TB Centre in Rawalpindi made responsible for National TB Control programme, but without any additional support. In 1998 Pakistan was declared 1 of the 16 countries without an appropriate NTP. Recently it was decided that each Province would be responsible to plan and manage its own NTP under Federal NTP guidelines. Funding for the plans will be provided through SAPP II.

Critical Analysis of the NTP

Given the magnitude of the TB problem in Pakistan as well as the size of the country, a vertical TB control programme is financially prohibitive and difficult to sustain. Integration of the TB control programme in PHC has recently been opted for, as a solution to its technical and managerial deficiencies. Hereto, a network of laboratories needs to be created as well as a system for ensuring quality of sputum smear microscopy put in place.

The Objectives of the NTP Policy

The two major objectives are:

a) To increase the cure rate of sputum smear positive cases to at least 85%;

b) To increase the detection of new cases to 70%, once the first objective is reached.

Federal role in the NTP

Provision of a policy framework, technical assistance, supervision, surveillance, co-ordination, research and development and advocacy.

Provincial role in the NTP

Planning, accessing funds, management of programme, implementation of DOTS through integration with the PHC.

Practice

The NTP has been unable to come close to, let alone achieve, its ambitious objectives. TB control activities in Pakistan have suffered during the last five years because of the dilemma of either managing the programme from the federal level or handing it over to the provinces. A decision in favour of the latter option was taken as late as mid-1998. Under this arrangement the roles of the provinces and the fedral government have been well defined. The provinces have been given the responsibility of independently developing and implementing their own TB control programmes. TB control activities suffered in the past as there were no funds earmarked for TB control in the provinces. District managers were expected to support TB control activities from their already insufficient regular budgets. For the fiscal year 1999-2000 the federal government has indicated support and earmarked funds for all the provinces as well as for the federal component. Health sector reform is a major driving force for improving the health systems throughout the world.[6] Proponents of this reform believe services to be more cost-effective and sustainable if they are integrated into and delivered through a comprehensive district health care system.

Programmatic reforms in the health sector of Pakistan have over the years improved public health services through better targeting of populations, funds and services. The TB Control Programme is one example. Recently there has been an effort on the part of the provincial health departments to introduce structural and management reforms in the health sector in order to improve the efficiency of services delivery and resources development.

Interest in the control of tuberculosis has been further renewed through a recent policy initiative to strengthen PHC services through an integrated approach. The Social Action Programme, with multi-donors' support, has also pushed TB high on the agenda, and the programme priorities of Provincial Health Departments have been redefined.

Screening and Diagnosis Policy

According to the NTP guidelines, detection of pulmonary TB should be based on sputum examination.[7] From TB suspects at least 3 specimens should be collected and examined.

Criteria for "AFB + caseness" consist of 2 positive smears OR one AFB+ sputum as well as radiographic abnormalities consistent with active pulmonary tuberculosis, OR if determined by a competent medical officer.

The diagnosis of a "Smear-Negative" TB case is made if the following 3 criteria are met:

- At least 3 specimen AFB sputum by microscopy.
- Radiographic abnormalities consistent with active tuberculosis.

◆ Clicical evidence substantiated by a competent medical officer.

Practice

In Pakistan TB detection and diagnosis is generally based on X-ray, clinical impression and blood examination rather than on sputum examination. Some clinicians rely on Mantoux results, although tuberculin is rarely available.

The network of laboratories able to correctly carry out sputum examinations is inadequately developed with virtually non-existent supervision. Consequently many laboratory results are not reliable. These unreliable test outcomes weaken the trust of the clinicians in the laboratory results and strengthen their belief in clinical impression, ESR and/or X-ray as diagnostic tools.

Many centres start TB treatment even when no sputum is available: in the Rawalpindi study[8] no sputum was available for 6.2% of the patients. In Delhi, India[9] it was found that for only 12% of the TB suspects, a sputum examination was advised.

In practice the number of diagnostic AFB exams is limited to two. A recent study has shown the sensitivity of 2 AFB exams to be 93% of that of 3 AFB exams.[10] PCR (Polymerase chain reaction), although more sensitive and specific than smear microscopy, is prohibitively expensive,[11] and is not routinely used in Pakistan. As a routine exam, the ELISA test for detecting tubercular antigen in sputum has not yet been implemented in the country.

Contact Tracing Policy

Bacteriological examination of all the contacts with a smear positive index case. Especially children and young adults should undergo 3 sputum examinations.

Practice

In Pakistan only some specialized centres routinely perform contact tracing, although not appropriately. Since the NTP guidelines do not detail the mechanisms of contact tracing; this is an area that needs attention, especially for operational guideline preparation.

Treatment Regimens Policy

The NTP proposes short course chemotherapy for all sputum positive cases for 8 months duration. The guidelines distinguish 3 main categories of patients:

◆ Category I patients are new AFB smear positive cases;

◆ Category II refers to smear positive re-treatment and failures after a full short chemotherapy course;

◆ Category III refers to sputum smear-negative and extra pulmonary cases and to children who are unable to produce sputum.

The recommended treatment strategies for these three categories are described in Table. NTP guidelines recommend daily dosages according to weight.

Table: National TB treatment strategy.

Category of patients	Intensive phase	Treatment Continuation phase
I	2HRZE (or 2HRZS)	6HT (or 6HE)
II	2HRZES	1HRZE + 5HRT
III	2HRZ	6HT (or 6HE)

Practice

General practitioners and specialists have a poor awareness of the WHO guidelines[12,13] and do not adhere fully to the national treatment guidelines. Almost all treatment centres are using strengths and combinations of drugs that differ from the accepted guidelines.

This situation is not unique to Pakistan. Unsatisfactory practices of private care providers have also been observed in India.[14] In Delhi 102 different regimens were being reported, 51% of the patients were over-treated and only 20% of the care providers did emphasis the importance of regular treatment.

Follow-up of Patients Policy

Patients should be monitored at regular intervals through:

◆ Sputum smear examination

◆ Regularity of drug intake, to be monitored by DOT

◆ Prompt recovery of defaulters

Sputum has to be examined at 2, 5 and 8 months after the start of treatment. For monitoring purposes, a single sputum specimen smear examination is sufficient. If the sputum results of a sputum smear positive patient are negative at months 5 and 8, he/she should be discharged from treatment after completion of the treatment course. If the sputum result is positive at 5th or 8th month, then the treatment must be changed to sputum smear positive re-treatment regimen.

No post-treatment follow-up is necessary for patients who have successfully completed their treatment.

Given that Rifampicin is part of the intensive phase treatment scheme, careful supervision is necessary and no Rifampicin containing regimens should be given to patients who are taking the drugs at home without supervision. When outpatients fail to attend more than two consecutive follow-up appointments during the intensive phase, they should be traced within a week of missing their second appointment. This means that a visit should be paid to the home of a TB

patient who did not attend the scheduled appointment for drug supply.

Practice

In Pakistan low treatment adherence prevails. In the sixties Sloan and Sloan observed dropout rates of 66% in Sindh,[15] similar rates were found in the recent Rawalpindi cohort study.[8] A characteristic of case holding in Pakistan, is the important very early defaulting. Several studies have shown behavioral factors,[16] including social stigma,[17] to contribute to non-adherence to treatment. Research has shown irregularity of attendance during the initial phase to be a major determinant for treatment adherence not only in the initial phase, but also in the continuation phase.[8] Incorporating DOT in the initial phase can thus have an important impact on early, as well as late defaulting. So far Pakistan has only launched a few pilot DOTS projects in selected districts,[18] but the DOT strategy needs far greater support than it has received thus far. Some centres hospitalize patients during the initial 2 months of treatment, to guarantee very close DOT supervision.

No firm data is available on defaulter tracing mechanism in Pakistan, but it is strongly suspected to be rather deficient. The objective is to bring the patient back to regular treatment in order to cure the disease, avoid development of resistance, and avoid spreading the disease in the community.

Drug Resistance and Re-Treatment Policy

Drug resistance is one of the consequences of low adherence to treatment. Sputum positive patients who have previously taken anti-tuberculosis drugs for 1 month or more must be suspected of discharging tubercle bacilli resistant to INH and/or other drugs. Such patients must be started on re-treatment regimen (2 SHRZE/1 HRZE/5 HRE).

Practice

In Karachi resistance rates to the four first line anti TB drugs were found to be 27% to INH, 15% to Ethambutol, 11% to Rifampicin and 13% to Streptomycin; MDR (multi drug resistance) was 8%.[19] The guidelines for re-treatment of resistant TB cases are based on WHO recommendations rather than on local studies.

Involvement of Private Practitioners Policy

There is no explicit policy for involvement of private practitioners in the treatment and follow-up of TB patients.

Practice

Eighty percent of the TB patients consult a private practitioner first;[20] these findings have been confirmed in the PMRC health seeking behavior study. Hassan has found an even higher figure of 96%. Marsh has demonstrated poor performance of some private practitioners in screening, diagnosing, treating and monitoring their TB patients.[20] Ekbal[21] has discussed the main errors in drug prescribing practices as:

Starting with a single drug, adding a single drug to a failing regimen, inappropriate prescription, ignoring DOTS, extensive prescription of combined anti-TB drugs and insufficient instructions to illiterate patients.

The fact that most TB patients first contact a private practitioner has been revealed by several surveys. In spite of this, official policies are directed towards detection, treatment and follow-up of TB patients at public sector health facilities only. Public sector managers should be more innovative and develop public - private collaboration. One way could be to train GPs in opportune diagnosis, treatment and follow-up of TB patients and encourage them to refer these patients to the laboratories of THQ hospitals for sputum examination and registration.

Integration of TB control into PHC services Policy

The official policy is to integrate TB control services into the PHC services. A network of laboratories will be established. 1 in each RHC and THQ hospital. Sputum collection and smear fixation will be done at BHU level, once personnel have been adequately trained. Human and material resources will be integrated into the PHC. NTP plans to ensure a continuous drug supply by establishing a system for national procurement, storage, and delivery and monitoring of anti-TB drugs. Continuous supervision will enable prompt detection of deficiencies in implementation motivation and skills of staff.

Practice

Pakistan has a relatively well-developed health care infrastructure. The centres have, in theory, sufficient manpower; a recent World Bank report[6] even speaks of overstaffing, mainly of general practitioners. But many rural areas lack female doctors, which limits the access of female patients to care. Contrary to NTP mandate, to date only sporadic training sessions for staff of public services have been held. There is limited involvement of the THQH in TB control activities and no involvement of the BHUs in case detection or follow-up.

Generally the laboratories at the RHC and THQH do not function due to either failure of necessary reagents, or insufficient training of laboratory technicians. Most of the time, however, the reason for the poor functioning of the laboratory is the lack of requests for sputum examination by the medical practitioners.

Many RHC and THQH have no regular TB drug supply, or the stock consists of a few selected drugs only. The danger is that the patients do not buy the other drugs and

consequently resistance develops. Visits to several first and second line centres in Pakistan have shown that the drug supply is very irregular, partial and insufficient.

Regular supervision of the TB program activities is one of the weakest elements of the system. The concept of supervision as continuous education has not been introduced yet. There is normally no back referral of diagnosed TB cases by the specialized centres.

Reporting System

The IUATLD (International Union Against Tuberculosis and Lung Disease) recognizes a reliable information system to be the key element for the success of national TB control programmes.[22] Experience from several countries shows the data generated by the NTP to be more reliable and complete than that generated by HMIS (Health Management Information System) and more suitable for programme management. Following IUATLD both information systems should complement each other; therefore NTP should collect the relevant TB data and communicate it to the HMIS managers at all levels of the health system.

Policy

The NTP has planned to introduce a standard system of registration and reporting, to monitor the results of treatment and to assess progress of the programme by means of ongoing quarterly analysis.

A series of standardized records have been created: TB treatment card; TB appointment card; District TB register; TB laboratory register; TB smear examination request/report form; TB culture/sensitivity. Test request/report form; TB referral/transfer form; Quarterly order form for TB treatment supplies; Quarterly order form for TB laboratory supplies.

The case finding, smear conversions at follow-up, and final results of treatment have to be reported to the NTP on a quarterly basis. A cohort analysis has to be carried out. A feedback mechanism will also be established.

Practice

At present there is no uniform system of recording and reporting in the public sector. The HMIS has a different format from that suggested by NTP. In some areas where DOTS is implemented a dual system exists. The method of recording and collecting information differs from one centre to another and is generally not in accordance with WHO guidelines. Case definitions for pulmonary and extra pulmonary cases may differ and cohort analyses are computed differently as well. Data is as yet not being used for the planning and management of TB services. No reliable national data is available concerning TB case detection and TB case holding. The quality of the HMIS data is interior to the recommended NTP recording, it is not standardized and generally not in accordance with WHO recommendations.

NGO's Policy

The NTP proposes to strengthen cooperation and coordination with NGO's.[23] The latter are expected to play a crucial role in enhancing patient education and community assistance.

Practice

The majority of NGO's are working in isolation, involved mainly in the treatment and drug provision. Some NGO's have not yet adopted the NTP guidelines. Little effort has been undertaken to streamline the NGO's efforts.

Role of Communities Policy

Four main roles for the communities are envisioned:

- To encourage the TB suspects to promptly visit a health facility for assessment.
- To support the diagnosed cases to complete treatment.
- To improve general understanding of the disease and its prevention.
- To supervise treatment.

Practice

The national policy makers perceive the community as a natural partner for public sector development. However, hardly any sustainable model has been designed and practiced in the health sector and almost none for either reductin or control of TB. In pilot projects going on in Balochistan and NWFP provinces, LHWs are being used to implement the DOTS, with encouraging outcomes. However, to fully realize the additional benefits obtained from community participation, the NTP may have to design some culturally appropriate, socially acceptable and sustainable partnerships between the people and the public health sector of this country.

Political Commitment Policy

A strong political commitment is essential for the success and sustainability of any TB control programme.

Practice

The political commitment at the federal and provincial levels is rather weak, although interesting pilot projects are at present being undertaken in the provinces of Balochistan and NWFP.

Future Strategies and Recommendations

The weaknesses and shortcomings at each level of the NTP need prompt political, technical and/or

managerial solutions.

At the political level: TB should be given much greater importance, and commitment, as well as support and resources. The Federal NTP unit should be made fully operational.

At the technical level: All care providers working in both the public and private sectors should be updated on the NTP guidelines. District and Tehsil headquarter hospitals should be equipped to carry out reliable sputum exams. Laboratories should adhere to quality control principles. DOTS will have to be applied throughout the country, and lessons learned from patient counseling experiences should be incorporated in patient management. The communities should be involved in the DOTS scheme.

At the managerial level: The NTP has to be strengthened, and specific tasks for all levels (federal, provincial, district and community) have to be planned. The activities have to be implemented, monitored and assessed with clearly defined indicators. Following the lessons learned from neighbouring countries, private practitioners should be involved. The cooperation with NGO's has to be strengthened. The public should be much better informed, and the message that the disease is curable should be spread through all means of communication. There is a need for continuous laboratory supplies, as well as for a continuous drug supply system. There is a need for a drug resistance surveillance system. The personnel in charge of Tehsils and districts should be trained in data management and analysis, so that programme management will become more evidence based.

At the community level: Strategies to overcome the stigma attached to TB have to be developed.

At the individual care level: The continuity of the care has to be addressed in the context of the socio-economic constraints of the households and communities. Specific treatment should be given free of charge, and efficiency improved by reducing the number of visits to the least required, and by following up the patients as close to their homes as possible.

At the research level: Operational research is needed to find solutions for the constraints and to continuously optimize the programme output.

Behavioural research is needed to create awareness of the TB problem[24] and to contribute to its destigmatisation; as well as to develop a socially acceptable DOTS programme. Socio-economic research is needed to quantify the burden of disease, the cost of defaulting and the benefits of DOTS.

Epidemiological research is needed to determine the magnitude and spread of the disease, and the drug resistance in order to analyse the risk-factors for the incidence of infection and disease, and to determine the nosocomial risk.

Therapeutically research is needed to find more cost effective ways of treatment.

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Cutaneous Tuberculosis: a three year prospective study

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Abstract

Objective: To study the pattern of clinical presentation of cutaneous tuberculosis.

Methods: All patients with clinical suspicion of cutaneous tuberculosis, visiting outpatient department of Dermatology Unit, Jinnah Postgraduate Medical Centre, Karachi were included in this study. Total number of the patients enrolled were 74. The lesions were then classified into four clinical types viz: lupus vulgaris, scrofuloderma, tuberculids and tuberculosis verricosa cutis.

Results: A total of 0.1% patients visiting out patient department had cutaneous tuberculosis. Scrofuloderma was the commonest form seen in 48 (64.9%) patients, followed by lupus vulgaris in 16 (21.5%), tuberculosis verrucosa cutis in 6 (8.1%) and tuberculids 4(5.6 %).The presence of regional lymphadenopathy had correlation with the disseminated disease.

Conclusion: There is an increasing trend of cutaneous Tuberculosis over the years. Scrofuloderma was the most common clinical presentation, followed by lupus vulgaris, tuberculosis verrucsa cutis and tuberculids. Tuberculous gumma was not seen in any patient.

Introduction

Tuberculosis (T.B) has plagued humans and animals from ancient times. This human infections has been documented in history as early as 8000 B.C. Hippocrates (460 - 376 B.C.) gave T.B. the first intelligent description "phthisis" (to waste away).[1] The ancient Chinese literature reports its presence in China before the great wall was built. The history of systemic tuberculosis is well documented; little has been said about a tuberculosis skin lesion in the ancient medical scriptures.

However chronic draining sinuses of scrofuloderma reported by Rene Laennec (1918) forms the earliest of cutaneous tuberculosis lesion. In 1882 Robert Koch not only discovered tubercle bacillus but also found it to be the causative agent of lupus.[2]

Even after many centuries patients still suffer from this potentially curable illness. The fact that it is now more prevalent in developing countries suggests that low socioeconomic status, malnutrition and overcrowding play a role in its causation.

The lack of medical facilities because of poverty or poor health infrastructure has led to long standing and more extensive tuberculosis skin lesions. Another reason for chronic cases is misdiagnosis and subsequent wrong treatment by doctors or treatment by quacks or hakims.

Patients and Methods

The study was carried out in O.P.D of dermatology department, Jinnah Postgraduate Medical Center from 1 July 1999 till 30 June 2001 (3 years duration). A total of 83 patients with clinical suspicion of cutaneous tuberculosis were enrolled. Both sexes and patients of all ages were included. A detailed Performa stating age, sex, duration of illness, examination of lesion, site and number of lesions etc was filled in for each patient.

Investigation performed were ESR, Mantoux test and X-ray chest in all patients. Biopsy of the lesion was performed only in 28 patients. Nine patients were excluded from the study because of incomplete data. Finally the data of 74 patients was analyzed. The lesions were classified into four clinical types viz: lupus vulgaris, scrofuloderma, tuberculids and tuberculosis verricosa cutis (TVC).

Results

The patients mainly belonged to the city of Karachi or its outskirts. However some patients came from rural areas of Sindh and Balochistan. Four patients were Afghan refugees settled in Karachi. Females were 45 (60.8%) and males 29 (39.2%).

The age ranged from 1-80 years. Of these 10% were between 1-10 years, 37.8% between 11-20 years, 18.9% in range of 21-30 years, 16.2% in 31-40 years while 16% above 40 years.

Positive family history was present in 43.5% cases. Duration of illness of less than 6 months and 6 months - 1 year was 17.3% each, while 34.9% had lesion for 4-8 years before presenting to the clinic. Primarily the lesions involved the lower limbs (43.4%) of which thigh had 26% of lesions while those on the feet were present in 17.3%. Face, neck and trunk involvements was 17.3% each while genitalia were involved in 8.6%.

Most of the patients had more than one lesion (56.6%), solitary lesions were seen in 43.4%. (Figure 1) Scars and plaques were the main presenting feature (56.5% and 47.8% respectively) whereas nodules (39%), chronically discharging sinuses (39%) and ulcers (30.4%)

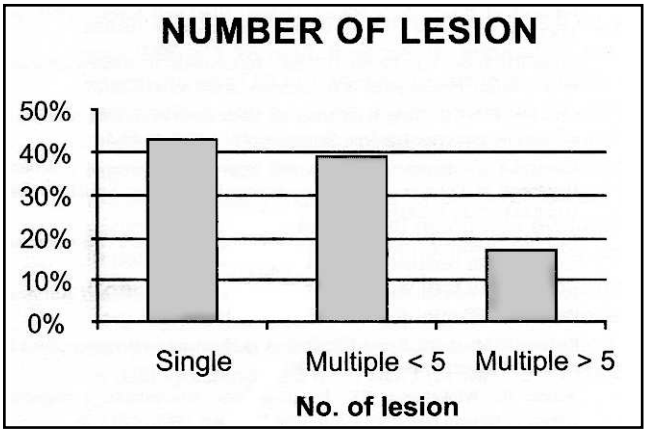

Figure - 1

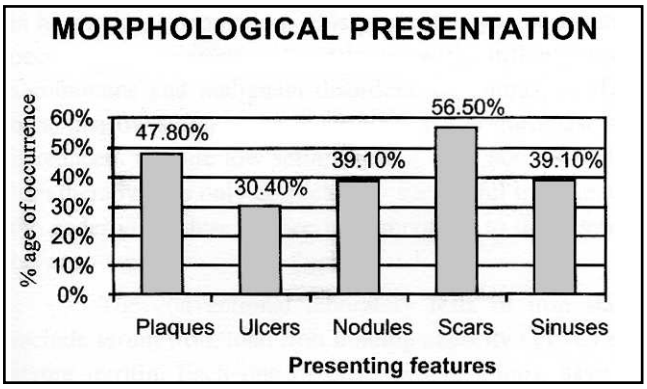

Figure - 2

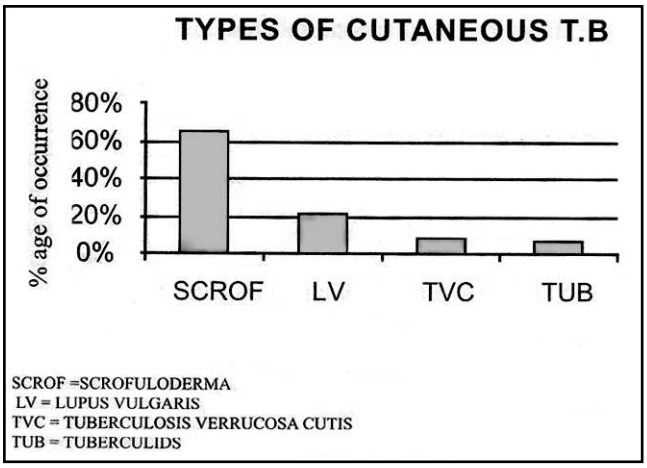

Figure - 3

were also seen (Figure 2). Some patients had a combination of different types of lesions. Scrofulderma was diagnosed in 65% followed by lupus vulgaris in 21%, TVC in 8.2% and tuberculids 5.6% (Figure 3) Mantoux test was done in 60 % patients and was positive in 26%, X-ray chest had hilar lymphadenopathy positive in two patients. Biopsy was done in 40% of patients and was consistent with clinical diagnosis.

Discussion

Cutaneous T.B is a relatively rare clinical entity in western countries but is still prevalent in the developing world such as in Far East it accounts for 0.4% of patients with skin disease.[3] The results of this study clearly show that cutaneous tuberculosis is still far from extinct. In fact it is still present in cities like Karachi. A rising trend over the years (from 1998 through 2002) has been observed. The exact reason for this increase in incidence could not be identified as this was not the aim of study. However, it may reflect the true rise of cutaneous T.B. (Such as systemic T.B.), or simply a better referral from regional centers. The fact that it forms 0.1% of outpatient visit is also important (total O.P.D. visits in three years were 73510). This is comparable to reports from northern India which reported 0.1% incidence in the population between 1975-95. Cutaneous T.B. was a common chronic skin infection in Hong Kong as reported to be 0.35% in a study in 1968. However it has dropped considerably in recent decades, reflected in another survey, where it accounted for only 0.067% of total skin cases.[4] Reported incidence from Europe (Madrid) is 0.14%. In USA skin involvement with tuberculosis is less then 1.5% of total skin attendances where HIV patients were more infected then immuno-competent patients. But in this study none of the patients had any immuno-suppressive condition like acquired immune deficiency syndrome (AIDS), Hepatitis B and C. Although age is no bar to cutaneous tuberculosis, unlike systemic tuberculosis which is more common at both extremes of age. The youngest child with tuberculosis skin lesion was 3 years old and oldest 75 years. However a case report from Vietnam has reported a 5 month old infant presenting with several erythematous nodules and localized adenopathy.[5] In the younger children scrofulderma was commonly encountered where as in older children and adolescent lupus vulgaris was more common.

A slight sexual predilection was observed in our study in all types cutaneous tuberculos lesions. Lesions were more commonly seen in females and primarily on limbs or face. There was a gross delay in seeking specialist advice for skin lesions especially in chronic ones like tuberculosis. This delay was partly attributed to personal indifference and partly to health care facility in the vicinity of residence. Cutaneous tuberculosis being a notoriously chronic lesion has been neglected for months to years before coming to a dermatological clinic by patient or care givers. One patient had a plaque for 8 years on the chest, in another case lesions in groin were present for 7 years. Both were treated by hakims or quacks for years.

The type of cutaneous tuberculosis differs from country to country and is closely related to social and health system development.[6] In our experience scrofuloderma was the commonest type involving skin overlying the tuberculous focus which is usually a tuberculous lymph node in the neck. However underlying tuberculosis of bone may also be found in some cases.

Groin involvement in scrofuloderma was also very common and the lesions were usually multiple. Lupus vulgaris was the next common type of lesion encountered; occurring on face or upper limbs. The lupus lesions were solitary with typical clinical appearance; central scarring with active margins. Tuberculosis verrecusa cutis (TVC) or warty tuberculosis was seen in 8% of patients mostly on limbs exposed forearms. A somewhat similar experience has been reported from other countries (Hong Kong 5%. India 14%).[7] The common type of cutaneous tuberculosis in developing countries, is in contrast to result from developed countries where tuberculosis was the commonest variety (85%).[8,9]

In conclusion it can be stated that a rising trend of cutaneous. T.B. has been observed which may be linked to global resurgence of T.B Cutaneous form of T.B mostly affects young or middle aged people with slightly higher female preponderance. Scrofuloderma is the most common type followed by lupus vulgaris. Delayed referrals leading to long standing extensive lesions are still common necessitating more awareness in general practitioners and mass education of general public.

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Assessment of Resistance in Multi Drug Resistant Tuberculosis Patients

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Abstract

Objective: To study MDR-TB isolates and to identify primary and secondary resistance at microbiology laboratory Aga Khan University, Karachi, Pakistan.

Methods: All samples positive for Mycobacterium tuberculosis (MTB) received during January - September 2004 were reviewed for drug resistance pattern as well as for history of previous antituberculous drugs exposure.

Results: Out of 216 Mycobacterium tuberculosis cultures, 138 (64%) showed resistance to one or more agents. Multi drug resistance (MDR) was observed in 102 (47%) isolates. Of 138 drug resistant isolates; primary resistance to any one or more agent was noted in 31(39%) and secondary (acquired) resistance in 107 (79%) isolates. On analysis of the 102 MDR-TB strains 8 (10%) showed primary resistance while 94 (69%) showed secondary resistance.

Conclusion: In this group MDR-TB was mainly associated with previous anti-tuberculous treatment. However, primary MDR was also observed and reflects dissemination of MDR cases within the community.

Introduction

Drug resistant tuberculosis is becoming a major concern in the control of tuberculosis (TB)[1]. A survey conducted by the World Health Organization and the International Union against Tuberculosis and Lung Disease in 35 geographic sites, revealed that drug resistant tuberculosis is ubiquitous and prevalence of primary resistance to at least one drug is around 10.7 percent.[2]

Multi drug resistant tuberculosis (MDR TB), defined as resistance of Mycobacterium tuberculosis to at least Isoniazid and Rifampicin[3] is a major threat to the tuberculosis control program. The mortality from multi-drug resistant tuberculosis is 40-60%[4] which is equivalent to the outcome of untreated tuberculosis. Therefore, the spread of resistant strains in poor countries would mean a return to pre-chemotherapy patterns of mortality.

Acquired drug resistance was defined as the acquisition of resistance to anti-tuberculosis drugs by the multiplication of

the resistant mutant strain of bacteria as a result of inadequate chemotherapy. Primary drug resistance, on the other hand, develops in patients who become infected with a resistant strain without ever having been treated with anti-tuberculosis drugs.[5] While resistance in previously treated patients is likely to reflect past incorrect or irregular treatment, resistance in new, untreated patients is evidence of transmission of resistant strains. Globally, the prevalence of MDR-TB is reported at 1.4% in primary cases and 13% in previously treated patients.[6] Early detection and treatment of MDR strains is important in disease control. In addition, knowledge of drugs susceptibility pattern in MDR clinical isolates is necessary in order to design appropriate treatment regimen.

In Pakistan, where incidence of tuberculosis is estimated at 181 per 100,000 populations, rising drug resistance is alarming.[7] Recent report[8] showed 28% of MDR TB strains from northern Pakistan, a marked difference from previously reported[9] rate of 16% MDR in 2001 (Table-1). Continuous monitoring of drug resistance pattern especially of MDR isolates to determine the extent of primary (1^o) and acquired (2^o) resistance is a crucial need for future TB control in Pakistan. In this study we assessed the primary and secondary MDR isolates.

Table 1: Reported antituberculous resistance from Pakistan.

Reference	Sample size	Overall Resistance (%)			Resistance (%)					MDR (%)		
		Total	1^0	2^0	INH	RIF	PYR	ETH	STREP	Total	1^0	2^0
Karachi 1993 (14)	145	-	17	36	-	-	-	-	-	-	-	-
Karachi 1996 (15)	156	45	-	-	27	11	-	14.5	13	8	-	-
Rawalpindi 1999 (16)	300	53	-	-	26	24	-	23	28	14	-	-
Lahore 2001 (9)	228	52	-	-	25	25	24	10	21	16	7.3	26
Sind 2002 (17)	50	73	-	-	60	24.4	-	22	38	25	-	-
Lahore 2002 (18)	100	36	-	-	25	15	-	12	19	11	-	-
Lahore 2003 (19)	678	53	-	-	26	28	29	15	24	16	-	-
Rawalpindi 2004 (8)	325	49	-	-	37	32	-	17	19	28	-	-

1^O= Primary resistance, 2^O= Secondary resistance, Overall resistance= Resistance to any antituberculous agent.
MDR= Multi drug resistance , INH=Isoniazid; RIF=Rifampicin; PYZ=Pyrazinamide; ETH=Ethambutol; STREP=Streptomycin
% Resistance= Resistant organisms as% of total isolates.

Material and Methods

This study was conducted in the Clinical Microbiology Laboratory of The Aga Khan University between January-September 2004. Detailed history of antituberculous therapy was obtained and reviewed in all patients with positive cultures for Mycobacterium tuberculosis (MTB).

All samples (except those from the sterile sites) were decontaminated with N-acetyl-L-cysteine (NALC) sodium hydroxide. Sterile body fluids were processed without decontamination procedure. The sediments were used for AFB microscopy and cultured on BACTEC (12Bvial Becton Dickenson) and LJ slant (Oxoid).

Smears for microscopy were checked using Auramine staining, positive slides were further confirmed by staining with Kinyoun modification of Z-N stain.

Cultures were performed using LJ slants and BACTEC 460. For LJ slant 0.1 ml of concentrated specimen was inoculated and incubated for 8 weeks.

Similarly BACTEC vials were inoculated with 0.5 ml of specimen and incubated at 37°C after supplementation of medium with PANTA; containing Polymyxin B, AmphotericinB, Nalidixic acid,Trimethoprim and Azlocilin. Growth index of inoculated vial were checked for four weeks. Growth from the positive vials and LJ slant tube were first stained with Kinyoun and confirmed using NAP test.

Indirect antimicrobial susceptibility test

Antimicrobial susceptibility for four primary drugs including Isoniazid (INH) 1.0 µg/ml, Rifampicin (RIF) 1.0 µg/ml, Ethambutol (E) 10.0 µg/ml and Streptomycin(S) 10.0 µg/ml was tested using modified agar proportion method. Disc elusion sensitivity plates were prepared using paper sensitivity disc (BBL).

McFarland No.1 standard suspension of isolate was made from growth on LJ slant and diluted to 10-2 and 10-4 dilutions. The inoculated plates were incubated at 35°C and examined for growth each week for 8 weeks. M.tuberculosis was considered resistant to

a given drug when growth ≥1% above the antibiotic free control was observed in drug containing area. MTB H37Rv was used as control with each batch of susceptibility testing.

Sensitivity of Pyrazinamide (PZA) was performed using BACTEC 7H12 medium pH 6.0 (BACTEC TM PZA test medium). Lyophilized PZA was reconstituted and aseptically 0.1ml of PZA solution was added to PZA medium vial. 0.1ml of freshly sub cultured organism was added to PZA and incubated at 37°C with daily check of test and controlled vial in BACTEC 460.

Results

We reviewed 216 cases for history and drug susceptibility pattern, 80 (37%) cases had no history of prior antituberculous treatment, while 136 (63%) cases had previous exposure to anti tuberculous therapy. Almost one third 78 (36%) cases were fully sensitive to all five first line drugs (Isoniazid, Rifampicin, Pyrazinamide Ethambutol and Streptomycin) while 138 (64%) showed resistance to one or more agents. Amongst these, primary resistance was seen in 39% and secondary resistance in 107 (79%) of our samples, whereas 60% of isolates were resistant to Isoniazid Figure 1.

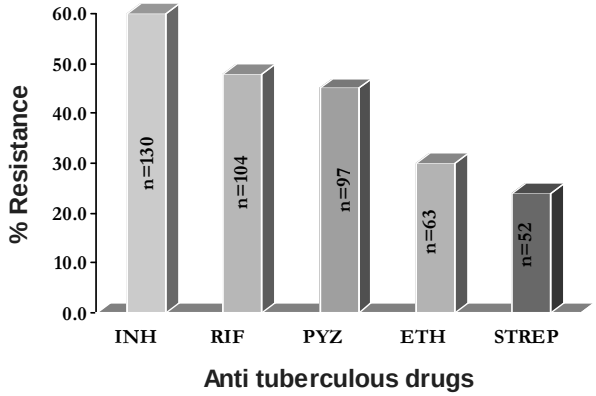

Figure 1: Individual Drug Resistance in M.tuberculosis isolate (n=216).

Resistance to a single agent was noted in 20 (15 %) of the 138 resistant isolates Figure 2, majority of which was against Isoniazid (n=13). Among the strains showing resistance to two drugs resistance to a combination of Isoniazid plus Rifampicin was highest (n=14), followed by resistance to Isoniazid plus Pyrazinamide (n=5) and Isoniazid and Streptomycin (n= 4). Thirty two strains showed resistance to three drugs. The largest amongst these were resistant to Isoniazid plus Rifampicin plus Pyrazinamide (n=28). Finally 25 (18%) isolates showed

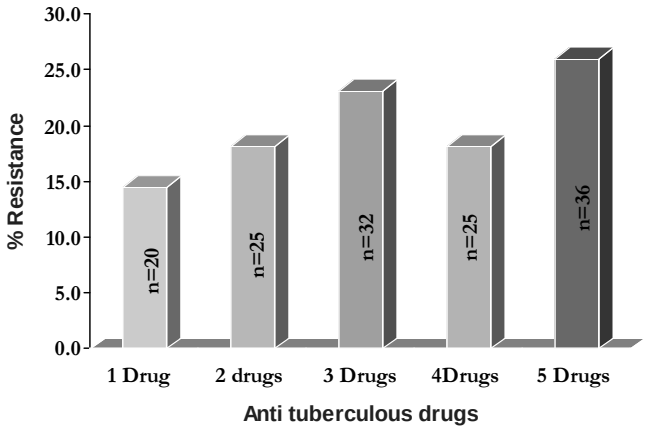

Figure 2: Analysis of drug resistant isolates in term of resistance pattern (n=138).

resistance to four drugs with combination of Isoniazid Rifampicin Pyrazinamide and Ethambutol in 21/25.

Multi drug resistance (MDR) was observed in 102 (47%) isolates studied.

Analysis of 102 patients with MDR-TB showed that 8 (10%) had primary resistance while 94 (69%) had a history of previous exposure to anti-TB drugs (acquired resistance)

No cross-resistance to other antituberculous drugs was noted in 14 (10.5%) MDR strains, while 28 (27%) showed cross-resistance to one other drug and 24 (23.5%) to two drugs and 36 (35.2%) of MDR isolates were resistant to all five first line antituberculous agents.

Discussion

Globally, prevalence of multi-drug resistance tuberculosis (MDR-TB) has increased over the past few years. World Health Organization (WHO) estimates suggest that over 50 million people worldwide are infected with drug-resistant tuberculosis.[10] A number of global hot spots with ≥3 % primary MDR-TB have been identified including Estonia, China, Russia, India and Iran.[11] WHO concerns have been raised indicating that levels of MDR-TB will reach an alarming state in South East Asia unless urgent steps are taken to control the increasing level of resistance.[12]

Pakistan ranks sixth among the list of 22 high TB burden countries with a TB related death rate of 43/100,000 population annually.[13] Resistance to TB drugs has been widely reported from various parts of the country[8-9,14-19], however, pertinent community based data that represents a national profile is lacking. In the absence of community data, hospital based studies provide indication of the levels of drug resistance and particularly of resistance trends over the years. Our study showing an overall resistance rate of

64% to the antituberculous drugs confirms 36-73% resistance rates reported in earlier studies.[8,9,14-19]

Thirty nine percent primary drug resistance to at least one drug however represents a marked increase from 17% resistance reported in 1993 by Khan et al.[16] We report an overall 79% acquired resistance, which indicates magnitude of non-compliance as well as partial treatment in TB patients.

Sixty percent of the isolates in this study were resistant to Isoniazid of which 80% (102/130) were MDR. More alarming is a fact that 67%(93/138) of total drug resistant isolates showed resistance to three or more agents. This finding is again consistent with the rising Isoniazid and Rifampicin resistance reported earlier from this country.[8]

The reported single drug resistance worldwide is 10%. Analysis of 138 resistant isolates in our study revealed 15 % (n=20) resistance to single agent with the majority being resistant to Isoniazid (a risk factor for future MDR) with 39% being primary resistance. It has earlier been reported that 70.8% of tuberculosis patients with either Isoniazid or Rifampicin resistant strains acquire MDR-TB following treatment failure.[20]

We observed very high level of MDR-TB strains (47%) in our isolates. This finding support the rising MDR trends reported in earlier hospital based studies from the country and is consistent with a recent hospital based study from Mumbai (India) indicating 51% MDR rate in their isolates.[21] The high MDR rate noted in this study and reported elsewhere in the country and region is a matter of great concern. We report 10% primary MDR cases which again supports the hypothesis of rising trend of primary and secondary resistance when compared with 7% primary MDR reported by a hospital based study in 2001.[9]

Finally this study is reflecting the rising trend of resistance in community, however pure community based studies are needed to confirm these findings.

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BCG Scar Survey in Karachi Schools

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Introduction

Scar surveys at regular intervals are a measure of BCG coverage in a population. BCG has been the main stay of tuberculosis control in Pakistan since 1952. In 1977 mobile teams were disbanded and responsibility for BCG was given to rural health centres and tehsil hospitals. Recently BCG vaccination has been integrated with extended program of immunization (EPI).[1] According to 1974-78 survey BCG scar was seen in only 9.4%[2] of children between the ages of 0-14, while in Sindh it was only 4.9%. This was a poor result, confirming very low BCG coverage.

The present study was planned to see the beneficial effect, if any, of BCG in making it a part of EPI programme by conducting a scar survey in Karachi school population.

Subjects, Methods and Results

A cross section of primary and secondary schools of Karachi both in upper and lower socio-economic areas were selected and all students of the selected schools were examined for BCG scars.

A total of 6214 students (2016 males and 4198 females) were examined. Male to female ratio was 1:2 and the average age was 10 years with a range of 5-19 years. Scars were seen in 2025 (33%) while 4189 (67%) had no scars. Amongst 2025 patients with scar, 769 (38%) were males and 1256 (62%) females (Table I). The percentage coverage was fairly constant in different age groups (Table II) which ranged from 32% amongst 10-19 years to 37% amongst 5-9 years.

Table I: Scars survey in Karachi school.

	BCG scars + ve (n = 2025)	BCG scars - ve (n = 4189)	Total (n = 6214)
Male	769 (38%)	1247 (30%)	2016 (32%)
Female	1256 (62%)	2942 (70%)	4198 (68%)

Table II: Age distribution in scars positive and negative.

Age group	Positive (n = 2025)	Negative (n = 4189)	Total (n = 6214)
9-May	368 (37%)	621 (63%)	989 (16%)
14-Oct	1294 (32%)	2812 (68%)	4106 (66%)
15-19	363 (32%)	756 (68%)	1119 (18%)

Comments

The 1974-78 national tuberculosis prevalence survey showed BCG scar in 9.7% of the Pakistani population and for Sindh province the figures were half that of national figures, being only 4.9%.[1] Though break-up for urban and rural population is not available, one would presume that percentage for urban areas would be higher.

Situation seems to have improved some what but coverage still remains very low. Karachi being the most developed city of the province with better medical facilities showed that only 33% had scar; the figure would be even lower for the rural areas. The percentage of those who actually develop immunity would be even lower when other factors like break-down in the cold chain and faulty technique are taken into consideration.

For BCG to have any epidemiological effect the coverage of BCG will have to be at least 80% or more.

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Factors affecting tuberculosis control: Decision-making at the household level

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Abstract

Objective: To explore the factors influencing decision-making process at household level vis-à-vis decision to seek health care, decision regarding the type of care and the decision to continue treatment.

Design: Cross-sectional study.

Place and Duration of Study: Government TB Center, Rawalpindi, from 16th January 2002 to 28th February 2002.

Subjects and Methods: In total, 100 smear positive patients were included in the study. First questionnaire was administered to first 50 randomly selected patients. The ethnographic decision models (EDM) were developed from the responses. The second questionnaire, derived from these models, was administered to the second group of randomly selected 50 patients to test the predictive ability of the EDM.

Results: Decision-making regarding treatment of tuberculosis was influenced by patients' knowledge about the disease itself as well as its severity, infectivity and curability. Close relatives were found to play a critical role at all the decision-making levels. The EDM developed on these results had 80-90% ability to predict the decision-making in tuberculosis patients.

Conclusion: Effective health education, easy accessibility to treatment centres and trained and motivated health care providers can go a long way in making national TB control program a success.

Introduction

Health and well-being is the net result of multiple, inter-linked biological and socioeconomic factors. Management and control of any known disease depend on knowledge, social acceptance, norms and attitudes not only towards the disease but also towards persons suffering from that disease. Communities asually perceive tuberculosis (TB) as a dangerous, contagious and untreatable disease.[1] This understanding has many social implications particularly stigmatization[2] and social isolation of TB patients and even their families. Due to the social connotations, patients are often reluctant to accept or reject the diagnosis and treatment.[3] The success of any tuberculosis control program depends upon early diagnosis, treatment initiation and treatment adherence for a prescribed period of time.[2] In this context the socioeconomic factors that influence the decisions made at the household level are very important as these directly affect the above variables.

Pakistan is included in the sixteen countries where lack of progress in fighting tuberculosis is threatening global TB control efforts.[4] Case detection (25%) and case holding (50%) is very poor.[5] Household decision-making has a role in utilizing public sector health facilities for tuberculosis control.

Medical decision-making process is three tiered comprising of decision to seek care in case of illness, type of health care and continuation of treatment for the prescribed period of time. These levels are influenced by various factors related to the patients, the health care system and treatment outcomes.[6] Perceived susceptibility to and severity of the disease are of paramount importance in decision-making.[7]

Ethnographic decision models (EDM) are qualitative causal analyses that predict the choices people make in certain illness conditions.[8,9] They have been used to study how people decide and select the type of treatment for an illness and chose among various available alternatives. In the first instance, the patients are asked relevant questions without directly addressing the dependent variable or the actual decision. Their answers are used to develop an ethnographic model that can predict responses in similar patients. Later a second set of patients is directly asked about the variable of interest. A good model should have the ability to predict 80-90% of the decision. Prediction of dependent variable (like decision to seek health care, decision to continue the treatment) on the basis of some independent variable like family involvement, education of the patient and socioeconomic status is the objective of analysis.

The objective of this study was to explore the factors influencing decision-making process at household level vis-à-vis decision to seek health care, decision regarding the type of care and decision to continue care .

Methodology

This cross-sectional study was based on ethnographic decision modeling (EDM). The study was completed in two phases. In the first phase, the factors influencing the decision-making were identified and used in developing three separate EDM trees, corresponding to the three levels of decision-making. These models were then tested during the second phase to determine their ability to predict the decision of a different group of patients.

All the sputum-smear positive patients registered at TB Center, Rawalpindi and being treated at this center, during

January-February 2002, were included in the study. Every 5th patient was administered exit questionnaire, a total of 50 patients in each group. Sputum-smear negative patients, extra-pulmonary tuberculosis patients and patients under 15 years of age were excluded from the study.

A structured questionnaire, used for the first phase of study, was developed which sought information about factors influencing their decision to seek care, choosing type of health facility and treatment continuity. EDM for three levels of decisionmaking process were built upon the responses of the interviews. A second structured closed-ended questionnaire was derived from these models which had four sections, first section required general information while the rest three sections dealt with the factors determining the three decisions. The questions were constructed in such a way to get Yes/No response. At the end of each section there was one open-ended question to seek any new information which was missed in the first round of interviews. It was administered to the second group of 50 patients to test the predictive ability of the EDM. The two types of questionnaires were translated into Urdu and pre-tested. After minor additions and modifications these were administered to the selected respondents. All the information gathered was pre-coded and entered in Statistical Package for Social Sciences, version 7.5 (SPSS 7.5). Both the data sets were analyzed separately.

Results

In the first phase, data was collected from a total of 50 patients. This group comprised of 60% males and 40% females. The mean age of the respondents was 34.2 years (± 16.03), with an overwhelming majority (90%, n=45) in the economically productive age group (15-59 years). Most of the respondents (60%) were illiterate and living in 1-2 rooms house. Threefourth of the respondents reported an average of 8 family members in their households.

The factors influencing the three tiers of decision-making process, namely seeking health care, choosing a specific health care facility and continuing the prescribed treatment, were explored in detail through individual interviews with the respondents.

Symptoms suggestive of TB, like cough, fever, chest pain and general ill- health, were cited as the reason to seek medical care by all (100%) respondents. Although all the respondents were aware of the seriousness of the disease, it was the severity of symptoms that prompted 62% of the patients to seek medical care. Family advice influenced this decision in most (68%) of the respondents, while 32% decided on their own. Family support was a very important factor for a vast majority (94%). The other contributory factors were inability to work, fear of harming one-self and other family members due to the disease and the patient's knowledge about the curability of tuberculosis. The EDM tree regarding decision to seek medical care is shown in Figure 1.

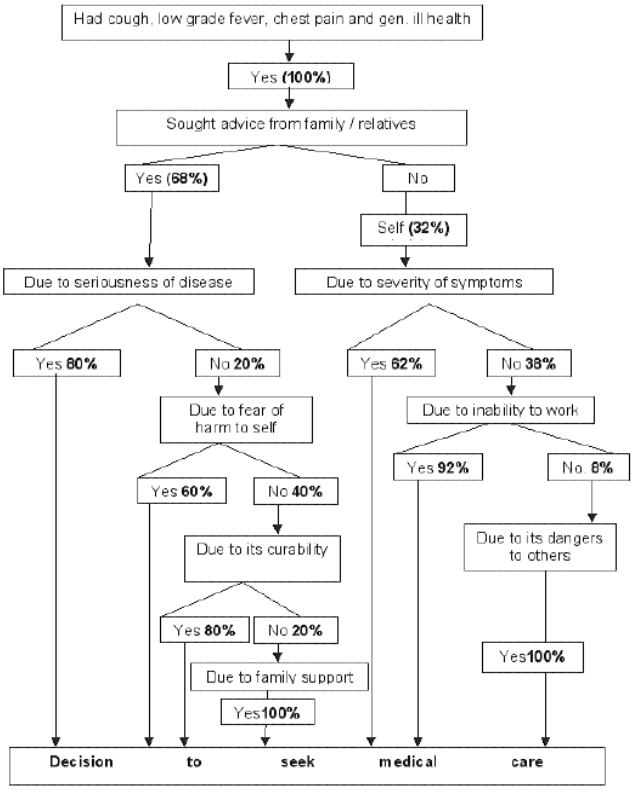

Figure 1: EDM tree for decision to seek care.

Family and relatives played important role regarding the selection of a particular type of health care and 68% of respondents decided after taking advice from them. The other factors that influenced their decision in this context were favorable distance from their place of residence, waiting time and the cost of treatment. The EDM tree for this decision follows in Figure 2.

An important factor for continuation of care decision was the continuing family support and encouragement. However, 70% of patients acknowledged the positive attitude of the health care provider. The availability of free medicines at the health care facility and improved ability to work due to treatment adherence also contributed towards continuity. Other factors found to be important were fear of social isolation, developing complications and infecting close family members. Knowing about someone who had been cured of TB, due to successful treatment, was also given as a positive influence on the decision to continue treatment.

The three decision models based on the responses of the first group of patients were then tested on a second group, in order to find out their ability to predict the most likely

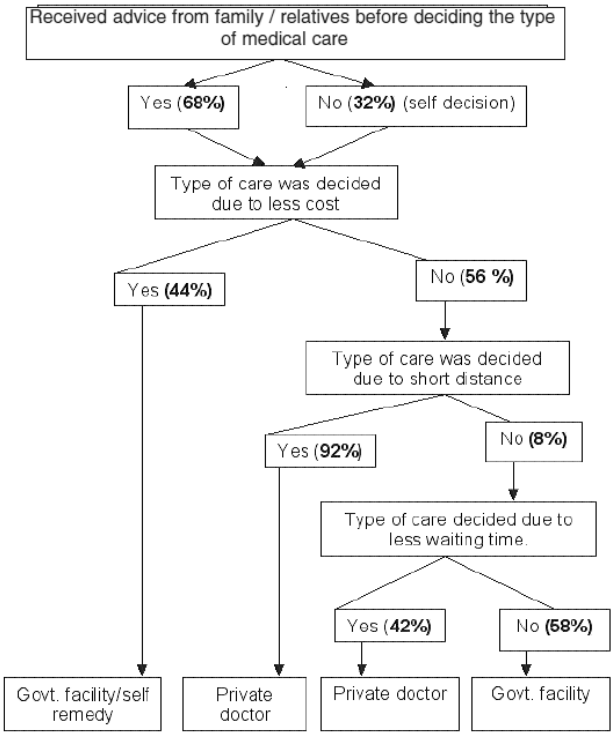

Figure 2: EDM tree for decision regarding type of medical care.

option in decision-making. The second group had 26 (52%) males and 24 (48%) females. These EDMs were able to predict the decision to seek care in 88% respondents, decision regarding the type of care in 83% of the patients and the decision for the continuity of care was predicted in 89% of respondents. Figure 3 illustrates these results.

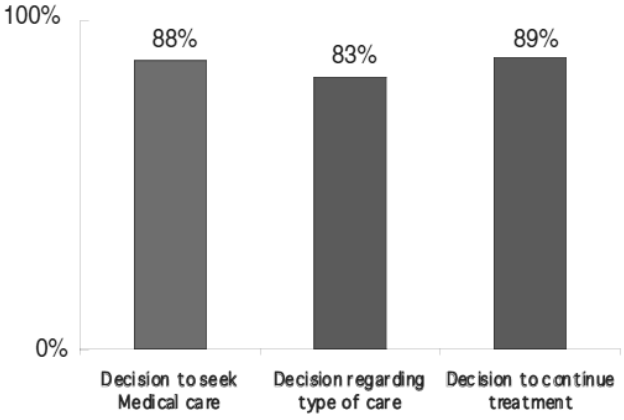

Figure 3: Results of EDM testing in 2nd phase.

Discussion

It is important to identify the factors influencing decisionmaking process at household level in tuberculosis patients in any society, which can either facilitate or delay appropriate remedy for any disease.[10]

In this study the mean age of the respondents was 34.2 years (± 16.03), and most of the patients (91%) were in the economically productive age group of 15-59 years. This finding is comparable and consistent with those reported for tuberculosis cases in developing countries.[11,12] The low rate of diagnosis, in-effective treatment, insufficient health services and patients' non-adherence are the cause of high prevalence of tuberculosis in Pakistan.[3]

The gender distribution of the study population shows the predominance of males (56%) over females. This trend, as also reported from other areas of Pakistan,[13] may be due to the fact that males have less social constraint in seeking medical care as compared to females in Pakistani society. Most of the respondents (60%) were illiterate and belonged to the low socioeconomic strata. With as many as eight family members living together, congestion is taken as an indicator of poverty. Similar findings in other studies support that tuberculosis is basically a disease of the poor, not only in a developing country like Pakistan, but also in the developed world.[14]

A majority of respondents 85% (n=85), suffering from symptoms suggestive of tuberculosis, decided to seek medical care after getting advice from close family members usually living under the same roof (75 %, n=75). The facilitative role of close family members in deciding to seek care was also observed in a study done in India.[15]

The majority (>80%) decided to seek care because the symptoms were severe and they also realized the seriousness of disease. Patient's understanding about the disease was an important factor, which influenced their decision to seek care. Here, 85% of respondents thought it was a harmful disease if not treated, and 75% perceived it to be dangerous to other family members.

The choice regarding type of medical care was influenced by recommendation from family and relatives (68%). This factor influencing choice of a particular healthcare provider was also noted in a Karachi-based study.[14] More than 80% of the patients had decided on privately practicing doctors for treatment, giving reasons such as perceived competence of the health care provider to treat a serious disease like TB, less distance and less waiting time at the health care facility. Reduced cost was also an important factor in those respondents who opted to utilize a public health care facility. Comparable findings were also reported in an Indian study.[16] Unfortunately their first contact health provider diagnosed only 36% of the respondents, although this is higher than what is reported elsewhere.[5,16] This difference may be due to the fact that many urban respondents were also consulting government doctors in other hospitals at Rawalpindi. Family members of the

respondents played an important role in choosing the type of health facility. This is similar to other studies found in literature.[3,9]

Lack of treatment completion is an important problem in tuberculosis control program in Pakistan. It is estimated that over half of the patients taking anti-tuberculosis drugs do not complete their treatment.[3] In this study, the factors that contribute to completion of TB treatment vary from individual and family, to provider. Majority of respondents (90%) said that the support and encouragement extended by their family enabled them to complete TB treatment. Health education and counseling to the patients and their families by the staff of TB center was mentioned by 85% of respondents as a positive influence in this regard. Comparable observations were made in other studies.[10,13] All of the respondents mentioned general improvement in health as an important reason for their decision to continue treatment, while improved ability to work was found to be an influential factor for 54% of respondents, particularly married women and breadwinner of the family.

The patients' perception about seriousness and infectivity of tuberculosis and their belief in its curability were major contributory factors in the decision to complete the treatment period. Fear of infecting others and developing complications were also stated as reasons for compliance with treatment. Knowing someone who had been cured of the disease was also an important factor to continue the treatment. Free treatment, including tests and regular provision of anti-TB drugs, was also found to be a reason for continuation of treatment in a study conducted at Services Hospital, Lahore.[18]

Conclusion

In this study the factors affecting decision-making process were explored at three levels, vis-à-vis decision to seek medical care, decision regarding type of health care and decision to comply with the treatment regimen.

Family support, free and uninterrupted supply of drugs, motivation by the health care providers and the knowledge about tuberculosis are the factors operative at all three levels of decision- making.

Recommendations

To strengthen the TB control, the study recommends some interventions, both immediate, for shortterm improvement, and long-term, for a sustainable change.

1. Correct knowledge and increased awareness about TB among the common people can remove their misconceptions and influence their health-seeking behavior favorably.

2. Public-private collaboration is very important as nearly 80% of the population go to private sector but can only be effective after strengthening the public sector first. Very few of TB patients are correctly diagnosed and properly treated.[5] Providing organized educational inputs and guidance to the private sector health care providers, in line with the standard TB control guidelines, can rectify this problem.

3. The program should be more patient-friendly. Diagnosis of TB, its treatment, and follow-up of patients till they are cured are all, simple enough to be effectively carried out at the level of primary health care.

4. Field-based research at community level is recommended to explore the problems and their solutions in order to improve program utilization.

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Frequency of dual tuberculosis/human immunodeficiency virus infection in patients presenting at Tertiary Care Centers at Karachi

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Abstract

Objective: To determine the frequency of dual infection of Tuberculosis and Human Immunodeficiency Virus (HIV) and document the sexual practices of infected patients.

Design: Cross-sectional study.

Place and Duration of Study: Medical Unit-IV of Civil Hospital, Karachi, Pakistan, in collaboration with Sindh AIDS Control Program at Services Hospital, Karachi, from January 2003 to December 2004.

Patients and Methods: Patients were recruited in the study at both centers and tested for both HIV and TB if any one disease was identified. Diagnosis of TB was based on positive sputum AFB smear / caseous granulomatous lesion on histopathology. Diagnosis of HIV was based on positive anti-HIV serology by LISA technique. A questionnaire was also administered to all the study participants regarding demographics, sexual practices, blood transfusion and intravenous drug abuse.

Results: A total of 196 patients of HIV and TB were screened for the presence of dual infection (TB/HIV). Dual infection was present in 38 (19.39%) of patients. Out of 126 patients of HIV, evidence of TB was detected in 38 (30.16%). During the same duration, 70 patients of tuberculosis were screened for HIV and none was tested positive for HIV. History of illicit sexual relationship was found in 121 (96.03%) patients and 5 of these were homosexuals.

Conclusion: Dual infection was present in patients of HIV with TB but vice versa was not documented in this study.

Introduction

Globally, tuberculosis (TB) is becoming a leading cause of HIV-related morbidity and mortality. In developing countries, HIV-infected people run 10% annual risk of developing TB.[1] At least one in three people with HIV are likely to develop TB.[2] HIV fuels the TB epidemic, since it promotes progression to active TB in people with mycobacterium tuberculosis infections, either acquired recently or in the past.[1] Increased risk of TB is present across the entire spectrum of immunodeficiency. The implication for TB control in high HIV prevalence populations is that prevention of HIV is crucial to control TB.[3] HIV- related TB can occur at any stage.[1] The risk of death in HIV infected patients with TB has been reported to be twice that in HIV infected patients without TB independent of the CD[4] cell count.[5]

Pakistan has been ranked sixth by WHO in terms of the estimated number of TB cases. The South East Asian statistics for TB per 100,000 population reported the incidence at 182, smear positive cases at 81, prevalence at 304 and mortality at 33.[6] HIV is now increasingly being documented in patients suffering from TB in various parts of the world including neighboring India.[7-10] Pakistan has a very strong private health sector, particularly in the major cities, and it is estimated that approximately 80% of TB patients, seeking treatment, initially report to private medical practitioners for their diagnosis and treatment.[11] HIV in Pakistan is on the rise. According to the UNAIDS report on Global AIDS Epidemic 2006, there are 85,000 cases of HIV/AIDS in Pakistan. Among them 84,000 are more than 15 years of age and 14,000 are adult females. The report also states that there were 3000 deaths related to HIV/AIDS in the year 2005.[12] The prevalence of dual infection of TB/HIV is not reported from Pakistan. The purpose of this study was to document the frequency of dual infection of TB/HIV and sexual behavior in infected persons.

Patients and Methods

This cross-sectional study was conducted at Medical Unit IV, Civil Hospital, a tertiary care teaching hospital in Karachi, Pakistan, in collaboration with Sindh AIDS Control Program from January 2003 to December 2004. Patients were recruited in the study at both centers. Patients presenting with tuberculosis were enrolled at medical unit of tertiary care teaching hospital (CHK) and allocated to group A; while patients with HIV were enrolled at the Sindh AIDS Control Program at Services Hospital, Karachi and allocated to group-B. Informed consent was obtained from the study participants and counseling for HIV and TB was done before subjecting the patients for further testing. Exclusion criteria included those unwilling to participate and patients less than 16 years of age. Investigations carried out in all patients included complete blood counts (CBC), ESR, sputum for AFB smear, anti HIV-I, anti HIV-II, chest X-ray and in selected cases ultrasound, CT scan, MRI and biopsy with tissue histopathology, if indicated. CBC was done on Sysmex auto-analyzer, AFB smear was reported after Ziehl-Neelsen staining by microbiologist, tissue histopathology by histopathologist and chest X-rays were

reported by radiologist. HIV-antibody tests were carried out according to WHO and national HIV testing guidelines at referral laboratory of Sindh Aids Control Program. All samples were initially tested for HIV-I and II on Dade Behring (EIA) kit (WHO listed) on multiscan MS system. All reactive samples were further tested on Organon EIA plus Abbotdetermine (ICT method) kit as a part of protocol based on WHO guidelines. All reactive samples were further tested on western blot assay (Gen lab kit), which confirms HIV-I infection. All HIV positive patients were subjected to chest Xrays and sputum for AFB smear testing. Three morning fasting sputum specimen were collected. Those who were not producing sputum were nebulized with saline to get the required sample. Patients having lymphadenopathy were subjected to fine needle aspiration cytology/excision biopsy.

A questionnaire was also administered to all the study participants. It collected information regarding demographics, sexual behavioral characteristics, blood transfusion and intravenous (IV) drug abuse.

Frequency of patients positive to both TB and HIV was estimated from the total number of patients enrolled. Percentages were calculated for ethnic, sexual practices and drugs. Mean ± standard deviation were calculated for age. As no comparative analysis was done, p-values were not calculated.

Results

A total of 196 patients of HIV and TB were screened for the presence of dual infection of TB/HIV during the study period. Dual infection was present in 38 (19.39%) of patients (Figure 1).

During the study period, 126 patients of HIV were detected at Sindh AIDS Control Program and all of them were screened for tuberculosis. Mean age of these patients was 36.8 ± 6.4 years. Ethnic distribution of these patients was Balochi 50 (39.68%), Sindhi 20 (15.87%), Urdu-speaking 25 (19.84%), Punjabi 15 (11.90%) and Pathan 16 (17.70%, Figure 2). Evidence of TB was detected in 38 (30.16%) patients. Eighty seven (69.04%) patients were married.

All patients were not aware about the mode of transmission of HIV before acquiring the disease. History of needle sharing for drug was present in 5 (3.97%) patients. One hundred and twenty (95.24%) had acquired the infection out of Pakistan and all of them were working in Gulf countries. They were deported when their HIV status was checked at the time of renewal of visa. None of these patients gave history of blood transfusion.

For the same duration, 70 patients of tuberculosis presented at medical unit and were screened for HIV. None of the patients tested positive for HIV. The mean age of these patients was 30.6 ±11.3 years. These included 58

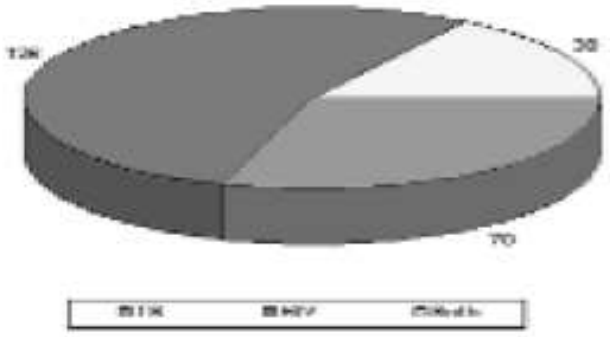

Figure 1: Frequency of TB and HIV.

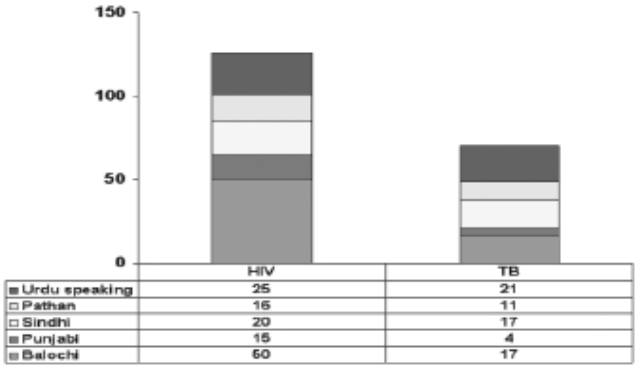

Figure 2: Ethnic distribution of HIV and TB patients.

(82.86%) males and 12 (17.14%) females. Among this group, 56 (80%) patients were married. Ethnic segregation in this group was 21 (30%) Urduspeaking, 17 (24.29%) Balochi, 17 (24.29%) Sindhi, 11 (15.71%) Pathan and 4 (5.71%) Punjabi (Figure 2). Thirty nine (55.71%) were uneducated and belonged to labor class whereas remaining had studied from 10-12 classes.

These patients were also questioned for the risky behaviors which were negligible. Only 3 married patients gave history of ever having sex out of wedlock that too not with any high risk group. There was no IV drug user in this group of patients. Only 2 patients had history of blood transfusion.

Discussion

While TB is highly prevalent in South East Asia including Pakistan, it is common among HIV infected patients also.[9,13] It is responsible for one-third of all the AIDS-related deaths in developing countries.[13] The present study showed about 30% of HIV patients found were suffering from TB on screening. This was in comparison to 25% by Indian author and 24% in Cambodia. These studies all support the WHO recommendations of screening HIV patients for tuberculosis before initiation of Highly Active

Anti-Retroviral Therapy (HART).[16]

Many parts of the world have witnessed high prevalence of HIV in patients with TB.[14] Due to this fact some countries have started screening for HIV in all the immigrants with TB.[15] In countries with high HIV prevalence, TB patients need testing for HIV co-infection for the potential benefit of early diagnosis.[17] However, absence of HIV infection in patients of TB in our study does not support this recommendation for implementation in our area at present. In the African region where HIV prevalence is very high and the prevalence of TB has also been found quite high, ranging between 40-50%.[18,19] In developed countries where TB had become a problem of only immigrant population, it has re-emerged as a result of HIV emergence and is rapidly becoming common.[20]

HIV is still restricted to high risk groups in Pakistan. The infection is rapidly increasing among injection drug users (IDUs) in Sindh as well as other parts of the country.[10] The infection has not yet gained a solid place among the general population. However, TB has a stronghold throughout the country. The implication for TB control in high HIV prevalence populations is that prevention of HIV is crucial to control TB.[3]

The implications for HIV/AIDS control programmers are substantial as TB has now become an integral part of HIV/AIDS care.[3,4] However, so far, TB and HIV control programs have largely pursued separate courses. It is necessary to improve the joint support of TB and HIV programs at Primary Health Care (PHC) level, in responding effectively to the needs of people infected with HIV.[4]

The study was limited to a small number of cases, however, in the absence of local data this could be used as a baseline and well-designed epidemiological studies can be conducted in future.

Based on the findings of the current study, all newly diagnosed HIV cases are preferably assessed for TB as a baseline and all HIV cases with fever and cough must be evaluated for tuberculosis. In addition, TB patients with high risk behaviors (like sexual promiscuity, homosexuals and IV drug users) also need to be tested for HIV status.

Conclusion

Dual TB/HIV infection was present in patients of HIV with TB super infection but vice versa was not documented in this study. Screening for HIV in tuberculosis patients without high risk behavior is not mandatory in our region.

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An update on the diagnosis of tuberculosis

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Abstract

Tuberculosis (TB) continues to be the bane of mankind. Early diagnosis is the cornerstone of tuberculosis control strategies. Recent years have seen major advances in the fields of biotechnology and molecular biology with introduction of several new diagnostic techniques for tuberculosis and improvement in the existing ones. The new automated culture techniques have appreciably reduced the time required for detection and antimicrobial susceptibility testing. The molecular amplification techniques like the Polymerase Chain Reaction (PCR) have made the same-day diagnosis a reality. Improvements in serology and introduction of novel new techniques like the bacteriophage assays have also shown a lot of promise. However, most of these new techniques are too expensive and sophisticated to be of any practical benefit to the vast majority of TB patients living in underdeveloped countries like Pakistan for whom an early and inexpensive diagnosis remains as elusive as ever. In this article various existing modalities as well as the new advances in TB diagnostics are reviewed.

Introduction

Tuberculosis (TB) describes a broad range of clinical illnesses caused by Mycobacterium tuberculosis complex. Characteristic features include a generally prolonged latency period between initial infection and overt disease, predominantly pulmonary disease (80% of all cases) and a granulomatous response with intense tissue inflammation and necrosis.[1]

Man's association with tuberculosis goes back to antiquity. Recent DNA fingerprinting of Mycobacterium tuberculosis complex using the Restriction Fragment Length Polymorphism (RFLP) analysis has suggested that the common progenitor of the tubercle bacilli had evolved around 15-20,000 years ago and was already a human pathogen.[2]

Mycobacterium tuberculosis is probably the most important human pathogen today and TB one of the deadliest diseases known to man. According to World Health Organization (WHO) estimates, one-third of the world's population is infected with Mycobacterium tuberculosis. Each year more than 8 million new cases occur worldwide and 3 million people die from the disease. Tuberculosis is the leading cause of death worldwide due to any single infectious agent. Ninety-five percent of these cases occur in the underdeveloped world where diagnostic and treatment facilities are rudimentary or nonexistent.[3,4] In Pakistan, its incidence is estimated to be 175 per 100,000 of population.[5]

Robert Koch's famous discovery of the tubercle bacillus in 1884 was the first step in man's fight against tuberculosis. Soon new diagnostic techniques were being developed and with the discovery of streptomycin in 1944 and introduction of other anti-tuberculosis drugs, it was thought that TB would soon be conquered.[6,7] However, the emergence of multi-drug resistance and association of tuberculosis with the Human Immune Deficiency Virus (HIV) has led to the return of TB with a vengeance.[7] By 1993, the situation had become so alarming that WHO declared TB, a global emergency.[1,3]

Rapid and accurate diagnosis of symptomatic patients is a cornerstone of global tuberculosis control strategies. Diagnostic mycobacteriology is a complex and technically demanding branch of clinical microbiology. The TB clinical laboratory plays a critical role not only in the diagnosis and management of the disease, but also in control and elimination strategies.8 Early diagnosis, proper treatment and effective prevention strategies are essential for tuberculosis control.[9,10] The last two decades have seen rapid technological advances in the field of biotechnology with the introduction of new and better techniques for the diagnosis of various infectious diseases including TB. This article reviews both traditional and modern methods of diagnosing tuberculosis with a special emphasis of their implications for our population.

Clinical Diagnosis of Tuberculosis

Traditionally, diagnosis of tuberculosis, especially in the underdeveloped countries, has been based upon clinical presentation and radiological findings on chest x-rays. Clinical signs and symptoms, however, are variable and non-specific, often being absent in early disease, and physical findings in tuberculosis are generally not very helpful in establishing the diagnosis.[1,11]

Chest x-rays have been the cornerstone of TB diagnosis for almost a century and would continue to play an important role in future. Although pulmonary tuberculosis almost always shows abnormalities on the chest x-ray,[11] radiological diagnosis alone can only be presumptive since the diagnostic criteria are non-specific.[1] As clinical picture and chest x-ray pattern cannot always be used to distinguish between TB and other pulmonary

pathologies,[12] the diagnosis can be misleading.[13] Association of HIV with TB has further complicated the issue. Both the clinical as well as radiological presentation in such cases can be atypical or even non-existent.[1,7,11] Furthermore, almost one-fourth of all TB cases are extrapulmonary[14-16] and in such cases x-rays are of limited use while clinical presentations are protean.

Conventional Laboratory Diagnosis

Laboratory plays the definitive role in diagnosis of TB. Conventionally, laboratory diagnosis of tuberculosis has been based upon smear microscopy, tuberculin skin test and culture. However, many other different diagnostic techniques have become available in recent years. A brief discussion of these is given below.

Microscopy: Identification of acid-fast bacilli (AFB) on microscopy of specimen smears is the primary laboratory tool for the diagnosis of TB. In underdeveloped countries like Pakistan, it is often the only diagnostic test available.[8] WHO recommends this technique as the primary laboratory diagnostic test for the underdeveloped world, as it is cheap and simple, and would detect the most infectious cases of TB, thus breaking the cycle of transmission.[13] Advantages of the technique include low cost rapidity and simplicity, and its high specificity. It detects the most infectious subsets of patients and is useful in monitoring response to treatment.[8,17] However, the technique is hampered by several drawbacks: it fails to differentiate between dead and viable bacteria, speciation is not possible and most importantly, its sensitivity may vary from 33% to 75%.[8,10,11,17,18] The reason for this reduced sensitivity is that a large number (at least 5 x 103 AFB/ml) of bacilli must be present in a specimen for the smear to be positive.[11,17] This lack of sensitivity has limited the utility of the technique. The sensitivity of the test can be increased by examining multiple specimens[10,11,19,20] and by processing the specimens by centrifugation[10,11] and liquefaction techniques using sodium hypochlorite,[21] chitin[22] or N-acetyl-L-cysteine in 1% sodium hydroxide solution.[11]

An adequate volume of sputum must be processed to get better results; at least 5 ml has been recommended. Sometimes it is not possible to obtain adequate amount of sputum, especially in children who cannot expectorate. In such cases sputum induction can be of use in obtaining the required amount of sputum.[11]

Tuberculin Skin Test: It is estimated that two billion persons around the world have latent tuberculosis infection and about 10% of these would develop active disease.[23,24] The tuberculin skin test is the only proven method for identifying latent infection with M. tuberculosis.[4] Although the available tuberculin skin test antigens are not very sensitive and specific for detection of infection with M. tuberculosis, no better diagnostic methods have yet been devised.[25] The tuberculin skin test is one of the few tests developed in the 19th century that is still in present use in clinical medicine. Robert Koch prepared the first tuberculin test material and Von Pirquet first used it to detect TB in 1907.[26] Its design is based on the observation by Robert Koch that infection with M. tuberculosis caused cutaneous reactivity to tuberculin, a purified protein derivative (PPD) of heat-killed M. tuberculosis (delayed type hypersensitivity reaction). The tuberculin skin test is not 100 percent sensitive for infection with M. tuberculosis. Even among patients with proven tuberculosis without apparent immunosuppression, 10 to 20 percent will have negative skin reactions. Sensitization to tuberculin can also be induced by infection with nontuberculous mycobacteria (NTM) and BCG vaccination. It is not possible to distinguish between a tuberculin reaction that is caused by true infection and a reaction that is caused by BCG.[27]

Problems can arise with use of repeated tuberculin tests to detect new infection in high-risk populations such as initially tuberculin-negative contacts of active cases and workers with occupational exposure. Tuberculin reactions may decrease in size (reversion phenomenon) or increase in size because of random variability from differences in administration, reading or biologic response; immunologic recall of preexisting delayed type hypersensitivity to mycobacterial antigens (boosting phenomenon); or new infection (conversion phenomenon).[25-27]

Tuberculin skin test results should be evaluated within the context of each patient's epidemiological and environmental potential of infection, individual risk factors for tuberculosis and prevalence of tuberculosis in the facility. The tuberculin test, like all medical tests, is subject to variability, but many of the inherent variations in administering and reading tests can be avoided by careful attention to details. The preferred skin test for M. tuberculosis infection is the intradermal, or Mantoux, method. Multiple puncture tests (Tine and Heaf) and PPD strengths of 1 TU and 250 TU are not sufficiently accurate and should not be used.[25] In high-risk groups (intravenous drug users, mycobacteriology lab workers, children less than 4 years of age and populations in high prevalence settings like Pakistan), an induration of 10 mm or more is considered as positive. However, in immunocompromised patients including HIV positive persons, an induration of 5 mm is considered as positive. In persons with no known risk factors for tuberculosis, an induration of 15 mm is taken as positive.[28]

Culture

A definitive diagnosis of tuberculosis is dependant upon the isolation of Mycobacterium tuberculosis by a

standard culture technique.[4,10,11,17] In general, the sensitivity of culture is 80-85% with a specificity of about 98%. The increased sensitivity of the technique is due to its ability to give a positive culture even when small numbers (10-100 AFB/ml) of bacilli are present in the specimen. Added advantages of culture are that species identification and drug susceptibility testing can be carried out.[11]

The main drawback of the culture technique is the long time required for mycobacterial growth to occur due to their slow doubling time of 18-24 hours.[1,29] It can take upto 8 weeks for visible growth to occur on solid medium and another 3 weeks might be required for antimicrobial susceptibility testing, which is unacceptably a long time in clinical practice.[11] The United States Centers for Disease Control (CDC) have recommended the identification of M. tuberculosis cultures and the determination of first line drug susceptibilities to be performed within 30 days.[30]

Haematology

Haematologic disturbances are frequently encountered in cases of tuberculosis. However, these are quite variable and non-specific. Although mild anaemia is invariably present, both leucocytosis as well as leucopenia may be encountered.[1,11] Lymphocytic leukemoid reaction has been described in miliary tuberculosis. Raised Erythrocyte Sedimentation Rate (ESR), a non-specific marker of chronic disorders has traditionally been used to monitor response to treatment. Granulomas in bone marrow are present in upto 50% of culture positive cases. Gelatinous transformation of bone marrow has been observed in tuberculosis. This transformation, however, is also seen in anorexia nervosa, and chronic debilitating illnesses such as carcinomas.[31,32]

Histopathology

Histological hallmark of tuberculosis is the epithelioid granuloma in which Langhan's giant cells and caseation necrosis may occur. AFB may be demonstrable in tissue sections on acid-fast staining.[1] However, AFB are frequently missed or underestimated with acid-fast microscopy on formalin-fixed, paraffin-embedded tissue.[33] Furthermore, the AFB seen in biopsy material may be non-tuberculous.[1]

Ridley and Ridley have divided patients with tuberculosis into three histological groups. Most patients in group 1 have chronic skin tuberculosis, the lesions have minimal necrosis and bacilli are rarely seen. Patients in group 2 have pulmonary disease and in the lesions show typical caseation necrosis but AFB are usually scanty. In group 3, patients have disseminated tuberculosis and in the lesions exhibit neither granuloma formation nor caseation necrosis. Instead there is extensive basophilic or eosinophilic necrosis with scanty nuclear debris and numerous AFB are present in the lesions.[34]

Although biopsies of tuberculous tissues like the lymph nodes can be histologically suggestive of tuberculosis,[35] a definitive diagnosis of tuberculosis cannot be made on histopathology.[1,36]

Serology

Since the introduction of enzyme-linked immunosorbent assay (ELISA) in 1972 and the availability of monoclonal antibodies as well as purified antigens, the serological diagnosis of tuberculosis has become more promising. Numerous serological tests based upon various modifications of ELISA or immunochromatographic methods have been developed for the detection of both antigens and antibodies.[37,38]

The serodiagnosis of tuberculosis has been the subject of investigation for a long time, but we still lack a test with widespread clinical utility. The available tests have both a sensitivity and specificity of around 80%.[8,39,40] While evaluating an enzyme immunoassay, utilizing the genus-specific lipopolysaccharide and the species-specific 38 kDa antigen, we found the sensitivity and specificity of the assay to be 70% and 98% respectively.[38] In HIV seropositive patients co-infected with tuberculosis, the sensitivity of antibody tests is much lower, between 10 and 40%.[8,40] One of the main problems encountered in serology, using ELISA is antigenic cross-reaction, which results from epitopes that M. tuberculosis shares with other closely related mycobacteria in the environment. This presents major difficulties in evaluating the antibody response in tuberculosis, as well as complicating any attempts to develop a specific and reactive serodiagnostic test for tuberculosis. Other reasons for false results could be background titres due to the presence of anti-M. tuberculosis antibodies in persons with latent tuberculosis, prior active TB disease, BCG vaccination, infection with NTM, persistent bacterial products following resolution of infection[40,41] and heterotypic humoral response to TB.[8,41] Incorporation of multiple antigens in a diagnostic test may increase the sensitivity of an antibodybased test.[8,38,40]

Serologic tests could be useful for those patients from whom specimens for culture are hard to obtain such as those with extrapulmonary tuberculosis, children and smear-negative cases.[37]

Miscellaneous Tests

Several different tests have been available for the diagnosis of tuberculosis but have not found wider use due to non-specificity and cumbersome procedures. These include serum protein electrophoresis, which measures the fall in serum albumin/globulin ratio that occurs in

many acute and chronic diseases including tuberculosis[42] and the adenosine deaminase (ADA) test. The enzyme adenosine deaminase (ADA) is found in high concentrations in cerebrospinal fluid (CSF) of patients of tuberculous meningitis and pleural fluid of patients with tuberculous pleural effusion. This enzyme plays a role in the differentiation of T lymphocytes. In tuberculous pleural fluid, the levels of ADA and CD^4 cells are raised, showing a positive correlation. ADA is considered a marker of cell-mediated immunity in pleural fluid and CSF. The test is not very sensitive or specific43,44 and is no longer used.

The bromide partition test can be done for the diagnosis of tuberculous meningitis when AFB are not demonstrable in the CSF. Normal serum to CSF bromide ratio is 1.6:1. Reduction in this ratio due to shifting of bromide from serum to CSF indicates probable infection with M. tuberculosis. Although a sensitive marker of meningeal inflammation,[43] the test is not diagnostic as such of tuberculosis[44] and is mostly obsolete. Other non-specific markers of tuberculosis are the cytokines interleukin 1 (IL-1), interleukin 2 (IL-2) and interferon gamma (IFNgamma), which are important mediators of host response to infections, inflammation and immunologic changes.[45,46] An in vitro assay of whole blood for cell-mediated immunity, based on the release of IFN-gamma from T lymphocytes in response to stimulation with M. tuberculosis PPD, has shown excellent agreement between the tuberculin skin test and the assay, for the identification of latent tuberculosis infection. The test overcomes some of the shortcomings of the Mantoux test like the need for return visits and reader variability.[47]

Animal pathogenicity tests were extensively used in the past for diagnosis of tuberculosis. These tests can be dangerous to the laboratory staff as there is an increased risk of infection and have been, superseded by the more sensitive modern techniques and are rarely performed nowadays.[29]

Advances in Laboratory Diagnosis of Tuberculosis

The last two decades have been characterized by a revolution in biotechnology especially molecular biology. The technical advances have led to introduction of several new diagnostic tools for tuberculosis as well as improvement of the existing techniques.

Automated Culture Techniques

Several new automated culture systems have been commercially introduced in the last few years, which have reduced the detection time significantly. These include the radiometric BACTEC 460 TB system, the colorimetric BacT/ALERT MB Susceptibility Kit,[48,49] Mycobacterial Growth Indicator Tube (MGIT) systems with an oxygen quenching-based fluorescent sensor[50,51] and the ESP (Extra Sensing Power) Myco-ESP Culture System II based on the continuous monitoring of pressure changes due to the consumption or production of gas resulting from metabolic activity of microorganisms growing in a liquid medium.[52] These are all liquid systems that allow for rapid growth (detection of mycobacterial growth within 1-3 weeks) and antimicrobial susceptibility testing.[11] The high cost and technical sophistication of these systems, however, precludes their use outside reference laboratories.

Detection of Lipids

Mycobacteria contain large amounts of lipids. Each mycobacterium species synthesizes a unique set of mycolic acids that are components of the cell wall. Mycolic acids are present in very specific configurations and the type of mycolic acid can be used to distinguish different mycobacteria.[11] Various techniques can be used to identify these mycolic acids such as gas chromatography, thin layer chromatography (TLC) and high performance liquid chromatography (HPLC).[17] HPLC can produce a pattern that reliably identifies and distinguishes more then 50 mycobacterial species. It can be performed in a few hours but requires organisms from pure cultures. The initial equipment cost for HPLC limits its availability.[11,17]

Molecular Techniques

One of the dramatic achievements in science during the last decade has been the advancement in molecular biology. The ability to detect small amounts of DNA or RNA by amplification techniques has led to the development and introduction of rapid and accurate diagnostic techniques in microbiology. Nucleic acid techniques for detection and identification of bacteria fall into three basic groups: (1) target amplification by polymerase chain reaction (PCR), transcription mediated amplification, nucleic acid sequence based amplification (NASBA), etc. (2) probe amplification using ligase chain reaction or Q-beta replicase; and (3) signal amplification, as in branched DNA assay.[53,54]

Several molecular methods have been developed for detection of mycobacteria direct from the specimens (the direct amplification tests or DATs), species identification of the mycobacterial isolates from culture, and drug susceptibility testing. These methods can potentially reduce the diagnostic time from weeks to days.[54]

Several assays for detection of mycobacterial nucleic acids by the polymerase chain reaction are now commercially available. Polymerase chain reaction assays have made diagnosis and specific identification of

Mycobacterium tuberculosis possible within a day. The test is rapid, sensitive and specific and can detect fewer than 10 organisms in clinical specimens, compared to 105 bacilli/ml necessary for AFB smear positivity.[1] Although the specificity of a well-developed PCR can be high, the sensitivity is significantly less than that of culture.[10,11,17,40,54] In clinical respiratory specimens that are AFB smear positive, the sensitivity of the amplification methods is approximately 95%, with a specificity of 98%.[11,39,54] However, sensitivity for smear negative cases has varied from 40% to 77%[1] although the specificity has remained approximately 95%. The American Thoracic Society recommends that DATs should always be performed in conjunction with microscopy and culture and that the result should be interpreted alongside the clinical data.[11] Another problem with the DATs is that they cannot differentiate between dead and viable organisms.[1,53] Thus, the response to chemotherapy cannot be assessed by PCR assays. Molecular amplification tests are also quite expensive and technically sophisticated.[10]

Mycobacterial isolates have traditionally been identified to the species level based on their reactions in a series of phenotypic and biochemical tests. However, the biochemical reactions of isolates of the same species may vary from each other and from time to time. In many cases no definitive identification is obtained. Because biochemical testing is slow, cumbersome and may yield ambiguous results, laboratories are increasingly using molecular methods for species identification.[55] Molecular methods are rapid, reliable and reproducible, and even mixed or contaminated cultures can be analyzed. Advances in molecular biology have also made it possible to investigate the genetic mechanisms of drug resistance in M. tuberculosis and to develop methods for rapid detection of mutations associated with resistance like the rpoB gene associated with resistance to rifampicin.[54]

The technique of DNA fingerprinting also referred to as Restriction Fragment Length Polymorphism (RFLP) is being extensively used for epidemiological surveys in the investigation of TB outbreaks, in other epidemiologic studies to distinguish between exogenous re-infection and reactivation, and in investigations of laboratory cross-contamination.[1,10]

Mycobacteriophage Assays

Bacteriophages are viruses that infect bacteria. The first mycobacteriophage was isolated from a strain of Mycobacterium smegmatis in 1947. Since then more than 250 mycobacteriophages have been described. Initial interest had centred on their potential use in speciation of mycobacteria by phage typing.[56] In the last decade, mycobacteriophages have been extensively investigated for their use in diagnostic microbiology.[8,13,56-58]

Two new techniques have been developed for the diagnosis of tuberculosis that utilize bacteriophage to specifically target Mycobacterium tuberculosis complex cells. In the Luciferase Reporter Phage technique, the fire fly luciferase gene (FFlux) is inserted into the phage genome, which is expressed when the phage infects the target cells to produce a detectable photon signal.[57,59] The other much simpler technique utilizes the principle of phage amplification and does not rely on recombinant phage or require light detection.[57,60] Recently, a bacteriophage assay, utilizing the principle of phage amplification for detection of viable Mycobacterium tuberculosis complex in sputum specimens, has been introduced. The phage is used as a reporter of cell presence and viability. The test is simple, does not require sophisticated equipment and is relatively inexpensive. The results are available in 48 hours. Early evaluation studies have shown encouraging results.[13,57,58,61] Another utility of the phage techniques is in antimycobacterial drug susceptibility testing where the same principles have been applied to detect resistance against rifampicin[62] and other anti-tuberculosis drugs.[63] Our own experience with the phage techniques has been quite encouraging with the overall sensitivity of 81% and specificity of 95%.[61] We have also utilized the phage technique for rapid detection of rifampicin resistance in Mycobacterium tuberculosis direct from sputum specimens with encouraging results (sensitivity of 87.5% and specificity of 80%).[64] The phage assays can be utilized as potential alternatives to culture in resource-poor countries like Pakistan which lack proper facilities for the more definitive diagnostic tests.

Implications of Modern TB Diagnostics

An early diagnosis is the cornerstone of tuberculosis control. However, regions with high prevalence of tuberculosis also lack the resources to institute effective control measures.[3,10] It is estimated that three quarters of all TB cases in Pakistan are never diagnosed.[1] The diagnosis is mostly based upon clinical suspicion or on therapeutic response to anti-tuberculosis drugs, rather than on the basis of culture isolation. This results in inappropriate use of anti-tuberculosis drugs. Furthermore, compliance with treatment remains poor. All these factors are responsible for the development of drug-resistant tuberculosis and spread of infection. Despite TB having been declared a national emergency in 2001, implementation of the national TB control programme in Pakistan has been hampered by the underdeveloped health facilities, lack of resources and poor management.[5]

Although advances in diagnostic mycobacteriology have been, at times, spectacular, we still have not come up

with the ideal diagnostic test for TB; one which is simple, rapid, inexpensive and accurate. The automated culture and molecular techniques are sensitive and have reduced the detection time, but they are too expensive and sophisticated for wider use in the resource-poor third world countries with the highest burden of tuberculosis.[8,17] The newly introduced phage assays have the potential of wider utility in underdeveloped countries like Pakistan as they are sufficiently sensitive and specific, rapid, simple and relatively cost-effective. Used in conjunction with smear microscopy, they have shown excellent results.[13,57,58, 61] However, they need to be further evaluated and improved before their validity can be firmly established.

At present no single test is adequate for the diagnosis of tuberculosis. While the advancements in TB diagnostics are encouraging, they are unlikely to have a major impact on the vast majority of TB patients for whom an early and inexpensive diagnosis remains elusive. There is a dire need for development of newer diagnostic techniques and refinement of existing ones to cater for the particular needs of the resource-poor third world. If the general trend in scientific advancement is any indicator, the future looks promising. In the meantime, we have to make the best use of what we already have, relying on a judicious combination of the existing laboratory tests in conjunction with x-rays and clinical presentation for the diagnosis of TB. The medical community must combine the best possible use of the tools already in hand with increased awareness of the magnitude of the problem, a high index of suspicion, early case identification and prompt and optimum treatment.

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Effect of providing free sputum microscopy service to private practitioners on case notification to National Tuberculosis Control Program

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Abstract

Background: This study was undertaken to see whether providing free sputum microscopy services to private practitioners helps in case notification to the national tuberculosis control program. The knowledge, attitudes and practices of these practitioners regarding tuberculosis were also evaluated.

Methods: A questionnaire was administered to all the private practitioners practicing in a densely populated area of Karachi. They were asked to fill tuberculosis notification cards for the first three months and then for another three months when an incentive in the form of free sputum microscopy was provided to the practitioners.

Results: Although the majority of the practitioners knew that cough, fever and weight loss are the main symptoms of tuberculosis, less than half knew that blood in sputum, poor appetite and chest pain could also be associated with tuberculosis. Only 66% of the practitioners indicated sputum microscopy as the preferred diagnostic method for tuberculosis. Only 50% of the practitioners self treated the patients, while the remaining half referred their patients to specialists. Around 80% of the practitioners were aware of the four first-line anti-tuberculosis drugs. Less than half of the practitioners considered sputum microscopy as the most useful follow-up investigation in a patient with pulmonary tuberculosis. Generally, there was a poor response in case notification by private practitioners on provision of free sputum microscopy.

Conclusion: An overwhelming majority of the practitioners had poor knowledge concerning the correct treatment practices in Tuberculosis. Providing sputum free microscopy does not significantly help in improving tuberculosis case notification. Strategies for public-private collaboration in tuberculosis control are needed.

Keywords: tuberculosis, private practice, sputum, microscopy, knowledge, attitude, behaviour, Pakistan.

Introduction

Tuberculosis (TB) constitutes a major public health problem in most developing countries of the world. The emergence of HIV/AIDS, increased migration and the deterioration of the health services in many countries, has compounded the problem and caused the incidence of TB to rise so rapidly over a few years' time that the World Health Organization (WHO) was compelled to declare it a global emergency in 1993,[1] the first declaration of this sort ever.

Globally Pakistan has been ranked 8th in terms of estimated number of cases by WHO, with an incidence of 175/100,000 persons.[2] Pakistan alone accounts for 44% of total TB burden in the Eastern Mediterranean Region of the WHO comprising 23 countries. In a country of 144 million, approximately 1.5 million people suffer from TB indicating a prevalence exceeding 1% of the total population while 210,000 new cases occur each year. Paradoxically, only one in four cases of TB are ever diagnosed in the country. The WHO Global Tuberculosis Report of 2002 mentions the case notification rate for Pakistan was 23/100,000 in the year 2001.[2] From 2000 to 2001, both the Directly Observed Treatment Strategy (DOTS) coverage and DOTS detection rate for Pakistan approximately doubled. At 5.6%, however, the DOTS detection rate is still well below the population coverage of 24% suggesting that many patients do not have access to DOTS even within the designated DOTS areas.[2]

Pakistan has a very strong private health sector particularly in the major cities, and it is estimated that from amongst the TB patients seeking treatment approximately 80% initially report to private practitioners (PPs) for their diagnosis and treatment.[3] Resultantly, PPs are currently diagnosing and treating a significant proportion of TB patients in the Karachi metropolis, which houses nearly a third of the population of Pakistan's southern province of Sindh. Furthermore, as yet, linkages of PPs have yet to develop with the Provincial TB Control Program along organized lines. The National tuberculosis control programme (NTP) of Pakistan aims at achieving 100% DOTS coverage by 2005, while Sindh is expected to do the same by August 2003. It is accordingly imperative to make DOTS more comprehensive by involving the private sector in our efforts for Tuberculosis control.

This study was therefore undertaken to assess the impact of free sputum microscopy services to PPs on case notification to the National TB program and also to evaluate their knowledge concerning the diagnostic modalities used and the treatment regimens commonly prescribed in TB.

Material and Methods

The study was performed between May 2002 and September 2002, in Karachi, Pakistan. The study comprised of two stages. Prior to the start of the study, a brief analysis

of the current situation of referrals from the PPs to the DOTS sites in Karachi was carried out to provide some baseline data.

In stage one of the study, all the PPs practicing in a radius of around two kilometers of a private sector hospital providing sputum microscopy facilities and located in a densely populated area of Karachi were identified. An attempt was made to develop linkages with the nearest government diagnostic and treatment center.

All private practitioners in this catchment area were invited to attend an awareness workshop regarding TB and its control. This program was facilitated by investigators of the TB program which included a provincial level TB control coordinator. At that time, all the PPs were requested to complete a previously prepared self-administered questionnaire related to knowledge, attitude and practices regarding TB. All the doctors present at the workshop completed and returned the questionnaire at that time while those who were unable to attend the workshop were contacted personally at their clinics and requested to fill the questionnaires. A total of 120 PPs completed the questionnaire. All the PPs were allopathic qualified doctors examining TB patients in their clinics. Anonymity was optional and confidentiality guaranteed. The questionnaire was designed to collect information on number of suspected TB patients seen on an average every month, the common presenting symptoms and the diagnostic, treatment and referral practices employed by the PPs. The workshop impressed upon the participants the need to follow the National Guidelines for the Treatment and Control of Tuberculosis commonly known as 'NTP Guidelines' and the WHO recommendations for TB control. TB notification cards were subsequently given to PP. They were asked to fill patient information on all suspected TB patients over a three month period. These were collected every fortnight by a field assistant specially hired for this purpose.

In stage two, at the end of first three months, PPs were invited to a seminar which again emphasized the importance of TB control and case notification. All the PPs including those who did not participate were delivered letters by hand informing them of free sputum microscopy facility at the local hospital in that area. They were requested to fill referral forms for sputum AFB. Again, these were collected over a three month period every fortnight by the field officer.

At the end of the study, all the PPs were sent a questionnaire. Those who were unable to fill any referral card were asked reasons for not doing so. All PPs were asked to make recommendations for TB control in Pakistan. This question was kept open-ended.

Responses to structured questions were entered and analyzed using Statistical Package for Social Sciences (SPSS) (Version 10.0.1, copyright SPSS; 1989-99). All information was coded before computer entry to retain the confidentiality of the respondents.

Productive cough for more than three weeks with or without symptoms of: fever, night sweats, weight loss, hemoptysis, pleuritic chest pain and dyspnea.

On the spot specimen was taken when the patient was identified as a pulmonary TB suspect. Subsequently, an early morning specimen was obtained by giving the patient a container with the requisite instructions. The third sample was collected when the patient reported at the laboratory.

Results

On an average each of the general practitioners saw 4-5 TB patients in a month. In response to the question about the main symptoms of TB, 94% of PPs mentioned cough, 86% fever and 74% weight loss. 41% thought blood in sputum was the cardinal symptom in TB, while 30% and 17% considered poor appetite and chest pain, respectively as the same.

PPs were inquired about the duration that the main symptoms should last before TB was suspected in a particular patient. 76% percent felt that the duration should be at least 2-4 weeks, whereas 30% considered it to be more than 4 weeks while 4% felt that it should be less than 2 weeks.

Nearly 70% of the PPs were confident of diagnosing patients themselves, whereas 23% referred their patients to a government TB center, and 7.4% referred their cases to specialist clinics. Regarding the possible diagnostic modalities that they would employ prior to making a diagnosis of pulmonary TB, 96% marked chest X-Ray, 48% sputum microscopy, 63% tuberculin test, while 25% thought that clinical examination itself would suffice for the purpose. Furthermore, when asked to name the single most important test to confirm the diagnosis of pulmonary TB, 66% opted for sputum microscopy, 22% favored chest X-Ray, and 4.8% mentioned tuberculin test while 5.7% preferred PCR.

About 50% of the PPs preferred to treat patients themselves, 23% sought the help of a government TB center, 22% referred the patients to a private consultant, while 6% considered it appropriate to let the patients decide for themselves.

When asked to write the prescription for a 60kg man recently diagnosed as smear positive TB, 83% gave the 4-drug regimen of isoniazid, rifampicin, pyrazinamide and ethambutol for the initial phase. Of these, 80% used individual drugs while 20% gave all 4 drugs in a fixed dose combination (FDC) regimen. Seventeen percent of

physicians gave incorrect regimens, including 2, 3 & 5-drug regimens. The correct daily dosage for the initial phase (2 months) was 300mg isoniazid, 600 mg rifampicin, 900 to 1500 mg ethambutol and 1500 to 2000 mg pyrazinamide. The anti-tuberculous therapy prescribed for the initial phase (Tables 1 and 2) indicate gross errors in dosages (only over

Table 1: Distribution of the private practitioners in terms of their dosing practices of TB medications for the initial phase.

Drug	Under dose (%)	Correct dose (%)	Over dose (%)
Rifampicin	20	76	4
Isoniazid	6	83	11
Pyrazinamide	15	52	33
Ethambutol	10	51	39
Streptomycin	0	60	40

Table 2: Distribution of the private practitioners in terms of the duration for which TB medications are given for the initial phase.

Drug	Under duration (%)	Correct duration (%)	Over duration (%)
Rifampicin	1	50	49
Isoniazid	0	52	48
Pyrazinamide	0	61	39
Ethambutol	0	53	47
Streptomycin	20	80	0
Myrin P	41	48	11

50% prescribed the correct dosage of pyrazinamide and ethambutol) and duration (only half prescribed the correct duration of rifampicin, isoniazid and ethambutol.

For the maintenance phase, the correct regimen was either isoniazid/thiacetazone or isoniazid/ethambutol and isoniazid/rifampicin according to the National TB and WHO guidelines respectively. None prescribed thiacetazone. Only 58% prescribed the correct dosage of ethambutol while less than 50% prescribed the correct dosages of rifampicin, isoniazid, ethambutol and thiacetazone. There were 11 different regimens prescribed for the continuation phase. Only 20 (21%) prescribed the correct regimens (Table 3).

42% of the PPs considered sputum microscopy as the most useful follow-up test for pulmonary TB. 33% opted for chest X-Ray, 19% preferred ESR, 5% chose liver function tests, while 1% recommended tuberculin test.

Only 22.5% of the PPs kept a record of their TB patients. All diagnosed cases of tuberculosis detected through sputum microscopy or otherwise were provided effective case management and follow-up using the DOTS strategy.

51 out of 103 PPs filled notification cards before the

Table 3: Frequency of the different Anti tuberculous medications prescribed during the continuation phase.

Drug name	Number (%)
H+I	19 (20.4%)
H+I+P	8 (8.6%)
H+I+P+E	7 (7.5%)
H+I+E	20 (21.5%)
H+I+E+Myrin-P	1 (1.1%)
H+P+E	1 (1.1%)
H+E	1 (1.1%)
Myrin	2 (2.2%)
Myrin-P	21(22.6%)
I+P+E	1 (1.1%)
I+E	12 (12.9%)

H= Rifampicin I=Isoniazid E=Ethambutol
P=Pyrazinamide Myrin=Isoniazid, Ethambutol, Rifampicin
Myrin -P= Isoniazid, Ethambutol, Pyrazinamide, Rifampicin

incentive of free sputum microscopy was provided while only 35 filled referral cards for sputum AFB after the provision of incentive. Of the 68 who did not fill the referral card, 32 said that they were too busy. 5 were of the view that filling of the referral card was not a good idea. 31 said that they did not see any patient during the three month period.

At the conclusion of study, PPs were asked about their views on how to control TB in Pakistan, 52 of 103 mentioned that sputum microscopy facility alone is not enough for the PPs and that there should be availability of free chest X ray as well as free blood tests for their patients. A few demanded for monetary incentive. Eighteen suggested conducting of frequent health education and awareness programs for the PPs.

All diagnosed cases of tuberculosis detected through sputum microscopy or otherwise were planned for being provided effective case management and follow-up using the DOTS strategy through government diagnostic and treatment center. However, during the period of our study, no paramedics or other government outreach workers were available to provide DOTS at the nearby facility.

Discussion

Private sector is the first source of help for a large number of TB patients in this part of the world. Patients go to private health care facility because of resource shortages in the public sector, and its inability to meet population expectations thus far.[5] Most patients go to private practitioners because of their more convenient hours and personalized services.[6] However, the knowledge and practices amongst these practitioners have not been found to be satisfactory.[7,8,9] Many PP in Pakistan practice after completing 5 years of graduate training. This is different from PPs in the west who obtain atleast three years of postgraduate training before practicing independently. The

poor performance of private doctors, in our part, clearly shows the inadequacy of their undergraduate as well as in-practice training.

Majority of the PPs in the study were aware that cough, fever and weight loss were the main presenting symptoms of TB, but less than 50% knew that blood in a sputum, poor appetite and chest pain could also be associated with TB.

While 70% of PPs were aware that TB needs to be suspected if the clinical symptoms last 2-4 weeks, 30% incorrectly thought the symptoms need to last for more than 4 weeks before the diagnosis of TB could be considered. Such delay in diagnosis would not only result in increased morbidity and mortality for the patients, but would also facilitate the spread of the disease amongst the contacts.

Over dependence of PPs on chest X ray[10] as the diagnostic tool as well as for follow-up of a case with pulmonary TB was noteworthy. Use of sputum microscopy with or without other investigations for diagnosis for TB by 48% and as a follow-up test by only 42% highlights the indifference of PP to public health implication of the sputum status of TB patients. It was surprising to note that 66% identified sputum microscopy to be the single most important test for diagnosis of pulmonary TB when actually only 48% recommended it. This shows that PP often do not practice what they know is medically correct. A probable reason for this could be that X-rays are financially more viable to the referring doctor than the cheaper sputum examination especially in cases where there is some financial arrangement between the doctor and the diagnostic center.[10]

In our study, 30% of the PPs were not confident enough to diagnose TB on their own and hence preferred to refer their patients either to government TB centers or to private clinics. This figure indicates lack of awareness amongst PPs who are the source of medical help for the majority of patients.[11] This high referral rate could be one of the possible reasons for the poor control of the disease, as it can lead to patients being lost to follow-up.

23% of the patients were being referred to a government TB facility. The figure of 38% was reported by a study done in Delhi, India.[12] This reflects the lack of faith PPs have in a government facility. Other reason is probably the loss of financial benefits PPs would incur on referring the patients to government run clinics.

In terms of treatment practices, a significant number were either giving inappropriate dosage or lower than WHO-NTP recommended duration of anti-tuberculosis therapy. This is consistent with the Nepal study which showed that about half the PPs were giving correct dosages, whereas 69% were treating for inappropriate duration.[6] Improper case management not only compromises patient outcome but also exposes family members to unnecessary risk.[6] These inappropriate regimens in terms of dosage and duration are probably the most important factor leading to a rise in multi-drug resistant (MDR) TB in Pakistan.[13] In Karachi alone, the resistance rates for the 4 first line drugs are 27%, 15%, 11% and 13% for isoniazid, ethambutol, rifampicin and streptomycin respectively.[13]

Only 25 % PPs kept a record of their patients which means that tracing treatment defaulters is close to impossible. It is universally accepted that a partially treated TB patient is worse than an untreated one as the chronic cases are the ones who excrete MDR organisms and increase the community burden of TB.[14] It cannot be over emphasized that essential record keeping and treatment of defaulters are of utmost importance for the control of TB.

It has been suggested by many experts that providing free sputum microscopy services to PPs can help increase the TB detection and notification leading to a better TB management.[10] Based on these recommendations, free sputum microscopy services were provided. It was disappointing to note that only 37 out of 103 PPs returned notification and referral cards for sputum AFB. The decline in the number could be because doctors were expecting monetary incentive for their participation in the study. Many PPs remarked that incentive for free sputum microscopy was for the patients and there was no incentive for them in the study. Another probable reason could be the lack of faith PPs have in the laboratory facilities.

Another very disturbing aspect was the fact that more than 50% PPs suggested of free chest x ray facility and other blood tests to control TB in Pakistan. This recommendation came despite the seminar on National guidelines for TB management at the start of the study which had emphasized on sputum microscopy as the best diagnostic modality for TB.

This study was one of the few ever projects carried out in Pakistan in the context of private/public collaboration in TB control. As the Provincial TB control Program is engaged in currently expanding the DOTS coverage in Sindh, a tremendous need exists for involving the huge private sector in the major cities in TB Control efforts. It was our hypothesis that better case notification could ensue through provision of certain incentives to PPs leading us to reach these patients and bring them under Provincial TB Control Program. However, the study revealed a very disappointing state of affairs. With the current situation, a multifaceted approach has to be adopted to improve TB management. The gaps in the knowledge and practices of PPs ought to be addressed first. As national resources of expertise, NTPs should be strengthened to advise,

contribute and monitor undergraduate, post-graduate and continuing medical education in TB treatment.[4] A simple booklet should be devised and distributed to PPs to provide clear information on TB treatment and prevention. Moreover, NTPs should help educate the public about TB, its treatment and where to receive it. The situation warrants better collaborative efforts between PPs and public health services.[15] These include inviting representatives of private doctors to participate in the planning process of TB control activities, involving them in case-finding activities within their areas of practice, providing them with free or subsidized but reliable laboratory services, making drugs available for the patient referred by the private doctor to the TB centre or supplying drugs to individual doctors on submission of reports and records. Linkages need to be established between DOTS and PPs. DOTS program need to expand rapidly. Currently, only 4-5 such centers exist in Karachi. The physicians have to be ensured that patients will not be snatched away from them despite their registration at the government diagnostic and treatment centre and that the patient will continue to retain his rapport with their PPs. It is important to provide recognition to PPs for their services. Private clinics working on the recommendations of National TB Guidelines could be made satellite DOT centers. This would allow more enthusiastic participation of the PPs. Last, the problems encountered by the PPs should be considered at each stage.

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Performance of ICT-TB test in the detection of pulmonary and extra-pulmonary tuberculosis

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Abstract

Background: Tuberculosis is a major public health problem of the developing nations including Pakistan. We need a simple, economical and non invasive test to make an early diagnosis of T.B. in order to avoid the complications.

Methods: A study was conducted at the Dept. of Pulmonology, PGMI LRH Peshawar & Ayub Teaching Hospital Abbottabad with the collaboration of Deptt of Pathology KMC Peshawar from Jan 1998 to Dec 2002. A total of 129 patients were included in the study. Out of these 129 patients 52 were pulmonary TB (PTB) smear positive, 30 were PTB smear negative, 30 pleural effusion & 17 were TB lymphadenitis. The control group consisted of 25 non TB patients and healthy subjects.

Results: Antibody was detected in 23 of 52 (44%) sputum positive patients, 11 of 30 (36%) sputum negative PTB patients, 10 of 30 (20%) patients of TB pleural effusion and 6 of 17 (35%) patients of TB lymphadenitis. Antibody was detected in none of the control subjects. The overall sensitivity for Pul-T.B. Sputum positive patients was 44%, 36% for sputum Negative Pulmonary TB, 20% for TB pleural effusion and 35% for TB lymphadenitis. The specificity was 100%. Conclusion: ICT-TB is a highly specific, but less sensitive aid in the diagnosis of Pulmonology and extra Pulmonolgy TB.

Introduction

Tuberculosis (TB) still ranks as one of the major diseases and is a leading killer of mankind.[1] Currently a large number of our population is infected with Mycobacterium Tuberculosis and is at the risk of developing the disease.[2] It is a major public health problem in Pakistan.

The diagnosis of tuberculosis depends upon a number of tests such as Chest X-ray, acid fast bacilli (AFB) stain and culture of sputum. These conventional methods are not satisfactory because sputum AFB stain is less sensitive and AFB culture takes more than 3 weeks to produce results.[3] More sensitive and specific tests such as Polymerase Chain reaction (PCR) are too expensive for routine laboratory diagnosis of TB.

The recently introduced serological test ICT-TB rapidly detects antibodies in the serum of pulmonary & extra pulmonary TB patients. It is said to be a reliable test to make an early diagnosis of TB.

Material and Methods

The study was conducted during the period from January 1998 to Dec 2002 at the Department of Pulmonology, Ayub Teaching Hospital Abbottabad and LRH Peshawar with the collaboration of Department of Pathology, Khyber Medical College Peshawar.

A total of 129 patients were selected from the patients who had been hospitalized in the Pulmonology unit of Lady Reading Hospital Peshawar and Ayub Teaching Hospital Abbottabad.

The control group consisted of 25 non TB patients or healthy subjects who showed no evidence of TB on Chest X-Ray and AFB Stains.

The sera were separated and ICT was performed according to the manufacturer's manual. Briefly 30 ml of serum and three drops of reagent consisting of antihuman IgG coated particles were applied to each side of the membrane, enabling reactions to takes place between the membrance fixed antigens and antibodies in the serum followed by antibody-antihuman IgG complex formation produc-ing one or more pink lines with in 15 minutes. The test was positive if the control band was observed and one or more positive bands were seen. The specificity and sensitivity were calculated.

Results

The percentage of patients and control subjects who showed positive antibody response are given in Figure.

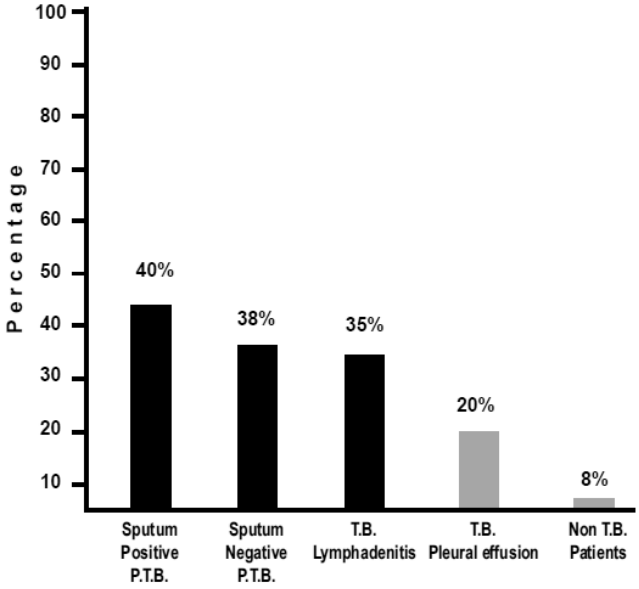

Figure: Percentage of Pul & Extra Pul T.B. patients with positive antibody response along with non T.B. patients.

The assay detected 44% (23 of 52) of sputum positive cases, 36% (11 of 30) of smear negative pulmonary TB, 20% (10 of 30 patients) of TB Pleural effusion and 35% (6 of 17) of TB Lympadenitis patients. None of the control subjects had positive ICT-T.B. The sensitivity for smear positive pulmonary TB was 44%. It was 36% for TB smear negative Pulmonary TB, 20% for TB Pleural effusion & 36% for TB Lymphadenitis. Specificity was 100% as all the control subjects showed Negative ICT. TB.

Discussion

Tuberculosis is the major public health problem in Pakistan. An early and accurate diagnosis is necessary to reduce the morbidity and mortality of this disease. No single test can detect all cases of Tuberculosis. ICT-TB test is a valuable tool to diagnose TB in addition to chest X-Ray, sputum exam for AFB Culture & PCR.

Chang et al found the diagnostic sensitivity of ICT-TB as 73% and specificity in the range of 88-4%.[3] Other studies found that tests using the 38 KDA antigen had a sensitivity of 92% for sputum positive. 70% for sputum negative patient and 76% for extra-pulmonary tuberculosis while the overall specificity was 92%.[4]

Our study gave a specificity of 100% almost similar to the studies conducted so far, while the sensitivity in our study was 44% for smear positive patients, 36% for smear negative Pulmonary T.B, 20% for TB Pleural effusion & 35% for Tuberculous lymphadenitis. The sensitivity is low as compared to other studies due to the reason that some people show poor antibody production due to genetic variations & differences in study populations.[5-7]

Conclusion

We conclude that ICT test is highly specific but less sensitive test for diagnosis of tuberculosis, however in conjunction with other diagnostic techniques, it may serve as a valuable aid in clinical diagnosis for both Pulmonary and extra pulmonary TB. Further larger trials are needed for its evaluation.

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Tuberculosis Control: Current status, challenges and barriers ahead in 22 high endemic countries

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Abstract

Background: Despite the fact that Directly Observed Treatment Strategy (DOTS) short course is cost effective and universally recommended by WHO for effective TB control, it is beyond the financial reach of several highly endemic countries. This article aims at identifying barriers in DOTS's implementation and progress in 22 high burden countries (HBCs) from TB.

Methods: Medline abstracts, published papers and WHO reports were retrieved, critically examined and compared keeping standard parameters of TB control in view.

Results & Conclusion: The increasing caseload, morbidity and mortality due to TB in high burden countries have become a major health challenge and threat to the health systems. The escalated burden of disease and deaths due to TB has posed a great threat to the international security. In the last decade little progress has been witnessed in the implementation of WHO's recommended strategy called DOTS in the 22 high burden countries. Afghanistan, Pakistan, India, Brazil, Zimbabwe, S. Africa and Uganda are some of the countries still facing challenges in the effective introduction, implementation and expansion of DOTS. Financial inabilities contribute greatly to the failure of respective national TB control programs. High burden countries are usually in the economic recession or passing through severe socio-political turmoil that has further reduced spending on TB control. Majority depends on the international assistance and put little domestic efforts. Coupled with the lack of political commitment to the issue of TB control, authors urge high TB control Program managers in HBCs to increase spending and pay a great deal of commitment to the universal implementation of DOTS, increase case detection and case management to attain their global targets.

Introduction

Since WHO declared Tuberculosis (TB) as a global emergency in 1993, TB eradication has become a matter of greater concern among the national, international and local health authorities. Contributing 85% to the total global burden, 22 countries have been identified and labelled as highly endemic countries by WHO.[1] In this battle, WHO is mutually struggling with the high burden countries and giving financial and technical assistance. Countries have launched TB control program so far but progress in achieving the desired global targets of detection (70%) and cure rates (85%) of the detected TB cases under WHO's standard therapy is still quiescent.[2] As a matter of fact only 23% of infectious cases were detected and treated under the DOTS strategy in 1999.[3] On the contrary reports show that the burden of new TB cases is not only linearly increased in these countries but also the number of advance TB states, multiple drug resistance due to poor control measures is on the speedy march. Alone from the South-East Asian countries, the situation is alarming in India, Indonesia, Bangladesh, Thailand, Myanmar, Pakistan and Afghanistan where 50% of global bulk of TB cases occur.[2] In order to fortify TB control WHO urges on countries to adopt Directly Observed Treatment Short-course (DOTS) strategy which is highly cost effective, ensures effective diagnosis and is considered a corner stone for treating infectious cases in any setting.[1] However many developing countries have been unable to expand coverage as rapidly as needed. One year after the Amsterdam Ministerial conference (2000) the recent effort of WHO in assessing progress in TB control among the high burden countries have revealed some valuable facts about the major obstacles in expanding TB control care under DOTS. According to the report DOTS coverage is profoundly slow and further expansion is overshadowed by lack of political back up, inadequate financial and technical resources and managerial inefficiencies.[3,4] Unless immediate action is taken, TB will continue to elude the brightest minds and challenge the human and economic resources of nations around the globe. More than 15 million people will die from tuberculosis in the next decade if countries do not fine tune their TB control programs and pledge to implement DOTS universally.[1]

Material and Methods

Using Medline search published research data (abstracts supplemented by full articles) and WHO reports on TB control mostly in high burden countries were retrieved and examined independently country by country. A significant amount of locally available data was also collected and critically appraised. With respect to financial contribution and DOTS implementation, each country was individually assessed, progress measured, incapacities and shortcomings in the TB control activities traced. Countries were compared in terms of political commitment, domestic contribution, and also in making efforts for an effective partnership with national and international agencies for the sustainability of

TB interventions. Information collected was presented in tables and graphics.

Results

Assessing Progress in Tuberculosis Control

With the exception of the Philippines, South Africa, Thailand, and to some extent India, recent data reveal that case detection and management under DOTS in the 22 high burden countries has increased very little from 21% in 1998 to 23% in 1999.[3] Among the same list of countries only Peru and Vietnam have achieved WHO targets of case detection and treatment. It is anticipated that countries including Cambodia, Kenya, South Africa, and the United Republic of Tanzania will reach their global targets in near future if enough efforts are put in.[5-7] Examining the data from 1999 (Table 1), one gets a clear impression that only a small

Table 1: TB Control in 22 HBCs (WHO, 1999).

Country	Incidence per 100,000	% New Smear + Cases under DOTS
Zimbabwe	562	55
Cambodia	560	57
S.Africa	495	68
Kenya	417	53
Ethopia	373	22
Uganda	343	59
UR Tanzania	340	51
Afghanistan	325	5
Philippine	314	20
Nigeria	301	12
DR Congo	301	53
Indonesia	282	19
Bangladesh	241	28
Peru	228	95
Viet Nam	189	80
India	185	6
Pakistan	177	2
Myanmar	169	33
Thailand	141	40
Russian F	123	2
China	103	32
Brazil	70	7

HBCs= High Burden Countries from TB

fraction of new sputum smear positive cases are managed under directly supervised therapy. Countries like Pakistan, Afghanistan and Brazil are far away from covering even half the number of detected cases under DOTS. In addition to the common problem of financial insufficiency, countries in different regions are confronted with diversifying challenges. Low-income countries like Zimbabwe, S. Africa, and Uganda are fighting the dual war of HIV/AIDS and TB.[8] War in Afghanistan, Vietnam, Angola and Guinea-Bissau has added heavily to the increasing sufferings, arresting progress and lessening the opportunities for establishing an effective tuberculosis control.[9-11,16]

However the examples of Peru, UR Tanzania, Kenya, Viet Nam, Cambodia, Uganda and China are worth mentioning here. They attained 100% DOTS coverage (See Table 2). This success is associated mainly to the domestic

Table 2: Population under DOTS (WHO, 1999).

Country	DOTS Population Coverage
Russian F	5
Brazil	7
Pakistan	8
Zimbabwe	12
Afghanistan	14
India	14
Philippine	43
Nigeria	45
Thailand	59
DR Congo	62
Ethopia	63
Myanmar	64
China	64
S. Africa	66
Indonesia	90
Bangladesh	90
Viet Nam	99
Peru	100
UR Tanzania	100
Cambodia	100
Uganda	100
Kenya	100

contributions by allocating reasonable amount of resources and effective partnerships and political motivation. For country wide DOTS expansion the contribution of private sector is considered a crucial element.[1,3,5,6,16] With the exception of Kenya, Philippines, and Viet Nam other countries have focused little on integrating the private sector and NGO's in the TB control. Government collaboration with other sectors is still a new concept, which greatly undermines their capacities and potential to expand the network of TB care.[3-7]

Kenya and China have established a well-organized public health system with respect to other countries where TB services are considered an integral part of the social services. The hallmark of their success is attributed not only to the dedicated leadership but also to adequate resource allocation, efficient information system and decentralized TB control system. In China TB units have been established in approximately 80 % of the country with the treatment success rate of about 96%.[3,5] China uses three modes of TB services with modified form of DOTS (free of cost), flexible subsidized payments depending on the socio-economic condition or insurance scheme of the patient and special case management approaches in the hospitals and other institutions. Peru has achieved 100% population coverage of

DOTS. Peru's effective governmental leadership and policy declared TB control as a public good. Mobilizing domestic resources and adopting a sector wide approach improved TB control. DOTS was additionally simplified and modified to the community needs and made accessible to majority of the population.[3,5,12-19]

Affective partnership and assuring sound funding resources have served a corner stone for the success in UR Tanzania, India and China etc. Pakistan and Afghanistan are among the slow progressing countries in terms of DOTS expansion. Lack of political motivation, war induced disruptions and apparent anomalies of the health systems in the region have curtailed the possibility of improving TB control activities.[1,3,14] Similarly DOTS progress has been severely bedevilled in Pakistan as well as in Afghanistan since the economic sanctions were imposed. With respect to the country's burden of TB cases, Table 2 illustrates DOTS coverage explicitly low in Russian Federation, Brazil, Pakistan, Afghanistan and Zimbabwe.[3,5-7]

Financial Contributions to the TB Control

Due to low spending and poor political attention TB control programs have been widely suffered particularly in 22 highly endemic countries.[3,5,6,15,17] The performance has been very well wherever TB was the focus of attention of the governments and private agencies.[5,14] The financial estimates of TB control for the 22 high-burden countries largely differ. Based on WHO data, Table 3 shows the level of domestic contribution with regard to the WHO estimated annual cost of TB control programs.

Furthermore the report on DOTS Expansion Plan 2001 says that realistic estimates for all high burden countries could not be made due to paucity of the credible data. More fair cost estimations need to be done by associating the number of patients who will get treated under DOTS if global targets have to be met. Of particular attention are the costs of drugs and the diagnostic supplies for the increasing number of diagnosed and treated TB cases. In addition, budgets also need to include spending to raise case detection and cure rates where targets have not yet been reached.

Report indicated that US$ 674.5 million per year is required, with existing funding totalling US$ 509 million from governments and US$ 26.5 million from grant funds. Still gap remains of US$ 64.5 million per year and an additional amount of US$ 74.5 million for which the distribution among regular budgets, loans, grants and gap is unknown. Report expressed uncertainty on the cost estimates for Indonesia, India, Nigeria, Bangladesh and Pakistan.

For cost estimation in these five countries it is important to have more accurate data due to their large contribution to the total number of tuberculosis cases in the 22 high-burden countries, and also due to their need to make substantial improvements in case detection rates if targets are to be reached. In Ethiopia, Kenya, S. Africa, Uganda and Thailand additional funds will be required to deal with the emerging HIV/AIDS and TB synergism and for multiple drug resistance in China, India and Russian Federation. Meticulous and country based estimations are required to raise case detection and cure rates and their associated costs.[3] With the exception of S. Africa, Peru, China where governments have been putting generous regular funds, spending in other countries was overtly low and potential sources to fill the increasing gap of resources were lacking. (Table 3).

Table 3: Estimated Costs Vs Governmental Contributions to TB Control (based on WHO 1998 Case Detection Rate).

Country	Est. Annual Cost TB Control Program in US$	Governmental Contribution (Regular Budgets only)
S. Africa	170	170
Russian F	150	120
India	100	50
China	88	43
Peru	20	20
Viet Nam	12	8
Kenya	16	12
Brazil	15	15
UR Tanzania	10	5
Thialand	10	10
Myanmar	2	1
Uganda	5	3
Afghanistan	2	0
Zimbabwe	11	-
Cambodia	4	1
DR Congo	10	0
Indonesia	9	8
Nigeria	8	3
Bangladesh	6	3
Pakistan	7	5
Philippine	13	9
Ethopia	8	1

Out of 22, Peru and Thailand have no resource gap. South Africa and Brazil are assumed to have no, or only a small, resource gap. The cost estimates of countries like Afghanistan, China, Ethiopia, Kenya, Myanmar, Nigeria, Philippines, Uganda, United Republic of Tanzania and Vietnam) depict significant deficiencies in the funds allocated by governments.[3,5,6] An interesting and important finding has been discovered that an overwhelming amount of debt has triggered reduction in the financial assets allocated to TB control in all high burden countries. Countries are left with no other choice rather than cutting their budgets on the health development and disease prevention (Figure 1).[20-22]

Countries apparently are unable to fund and launch a competent TB control efforts. External debt, in most of highly

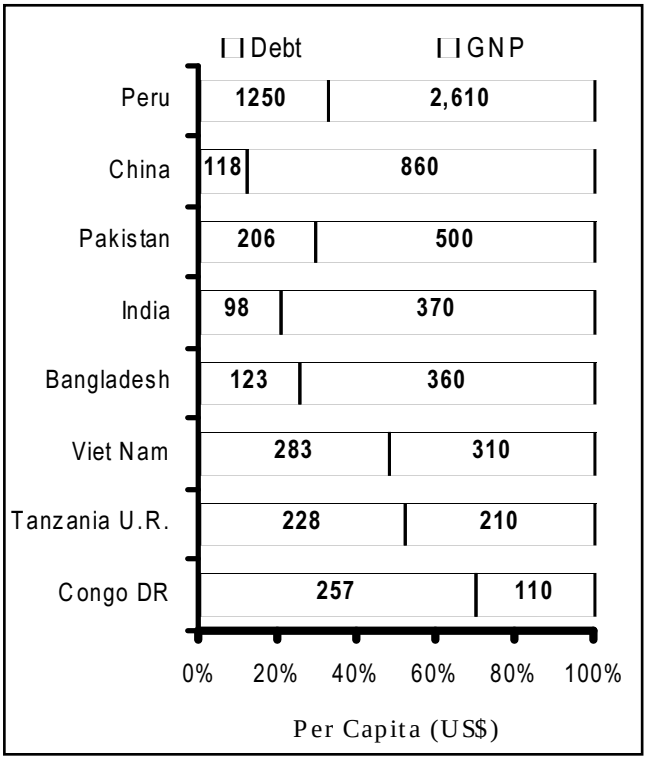

Figure: The burden of debt and GNP per capita in high burden countries (WHO, 1999).

TB endemic poor countries exceeds their gross national product. Similarly performance in TB control is worsened as the level of debts increased in the past.[23] Not only in these countries a negligible proportion of the financial resources are allocated but also TB control has suffered due to lack of motivation and poor political impetus. National health development in high burden countries has attained little attention due to such fiscal inequalities.

Knowing the fact that high burden countries have either less resources or are less willing to spend, the international community has shown significant motivation and interest in joining the battle against TB. Since the Amsterdam conference leaders of G8 nations and the European Community have increased their support in taking drastic steps against the diseases of poverty, with prioritized action for HIV/AIDS, malaria, and tuberculosis. In majority of these countries, international organizations such as WHO, World Bank and western Governments and charity organizations are assisting in one or the other way.[4,6,15]

Discussion and Recommendations

The article outlined the fact that success in TB control has been achieved wherever enough financial resources are allocate to the DOTS and made it an essential component of TB control program. Peru, Cambodia, Uganda, UR Tanzania, Kenya, Vietnam, Bangladesh and China have attained the highest cure rates under DOTS. Governmental spending on TB control is extremely insufficient in other high burden countries and does not comply with the increasing demands. With respect to the overwhelming TB cases in these countries a minute proportion is detected and treated under DOTS. DOTS implementation is static and prospects to achieve targets set by WHO are poor unless adequate resources combined with potent leadership are available. WHO report on DOTS progress is an important milestone in categorizing countries and identifying current challenges like TB and HIV/AIDS synergism, drug resistance and cost estimations for low-income countries. Gaps and barriers ahead are enormous and demand a great deal of political motivation and governmental support in eradicating TB. In the light of recent report by WHO, countries need to identify their (governmental) contribution, donor contribution, and understand resource gaps. To meet the global TB control targets countries like S. Africa, Zimbabwe, Indonesia, Pakistan, Afghanistan, India and the Russian Federation need to work aggressively to update their respective National TB control programs and adopt country specific approach in DOTS. Effective partnership and close incorporation of private sector are highly crucial for sustaining and expanding TB control activities. Countries need to build sound links of collaboration among countries, agencies, foundations, and nongovernmental organizations (NGOs) and prioritising health issues of their people. To accelerate the expansion of control measures under DOTS and to reach the targets for global TB control by 2005 more emphasis ought to be laid on the strict adherence of the high burden countries to the Amsterdam Declaration (March 2000 to Stop TB).

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Spoligotyping of Mycobacterium tuberculosis Isolates from Pakistan Reveals Predominance of Central Asian Strain 1 and Beijing Isolates

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Abstract

The estimated incidence of tuberculosis in Pakistan is 181 per 100,000; however, there is limited information on Mycobacterium tuberculosis genotypes circulating in the country. We studied 314 M. tuberculosis clinical isolates; of these, 197 (63%) isolates grouped into 22 different clusters, while 119 (37%) had unique spoligotypes. Eighty-nine percent of the isolates were pulmonary (Pul), and 11% were extrapulmonary (E-Pul). We identified Central Asian Strain (CAS), Beijing, T1, Latin American-Mediterranean, and East African-Indian genogroups. Beijing strains, reportedly the most prevalent spoligotype worldwide, constituted 6% of our strain population. The CAS1 strain comprised 121 (39%) of the study isolates. No difference was observed between clustered isolates from cases of Pul and E-Pul tuberculosis. However, E-Pul isolates included a greater number of unique spoligotypes than Pul isolates (P _ 0.005). The overall percentage of drug resistance was 54%, and that of MDR strains was 40%. While CAS1 strains were not associated with drug resistance, the relative risk of MDR was significant in Beijing strains compared to the non-Beijing groups (95% confidence interval, 1.2 to 8.9). The fact that the predominant strain, CAS1, is not associated with drug resistance is encouraging and suggests that an effective tuberculosis control program should be able to limit the high incidence of disease in this region.

Introduction

Globally, Pakistan ranks sixth in terms of tuberculosis (TB) burden, with a World Health Organization-estimated incidence rate of 181 cases per 100,000 persons or 272,000 new cases annually.[32] Pakistan shares geographical borders with four countries where TB is endemic, i.e., Afghanistan, Iran, China, and India. In addition, it is closely associated with other South Asian countries where TB is highly endemic, i.e., Bangladesh, Sri Lanka, and Nepal. Despite the high TB burden in the South Asian region, there are currently very limited data available pertaining to strains circulating in the country. Both treatment and detection of TB are significant problems; it is estimated that 4/5 TB cases in Pakistan remain untreated.[7] The situation is further confounded by a lack of availability of genotypic epidemiological tools that would allow contact tracing and identification of transmission patterns within the country.

The most commonly used methods of genotyping employ the IS6110 element to fingerprint strains.[24] In addition, spacer oligotyping (spoligotyping) based on the variation of spacers (36 to 41 bp) in the direct-repeat region of the Mycobacterium tuberculosis chromosome has been used with great efficiency to define predominant clades worldwide.[18] Although less discriminatory than IS6110

typing, spoligotyping is a rapid, quick, and robust method of genotyping M. tuberculosis and is particularly useful in the study of South Asian M. tuberculosis strains, which commonly have few copies of IS6110 elements.[8,14] Recently, data from international spoligotyping studies have identified a growing number of important clades or genogroups.[11,28]

Beijing strains are an aggressively expanding clone that has been identified in a number of populations across the world.[13] This family is characterized by a highly similar multibanded IS6110 pattern and a common spoligotype pattern with the absence of spacers 1 to 34 and the presence of only the last nine spacers.[30] It includes the M. tuberculosis W strain associated with multidrug resistance (MDR) in New York.[1,5,15] The Beijing family is reportedly the most prevalent spoligotype worldwide and constitutes 90 to 92% of the M. tuberculosis strains in China.[25,30] High rates of infection with Beijing strains in the countries neighboring China suggest that this particular strain may have radiated from Beijing to other regions. The prevalence of Beijing strains in Southeast Asia has been reported to be 30 to 100% in different studies. A lower prevalence is reported in South Asia and the Middle East, 8% in Delhi,[27] 10% from one region of Iran,[10] and 31% in a study in Dhaka.[3]

A second predominant cluster in the South Asian region is the Central Asian strain 1 type (CAS1) or Delhi type genogroup, which is characterized by the absence of spacers 4 to 7 and 23 to 34.[4] The presence of CAS1 strains in his region is supported by recent studies of M. tuberculosis isolates from India[27] and Bangladesh.[3]

To date, there is very limited genotypic information on M. tuberculosis strains circulating in Pakistan. The World Spoligotyping Database SpolDB3.0 describes an update on the global distribution of M. tuberculosis complex spoligotypes but shows little information about Pakistan.[11] In this study, we have typed M. tuberculosis isolates from specimens received at the clinical laboratory of The Aga Khan University Hospital, Karachi, Pakistan, in 2003 and 2004 in order to detect the presence of Beijing strains within the country. We have also investigated the association between predominant spoligotypes and drug resistance among our isolates.

Materials and Methods

This study was conducted with M. tuberculosis strains isolated at the clinical laboratory of The Aga Khan University Hospital between January 2003 and June 2004. During this period, 2,890 samples from suspected TB cases were cultured and 666 M. tuberculosis strains were isolated. Only one isolate was included per patient. Samples included in this study were from patients presenting to our laboratory units across the country; therefore, treatment history was not available. Representative samples from different geographical locations across the country were selected by using the stratified random sampling method. Fifty percent of the strains from each location were selected for inclusion in the study; a total of 314 strains (only one isolate per patient) were included. Of these, the largest proportion (135 strains [43%]) was from 14 different locations across Karachi. A further 179 strains were from the four different provinces of the country, i.e., 89 from the Punjab Province, 58 from the Sindh Province (excluding Karachi), 30 from Northwest Frontier Province, and 3 from the Balouchistan Province.

Two hundred eighty-four isolates were from pulmonary sites, i.e., sputum (n = 269), pleural exudate (n = 6), and bronchoalveolar lavage fluid (n = 9), while 30 isolates were from extrapulmonary sites.

Mycobacterial culture and antibiotic susceptibility. Mycobacterial cultures were performed with both liquid and solid media. Respiratory samples were decontaminated by using N-acetyl-L-cysteine sodium hydroxide prior to culture. Samples from sterile sites were processed without decontamination.[23] All specimens were concentrated by centrifugation (3,000 g) for 30 min, and sediments were cultured at 37°C with BACTEC 460 (Becton Dickinson Diagnostic Instruments Systems) and Lowenstein-Jensen medium. The growth index of inoculated BACTEC vials was checked for 4 weeks; Lowenstein-Jensen slants were incubated for up to 8 weeks. M. tuberculosis was identified by the BACTEC NAP TB differentiation test (Becton Dickinson).

Susceptibility testing was performed by the standard agar proportion method with enriched Middlebrook 7H10 medium (BBL) at the following final drug concentrations: rifampin, 1 µg/ml and 5 µg/ml; isoniazid, 0.2 µg/ml and 1 µg/ml; streptomycin, 2 µg/ml and 10 µg/ml; ethambutol, 5 µg/ml and 10 µg/ml.[17,22,31] Pyrazinamide sensitivity was tested with BACTEC 7H12 medium, pH 6.0, at 100 µg/ml (BACTEC PZA test medium; Becton Dickinson) in accordance with the manufacturer's instructions. To ensure the selection of strains with high-level resistance for this study, however, only resistance to the higher concentrations was used for analysis. MDR was defined in accordance with standard criteria of resistance to at least isoniazid and rifampin.

DNA methods: Mycobacteria were cultured on Middlebrook 7H10 agar. DNA extraction from mycobacterial colonies was carried out by the cetyltrimethylammonium bromide method.[16] Spoligotyping was carried out with a commercially available kit from Isogen Bioscience BV, Maarssen, The Netherlands,

according to the manufacturer's instructions. Spoligotyping based on the 43 spacers of the direct-repeat region of the M. tuberculosis complex was carried out with primers DRa (5'GGTTTTGGGTCTGACGAC 3') and DRb (5'CCGAG AGGGGACGGAAAC 3') as originally described by Kamerbeek et al.[18]

Data analysis: Spoligotyping results were analyzed with the Bionumerics software program (BioSystematica). Dendrograms were generated by the unweighted- pair group method using average linkages. A cluster was defined as two or more isolates from different patients with identical spoligotype patterns. We defined unique spoligotypes as those which did not cluster with any other sample in our study. The spoligotypes were compared with the 36 most prevalent M. tuberculosis subfamilies as identified by the World Spoligotyping Database SpolDB3.0 of the Pasteur Institute of Guadeloupe (www.cdc.gov/ncidod/EID /vol8no11/02-0125-Table.htm).[12] In addition, all clusters obtained were compared with the shared types (STs) present in SpolDB3.0 (http://www.pasteur - guadeloupe.fr/tb/spoldb3).[11] This database contains information on the prevalence of spoligotypes in different countries and their relative occurrence.

Pearson's chi-square test was used to determine statistical associations between strain types and specific parameters with SPSS software. Odds ratios were calculated with 95% confidence intervals. A P value of < 0.05 was considered evidence of a significant difference.

Results

Study population: The demographic information for patients whose M. tuberculosis isolates were studied showed that the majority of 314 M. tuberculosis isolates were from patients in the 15- to 30-year age group, with 73.4% in the 15- to 45-year age group, compared with 24% in the > 45-year age group. There were no differences in terms of gender distribution. The majority (n = 284) of isolates were from patients with pulmonary disease, of which 92% were smear positive. The 30 remaining isolates were from patients with extrapulmonary TB, of which 66.6% were smear positive.

Spoligotyping: All 314 isolates were spoligotyped and analyzed (Fig. 1). A total of 197 (63%) isolates were grouped into 22 different clusters, while 119 (37%) isolates had unique spoligotypes. Previously, 18 different STs had been identified as having geographic specificity to Pakistan as listed in SpolDB3.0 (11). We compared our 22 clusters with this list and found them to include six of the spoligotypes attributed to Pakistan in SpolDB3.0. These six spoligotypes included ST1 (Beijing strain), ST26 (CAS1), ST53 (T1), ST11 (East African Indian strain 3), ST25, and ST486 (11). Our isolates did not include ST27, ST37, ST48,

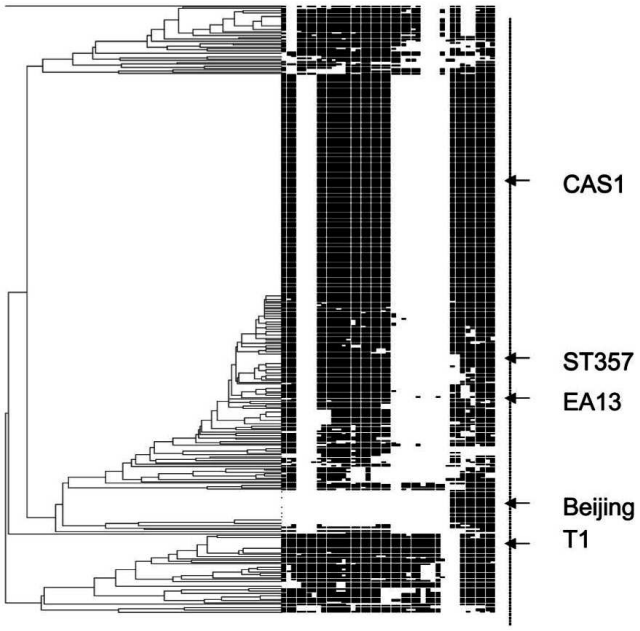


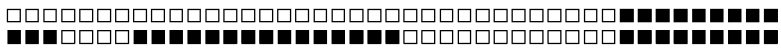
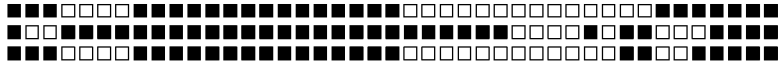
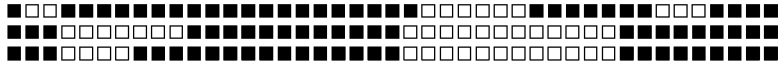
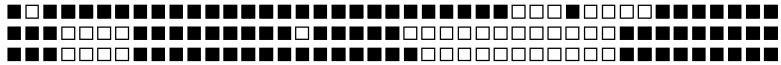
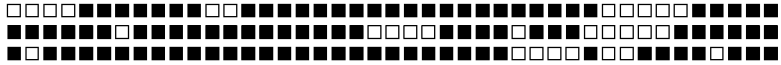
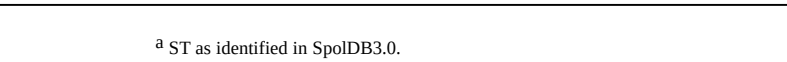
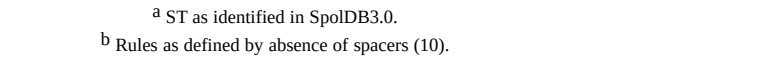
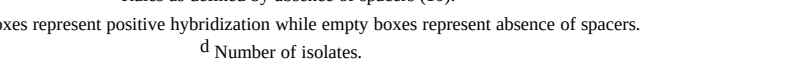
Figure 1: Dendrogram of Pakistani isolates (Pearson correlation). All isolates were spoligotyped, and data were analyzed with the Bionumerics software program. A dendrogram was calculated on the basis of the Jacquard index for pairwise analysis of strains by the unweighted-pair group method using average linkages. The clustering pattern of 314 isolates is illustrated. The five most predominant shared spoligotypes, CAS1 (n _ 121), Beijing (n _ 18), T1 (n _ 7), ST357 (n _ 7), and East African-Indian strain 3 (EAI3; n _ 5), are indicated.

ST50, ST52, ST172, ST236, ST281, ST381, ST428, ST520, and ST794, which have previous been identified by SpolDB3.0 as being present in Pakistan.

Six further clusters were also identified with homology to ST357, ST288 (CAS2), ST142, ST203, ST289, and ST127 (Table 1). Of these, only ST127 was identified as ubiquitous while the others had all previously been reported as rare or localized to regions of North America, Europe, and Australia, with the exception of ST288 (also in India and Iran) and ST357 (identified in Iran). Clusters Pak1 to -10 were unique and not homologous to STs within SpolDB3.0. We also compared our strains with the 36 most common STs in SpolDB3.0[12] and found one isolate homologous with ST64 or Latin American-Mediterranean strain 6. Overall, 18 Beijing strains (ST1) were identified, making up 6% of the isolates studied. These strains were from different locations in Pakistan; 9 were from the city of Karachi, 6 were from the Punjab Province, and 3 were from the Northwest Frontier Province.

The most prevalent shared spoligotype in our population, however, was ST26 or CAS1, also known as the Delhi strain (27); 39% (n = 121) of the strains analyzed belonged to this spoligotype. In addition, differing levels of homology with CAS1 was also shown by other strains in the study population; 13 strains showed 96% homology, 24

Table 1: Spoligotypes shared by M. tuberculosis isolates evaluated in this study.

Order	Class[a]	*n*[d]	Rule(s)[b]	Binary[c]	Octal
1	ST1	18	Δ1-34		000000000003771
2	ST26	121	Δ4-7, Δ23-34		703777740003771
3	ST53	7	Δ33-36		777777777760771
4	ST357	7	Δ4-7, Δ23-36		703777740000771
5	ST11	5	Δ2-3, Δ29-32, Δ34, Δ37-39		477777740173071
6	ST25	4	Δ4-7, Δ23-34, Δ37-38		703777740003171
7	ST486	3	Δ4-7, Δ23-34, Δ39		703777740003671
8	Pak1	3	Δ4-7, Δ23-37		703777740000371
9	Pak2	3	Δ2-3, Δ24-29, Δ37-39		477777760177071
10	ST288	2	Δ4-10, Δ23-34		700377740003771
11	ST142	2	Δ4-7, Δ23-34		703777740003771
12	ST203	2	Δ4-7, Δ23-35		703777700003771
13	ST289	2	Δ4-10Δ23-34, Δ38		703777740003571
14	ST127	2	Δ2, Δ29-31, Δ33-36		577777777420771
15	Pak3	2	Δ4-7, Δ17, Δ23-34		703757740003771
16	Pak4	2	Δ4-7, Δ24-34		703777740001771
17	Pak5	2	Δ4-7, Δ23-36		703777740000771
18	Pak6	2	Δ4-10, Δ23-36		700377740000771
19	Pak7	2	Δ1-4, Δ12-13, Δ34-38		037637777770171
20	Pak8	2	Δ7, Δ21-24, Δ29, Δ33-36		773777607560171
21	Pak9	2	Δ2, Δ29-32, Δ34-35, Δ40		577777777411731
22	Pak10	2	Δ4-8, Δ15, Δ31-41		701767777700011

[a] ST as identified in SpolDB3.0.

[b] Rules as defined by absence of spacers (10).

[c] Filled boxes represent positive hybridization while empty boxes represent absence of spacers.

[d] Number of isolates.

strains showed 92% ho mology, and 31 strains showed 80% homology. The related CAS2 strain was also present. The CAS clade included a total of 174 isolates.

Table 2: Cluster distribution among pulmonary and extrapulmonary M. tuberculosis isolates.

Spoligotype group	No. of isolates (% of total)		P value
	Pulmonary	Extrapulmonary	
CAS1	111 (40)	10 (28.6)	0.276
Beijing	17 (6)	1 (2.86)	0.697
Other clusters	56 (20)	3 (8.57)	0.167
Unique	95 (34)	21 (60)	0.005a
Total	279	35	

[a] Statistically significant difference between pulmonary and extrapulmonary M. tuberculosis isolates (95% CI, 8.794 to 43.106).

Analysis of agewise clustering of M. tuberculosis spoligotypes indicated that of the 228 isolates, 145 (64.4%) were clustered in the 15- to 45-year age group, compared with 45 (59%) out of a total of 76 isolates that clustered in the > 45-year age group. The difference was not significant (odds ratio, 1.6; 95% confidence interval [95% CI], 0.953 to 2.716). Similarly, there was no association between patient age groups and the occurrence of the CAS1 or Beijing strain.

Pulmonary versus extrapulmonary isolates: We analyzed the association between clustered and nonclustered (unique) spoligotypes and the source

Table 3: Association of antimicrobial resistance with spoligotypes.

Characteristic	No. (%) of strains				
	Clustered spoligotypes			Unique spoligotypes	All spoligotypes
	Beijing	CAS1	Othersa		
Sensitivity to first-line drugs[b]	6 (33)	57 (47)	22 (40)	60 (50)	144 (45.9)
MDR	12 (67)	49 (40.5)	19 (34.5)	45 (37.5)	125 (39.8)
Isoniazid resistance[c]	0	10 (8.3)	12 (21.8)	8 (6.7)	30 (9.6)
Rifampin resistance[b]	0	1 (0.8)	1 (1.8)	3 (2.5)	6 (1.9)
Resistance to other drugs[d]	0	4 (3.3)	1 (1.8)	4 (3.3)	9 (2.9)
Total	18	121	55	120	314

[a] Includes a total of 22 clusters.

[b] Rifampin, isoniazid, streptomycin, ethambutol, and pyrazinamide.

[c] Other than MDR.

[d] Resistance to one or more first-line agents other than isoniazid and/or rifampin.

(pulmonary or extrapulmonary) of the M. tuberculosis isolates (Table 2). There was no statistically significant difference in the distribution of clustered spoligotypes (CAS1, Beijing, or others) between the pulmonary and extrapulmonary groups. However, 60% of the isolates from extrapulmonary sources were unique, compared with 43% of the pulmonary isolates. This difference was statistically significant (P = 0.005; 95% CI, 8.8 to 43.1).

Drug resistance patterns: Of the 314 strains included in this study, 45.9% were sensitive to all five of the first-line agents tested. Among the 170 drug-resistant isolates, 74% were MDR (Table 3). Analysis of the association of MDR with cluster type showed that the Beijing strains in this population were highly associated with MDR (P = 0.017 [Pearson's chi-square test]). The relative risk of MDR in the Beijing strains at 3.024 is significantly higher than in the non-Beijing groups (95% CI, 1.182 to 8.872). In addition, ST Pak6 (Table 1) was also classified as MDR.

The MDR rate in the predominant CAS1 cluster, on the other hand, was not significantly different from that in other circulating clustered and unique spoligotypes (P = 0.844 [Pearson's chi-square test]).

Discussion

This report presents the largest amount of epidemiological data on M. tuberculosis isolates from Pakistan to date. Previously, the limited data available from this area were those based on the IS6110 restriction fragment length polymorphism genotyping method[21,26] or were from studies of immigrant Pakistanis carried out in Europe.[19] In this region where TB is endemic, it is critical to identify predominant strain types in order to study transmission patterns within the country and to understand the epidemiology of the disease in Pakistan. This is all the more important as Pakistan is host to a very large number of immigrant populations and migrant workers from neighboring countries where TB is endemic (Afghanistan and Bangladesh), and the movement of these populations would influence strain distribution in the entire region.

We found the CAS1 or type 26 strain[14] to be predominant (39%) among the 314 isolates tested, followed by Beijing isolates (6%). CAS1 has been also identified as a predominant strain in Delhi[27] and Mumbai, India.[2] Furthermore, our results also compare well to data from Delhi, India, where 22% of 105 isolates were of the CAS1 strain and 8% were Beijing isolates.[27] Another Delhi-based study showed that 75% of the strains belonged to the Delhi genogroup,[4] while a study carried out in Dhaka, Bangladesh, identified Beijing strains as the most common type in that population.[3] Geographically speaking, India provides us with the closest comparison. Additional clustered spoligotypes identified in Indian studies were ST18, ST23, ST31, ST21, ST13,[4] ST26, ST54, and ST1 (27). Of these, we identified ST26 (n = 121), ST1 (n = 18), and ST21 (n = 1) among our Pakistani isolates. The identification of a dominant spoligotype common to India and Bangladesh illustrates an important trend in the M. tuberculosis infection pattern in the South Asian region.

Recent transmission of TB is indicated by the increased incidence observed in the younger age group (15 to 45 years). However, we did not find any significant clustering between age groups and spoligotypes in our study. This is in contrast to other studies, which have indicated significant clustering in younger and also in older age groups.[27] Our data further confirm that the predominant genogroups CAS and Beijing are well established in the region and are not a result of recent introduction.

We found CAS1 to be equally associated with drug sensitivity or drug resistance and did not find it to be associated with MDR TB (P = 0.844). This correlates with a report by Singh et al.[27] but does not correlate with a study of 65 isolates from Bombay, India, reporting an association of CAS1 with MDR.[20] The difference may be attributed to the smaller sample size in the earlier study[20] and also to the fact the study in Bombay had only included strains from one hospital in an urban setting and was therefore likely to include a larger proportion of resistant strains.

As our study was based on referred patients presenting at a clinical laboratory, we were unable to determine any epidemiological associations between patients and strains. However, it was clear that the predominant clusters-CAS1 and Beijing - were present in locations dispersed throughout the country and were therefore not associated with a recent or epidemic strain.

We found that the extrapulmonary isolates were significantly associated with unique spoligotypes. There is little information as to the pathogen dynamics that result in dissemination to extrapulmonary sites in the host. A recent study by de Viedma et al.[9] suggests increased infectivity of strains which are found at extrapulmonary locations. Given that the predominant TB site is pulmonary and that extrapulmonary disease may be associated with more-virulent isolates, it is not surprising to observe less genetic variation in pulmonary compared to extrapulmonary isolates.

In our study population, we noted a higher relative risk of MDR among Beijing strains. Association between Beijing strains and MDR varies worldwide; whereas such an association is reported in studies in the United States, Estonia, and Vietnam,[6] it has not been noted in countries such as China and Indonesia, where the representation of the Beijing strains in the population is greater.[29] However, a

recent study in Mumbai, India, also showed a high frequency of Beijing strains (35%) among the MDR isolates.[2]

The diversity of global TB clinical isolates has been illustrated by the major spoligotype families and patterns identified by the World Spoligotyping Database at the Pasteur Institute, Guadeloupe. SpolDB3.0 shows that the 24 most prevalent isolates represent 53% of the strains present worldwide.[11] We did not compare all of our strains against SpolDB3.0. However, we ran comparisons of all of the clusters identified in our study (Table 1) with SpolDB3.0 and also of the 36 most common spoligotypes identified by the database. By using this methodology, in addition to the CAS and Beijing strains, we identified the East African-Indian family, the T group, and the Latin American-Mediterranean family of M. tuberculosis in our population.

In addition to the predominant groups identified, we also were able to identify the occurrence of clusters of rare or localized STs listed in SpolDB3.0 that have previously been found in North America, Australia, and Europe in addition to those found in neighboring Iran and India. While more community-based data are required in order to understand transmission patterns and to monitor strain resistance, our study provides essential information about M. tuberculosis strains circulating in Pakistan. Strain analysis, together with virulence studies, will also help in pinpointing isolates associated with higher morbidity and mortality, with the aim of directing efforts to limit the spread of those strains within the region. In addition, knowledge of prevalent strains will help evaluate the efficacy of commonly used TB vaccines in the region.

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Original Article

Defaulting Rate of TB Patients among Seasonal Migrants (A Case Study of Balochistan)

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Abstract

Objective: The objective was to bring evidence about the contribution of seasonal migration to defaulting and low treatment success rate (TSR) in Balochistan province of Pakistan.

Methods: Directly Observed Therapy (DOTS) has been implemented in 22 districts of Balochistan province. A cohort study was conducted in five randomly selected districts between October 2005 and March 2006. A total of 291 new PTB patients during the two quarters were interviewed before summer migration by using a structured and pre-tested interview schedule regarding their health seeking behavior and other determinants about seasonal migration to determine default and TSR among migrant and non-migrant patients.

Results: The overall default rate at surveyed districts was very low (2.4%) as compared to national level which is 17%, whereas it was 4.4% among migrant patients. It was evident that TSR was also high which was 96% and 100% among migrant and non-migrant patients respectively. It shows that migration has very low impact on default and low TSR. The main factors of low default and high TSR were the high commitment of patients for seeking their medical checkup as well as regularity in medication by both migrant as well as non-migrant patients.

Conclusion: The high degree of commitment for seeking medical checkup and regularity in medication were the two main factors for low default rate and high TSR in the surveyed districts.

Introduction

Tuberculoses is endemic in Pakistan. With the population of 152 million about 1.5 million people are infected and Pakistan ranks sixth among the 22 high-burden tuberculosis countries worldwide (177 per 100,000) and death toll due to TB mounts to round 50,000 annually.[1] About 75% patients fall in the earning age group 14-49 years.[1] According to the World Health Organization (WHO), Pakistan accounts for 43 percent of TB disease in the WHO Eastern Mediterranean Region.

The Ministry of Health of Government of Pakistan began implementing the DOTS strategy since 1995, with Balochistan as a pilot province. Between 2000 and 2002, DOTS coverage increased in Pakistan from 9 to 45 percent.[2] In 2001, the government declared TB a national emergency that is why DOTS is continuously expanding and overall TB control system is steadily improving.

From 2000 to 2001, both DOTS coverage and the DOTS detection rate for Pakistan were approximately doubled. Comparing 1999 and 2000 cohorts the default rate (17%) is still the highest among high burden countries (HBCs) and a major barrier to reaching the global target of 85% cure rate and 70% case detection rate (CDR) by 2005. In Balochistan more than 40% population always migrate from south to north and north to south. The relationship between migration and emergence/re-emergence of infectious disease has long been reported.[3] The National TB Program (NTP) therefore needs to address problems of case finding, diagnosis and treatment in migrant patients. The

present study was therefore undertaken keeping in view the same scenario for finding out the main reasons of default in Balochistan specially focusing on seasonal migration.

Material

A cohort study was conducted in five randomly selected districts (Bolan, Khuzdar, Nushki ,Sibi and Nasirabad) of the twenty two DOTS implemented districts of the province of Balochistan in (2005-6) using the random number list of Epi Info. By assuming that the least frequent predictor of defaulting exists in 2% of non-defaulters and 10% of defaulters, therefore, the least reliable sample size was 322 patients, at 95% confidence interval and 80% study power. With 20% drop outs, the total sample size was approximately 400 PTB patients. But it was only 291 positive cases during the period of two quarters.

A total of 291 new sputum smear positive pulmonary TB patients registered during the two quarters (1st October, 2005 to 30th March, 2006) were interviewed before summer migration by using a structured and pre-tested interview schedule regarding (age, sex, occupation, literacy, income level, causes and period of migration) to determine default and TSR among migrant and non-migrant patients. To train the field staff a training workshop was organized at each district. The data collected by the field staff and was cross checked with routine records maintained at center/health facilities. Statistical analysis was performed by using the Chi-square test for test of association between time of migration and main reasons of migration.

Results

There were 142 (49%) males and 149 (51%) females (Table 1). Out of these the migrant cases were 86 females and 83 males. The default cases among migrant female and male were 8.45% and 3.38% respectively whereas there were no default in non-migrant cases.

Majority of cases were from Bolan district 108 (37.1%) and most migrant cases 41.4% were also from the same district (Table 2). Most default cases were reported from Sibi district.

Migration due to season (Table 2) was the most commonly reported reason for migration. This was followed by search for job, heritage and others.

Table 2: Reasons /Period of Migration.

Reason of Migration	Month of Migration				
	April	May	June	July	Total
In Search of Job	10	10	07	04	31
Due to Season	40	16	27	32	115
Heritage	06	02	04	02	14
Due to Some other reasons.	04	01	02	02	09
Total	60	29	40	40	169

The main reasons of migration with the association of month of migration was checked for the independence of the two criteria at 5% level of significance, Chi-square test was applied and it is calculated as 8.65 and compared with the tabular value as 16.92. It is calculated that the two criteria are dependent.

The majority of patients migrate during the month of April and July, while the weather is hot in their basement areas. It has been also observed during the study that 56% of the respondents were not satisfied with the existence TB treatment services.

Karl Pearson's Coefficient of means square contingency is calculated as 0.2207 and lies in the range of $0 < c < 0.866$. It is evident that almost all TB carriers migrate during summer season due to hot weather to the area where weather is pleasant and some of them in search of job. Most of the patients migrate at the beginning of the hot season i-e in the month of April.

Table 1: Comparative Analysis of Migrants & Non Migrant and Default Rate.

Districts	Total Number of Cases	Migrant Cases	Default Cases	Percentage	
				Default in Migrant	Default in Total Cases
Sibi	28	15	5	33.33 %	18%
Bolan	108	70	0	00.00%	0 %
Nasirabad	51	26	0	00.00%	0 %
Noshki	25	16	1	6.25 %	4 %
Khuzdar	79	42	1	2.00 %	1.26%
Total	291	169	07	4.14 %	2.40 %

Discussion

The overall default rate at surveyed districts was very low (2.4%) as compared to national level, which is 17%, whereas it was 4.4% among migrant patients. TSR was evidently high, 96% and 100% among migrant and non-migrant patients respectively. The study shows that

migration has very low impact on default and low TSR. The low default rate is due to DOTS coverage by the NTP during last five years and awareness, commitment of patients with their treatment.

A pervious study from Tiruvallur district, Tamil Nadu (India), had reported irregular and incomplete treatment on account of migration is likely to increase the burden of TB in the community.[4] The main factors of low default and high TSR in the present study were the high commitment of patients for seeking their medical checkup as well as regularity in medication by both migrant as well as non-migrant patients.

Two most important sources of patients' information about TB were their physician and hospitals. The majority of patients (53%) reported fever followed by coughing were the major symptom motivating the patients to seek health care.

More than half 56% of the respondents were not satisfied with available services at the TB service centre and 87% of the respondent's emphasised that there is need to improve services of TB centers. The most important source of patient's information and awareness were physician and hospitals staff. This study was limited only up to five districts there similar such studies are required in other districts of the province.

Conclusion

It is concluded from the study that to over come the problems of treatment, the existing services in the TB centers should be improved. Coverage can be enhanced if treatment facility is provided through mobile network. For creating more awareness the electronic media may be used.

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Original Article

Impact of training of Religious Leaders about Tuberculosis on Case Detection Rate in Balochistan, Pakistan

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Abstract

Objective: to study the impact of involving religious leaders in increasing awareness of the community regarding timely care seeking with the ultimate goal of increasing case detection rate of tuberculosis in Balochistan.

Methods: An intervention study conducted between April 2005 and March 2006 in which baseline knowledge of religious leaders about Tuberculosis (TB) was assessed by a questionnaire interview followed by one day orientation and training workshop. Trained religious leaders launched TB awareness campaign by delivering speech (Surmon or Khutbaa) in Friday weekly prayers. The impact of this campaign was assessed by interviewing the patients attending the TB clinics of six districts and recording of Case Detection Rate (CDR) of 2nd, 3rd, 4th quarter of 2005 and 1st quarter 2006 in these districts.

Result: A significant increase in knowledge about TB and its symptoms (95-100%) and about duration of cough for TB suspects (90%) was noted among the religious leaders after training. They conveyed the message to masses in effective manner. 27.88 % patients attended the TB clinics

on advice of religious leaders The relation and trust of religious leaders on TB clinics increased significantly (100%). The CDR increased in intervention districts from 2 to 40%.

Conclusion: Awareness about TB in these religious leaders improved and they conveyed the message to the masses. Involving the religious leaders in raising awareness of the community proved to have a beneficial impact on the health seeking behavior of TB suspects, and on increasing CDR in the community.

Introduction

Pakistan has the seventh highest TB burden globally and account for 44% of the total TB burden in the Eastern Mediterranean Region of the WHO (EMRO). In Pakistan among the total population of 154.794 million., 101,562 TB cases (all forms) were notified (incidence: 66/100,000 population).[1,2]

Pakistan is an Islamic state with about 98% Muslims and 2% religious minorities including Christian, Hindu, Parsi.[8] Religion play a major role in the lives of the masses. Balochistan is the largest (218,400 sq ms) but the least populated province of the country with the literacy rate of 26.4%.[7] It has 400 tribes, sub-tribes and clans. It has three main language groups: Baluchi, Pushto and Brahvi, as well as Persian, sindhi, and saraiki is also spoken in various areas but Urdu is widely understood in all regions of the province. Though people speak different languages, there is a similarity in their literature, beliefs, moral order and customs. The cementing factor is religion which provides a base for unity and common social order.[7,8]

The National targets of DOTS strategy was to reach 70% Case Detection Rate (CDR) and 85% Treatment Success Rate (TSR) by 2005.[3-5]

Previously Balochistan reported 28% CDR, 80% TSR and 12% default rate. (PTP Balochistan 2005).[6] In order to raise the CDR to 70% and reduce the default rate less than 5%, there was a need to develop innovative interventions so that important targets set by WHO are achieved.

Muslims are directed to offer prayers (Nama'az) five times every day and Friday afternoon prayers (Jumma) hold special place when in addition to the Nama'az, leader (Ima'am) also deliver a speech (sermon or Khutba) before the Namaaz listening which attentively is mandatory..

Accordingly, it is importnat to assess the knowledge of their leaders, raise their awareness about the disease and involve them in motivating the community.

In other Muslim countries like Iraq,[9] Iran,[10-13] Syria,[14] Sudan,[15] Somalia[16] and Tanzania[17] other social groups like family physicians,[18] Health Care Workers and role of Laboratory 12 were studied for their role in awareness of TB and measure to make early diagnosis possible to facilitate the control of TB, but no such study has been done on the knowledge of Religious Leaders (R.L) and their role in awareness of TB.

In view of the above, an intervention study was designed to involve religious leaders, in raising awareness of the community about the adequate health seeking behavior with the ultimate goal of increasing the CDR. Three districts of Balochistan province were selected randomly to assess the knowledge of religious leaders about TB. Workshops were then held to educate RL about the importance of early case detection, proper health seeking behavior and other aspects of TB control. This was followed by a campaign, launched with the help of religious leaders, to raise awareness about TB among the local population. The impact of the intervention was evaluated by interviewing the patients who were attending TB clinics and CDR was compared between the intervention and control districts.

Material and Methods

An interventional study conducted in three randomly selected districts out of 29 districts of Balochistan province of Pakistan, from April 2005 to March 2006.

The qualified RLs regularly who had religious education and who were offering leading Friday weekly prayers in three interventional districts were offered to participate in this programme on voluntary basis. Those consented to participate were included in this study. Three more districts which were socially, geographically and ethnically identical with interventional districts were included as controls.

After base line interview by trained staff in all intervention and control districts, the R.Ls in interventional districts were provided one day orientation/ training workshop about knowledge of symptoms, duration and treatment of TB and facilities available regarding TB in their area. The training material about TB was developed in Urdu, the spoken language of all participants, which included topics like history, symptoms, duration of treatment of TB and the importance of completion of treatment. The role of religion to help patients of TB was described by one senior religious leader. Posters and other relevant literature about TB published by National and Provincial Tuberculosis control Programme was also distributed among the participants of workshops. After workshops a campaign was started in intervention district by religious leaders about awareness of tuberculosis, in which they delivered speech about TB during Friday afternoon sermon (Khutbaa-e-Jumma).

The response of this campaign was assessed by interviewing consented patients at seven TB clinics of six districts. Patients were asked that who has prompted them to come to TB clinic for treatment. The CDR was noted in all six districts from 2nd quarter to 4th quarter of 2005 and 1st quarter of 2006.

Results

Eighty seven religious leaders were included in this study. Out of which, 76 (87.35%) were Muslim, 7 (8.04%) Hindu and 4 (4.59%) were Christian. Ethnically 47 (54.04%) were Baloch, (including Balochi and Brahvi speaking) 27 (31.03%) Pashtoons and 13 (14.94%) other tribes. The majority of people in Killa Saifullah (intervention district) and Pishin (control district) speaks Pashto, in Nushki (intervention district) and Kharan (control district) speak Balochi and in Mastung (intervention district) and Kalat (control district) speak Brahvi.

Forty two R.Ls consented to participate in the program in 3 intervention districts, only one religious leader in Nushki district refused to participate. Total forty two RLs in three districts and forty five RLs in three control districts contacted and interviewed..

After the intervention, in intervention districts, these Religious Leaders were interviewed again to assess the knowledge and practice about awareness of TB. Three religious leaders were excluded from the study who were not available, as two were relieved from their duties and one was not available who went on "Tableegh" (the religious duty) for 4 months.

Table 1: Response of Religious Leaders to advised people about Tuberculosis.

Response	Before Intervention n=42		After Intervention n=39		Control District n=45	
	#	%	#	%	#	%
Yes	17	40.48	39	100	32	71.11
No	10	23.81	0		13	28.89
Don't Know/ No Answer	15	35.71	0		0	0.00

Table 2: Patients response at TB clinics, in intervention and control districts.

	Intervention District .n=226		Cont District .n= 202	
Response	#	%	#	%
Religious Leader	63	27.88	36	17.82
Doctor	76	33.63	44	21.78
NGOs	1	0.44	11	5.45
Others (Relatives and friends)	86	38.05	111	54.95

Table 3: Number of Religious Leaders(RL) and the rise in Case Detection Rate (CDR).

District	No of RL	Ratio in Population	Rise in CDR
K. Saifullah	8	1:29316	2%
Mastung	15	1:13333	20%
Nushki	16	1:6250	40%

Discussion

The religious leaders basic knowledge about TB was based on wrong sources of information, mostly on "Unani" non medical books, and they were also consulting non medical ways of treatment. This situation exist in Asian countries, in India even family physicians had many misunderstanding about the diagnosis and treatment of TB. After training workshops and distribution of literature about TB, the knowledge and attitude of religious leaders significantly changed and 92.3% religious leaders became in contact with TB patients. In Iran such programme was launched for the training of private sector Physicians and emphasizing for continuation of such programmes for control of tuberculosis.[12] In Iraq, Hashem Dhafer found that the optimal knowledge of patients about TB is 64.4%.[9] In other countries also people has false concepts about TB and

Table 4: Impact of awareness of religious leaders on case detection rate. Case notification and detection rates in the intervention and control districts.

		Killa Saifullah (I.D)†	Pishin (C.D)‡	Nushki (I.D)	Kharan (C.D)	Mastung (I.D)	Kalat(C.D)
2nd Quarter 2005	Smear +ve	75	61	60	23	10	13
	Case Notification rate	32	19.5	60	11.6	5	4.1
3rd Quarter 2005	Smear +ve	17	47	20	60	8	7
	Case Notification rate	32.8	15.05	20	32.27	4	2.21
4th Quarter 2005	Smear +ve	46	28	60	47	3	4
	Case Notification rate	19.6	8.97	60	23.71	1.5	1.26
1st Quarter 2006	Smear +ve	39	43	64	28	23	19
	Case Notification rate	16.6	13.77	64	14.13	11.5	6
total notified ss+ve		237	179	204	158	44	43
Case notification rate*		101.05	57.33	204.00	79.72.	22.00	13.57
estimated no ss +ve		211.1	281.0	90.00	178.4	180.0	285.1
CDR**		112.3	63.7	226.7	88.6	24.4	15.1

*Case Detection Rate, †Intervention District, ‡Control District, **Significant rise in CDR in intervention districts, $p< 0.05$.

cultural beliefs about TB may become risk factor in spread of disease.[18] In United states Jane E. Poss found that etiology of tuberculosis varies by cultures.[19]

In our study religious leaders visited and trusted more after intervention campaign as compare to control districts, indicates that TB awareness programme is acceptable for religious leaders, which resulted in increase of CDR from 2-40%. In other countries, specially in big cities people become influenced by electronic media, in Colombia health education campaign in media resulted in 52% rise in smear positive cases.[20] In Iran and Iraq private physicians were involved in diagnostic and preventive programmes to control the TB.[9]

The role of religious leaders is becoming eminent in Pakistan. Many social and medical programmes are including religious leaders, like Polio eradication programme, AIDS control programme and Population planning because Political support, the support of health professionals and the community are vital for success of these programes.[21]

In Ethiopia when religious leaders were included in awareness programme, it resulted in increased awareness about TB.[22] The impact of involving the RL was significantly higher among the illiterate members of the community, who brought their female family members for treatment to the TB clinic based on the advice of religious leaders. The over all effect of awareness in religious leaders resulted in increase in CDR in these districts.

Conclusion

As a result of intervention, the knowledge of religious leaders about TB increased significantly and they successfully conveyed the massage to their audience which resulted in visit of 27.88% more patients to TB clinics. The intervention resulted in increase in case detection rate from 2 to 40 % in intervention districts.

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Original Article

Screening of TB Patients for HIV Infection in Concentrated HIV Epidemic Setting in Sindh, Pakistan

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Abstract

Objective: To determine the prevalence of HIV among registered TB patients including Multi Drug Resistant TB cases and also to evaluate acceptability of HIV testing among TB patients.

Methods: A cross sectional study was conducted at five different sites between 7th April & 7th June, 2008. The sites included three satellite clinics of Dow University of Health Sciences, Karachi which were Dr. Iqbal Yad Chest Clinic, MDR Clinic and Malir Chest Clinics. DOTS Centre of Liaquat University of Medical & Health Sciences Hospital, Hyderabad (LUMHS) and Civil Hospital Sukkur. Informed consent was obtained prior to collecting information. All diagnosed TB patients registered with designated study sites for anti TB treatment, including sputum smear +ve, sputum smear -ve, MDR TB and extra pulmonary TB were explained the objectives of the study and invited to participate and those who consented were enrolled using a take all approach. A total of 729 persons participated in the study. All confirmed HIV positive study participants were transported and referred to the ARV Center of Sindh AIDS Control Programme by one of the team members for further assessment and anti-retroviral treatment.

Results: There were 729 study participants. Four hundred and three (55.3%) were males and 326 (44.7%) were females. More than half (57.8%) of the subjects were married. Mean age of the study participants was 31 years. Average age of males was 32 and females 29 years. Five hundred and seven (69.5%) were sputum smear + ve and 138 (18.9%) were sputum-ve while 77 (10.6%) had extra pulmonary and seven (1%) had MDR TB. Four (<1%) study subjects were confirmed HIV positive. Significant association was found in confirmed HIV +ve study subjects and risk factors for HIV transmission. Only two persons declined to participate in the study.

Conclusion: The prevalence of HIV among TB patients in Pakistan is still low but with evolving HIV epidemic in the country, the HIV prevalence among TB patients is likely to increase. Therefore screening of TB patients for HIV and coordinated collaborative efforts of TB and AIDS control program at national, provincial and district level are desirable for proper management and control of both diseases.

Introduction

Pakistan is currently experiencing a concentrated HIV epidemic in the country with HIV prevalence of more than 5% among some high risk populations.[1] Recently conducted studies by the National AIDS Control Program under HIV/ AIDS Surveillance Project (HASP) have documented HIV prevalence among IDUs from 5% to 31% in different cities of Pakistan. Similarly 2% & 7% HIV prevalence among Hijras in Larkana and MSM in Karachi respectively has been documented.[2,3]

Disease burden of Tuberculosis in Pakistan is the eighth highest in the world[4] and contributes 44% of total TB cases in the EMRO region of the WHO while estimated incidence and prevalence of TB in Pakistan is 181/100,000 and 329/100,000 respectively.[5]

Data from all over the world suggests that both HIV and TB facilitate (complement) each other.[6-8] HIV infection accelerates the progression of TB infection to active disease and TB infection accelerates the progression of HIV to AIDS possibly by activating dormant lymphocytes, viral replication and increasing rate of decline of CD 4 cell count.[9,10] People with both HIV and TB infection are 30-50 times more likely to get active TB.[6-8] Risk of death due to concurrent HIV/ TB is twice that of HIV or TB alone.[6-8] Patients with both TB and HIV infection are five times more likely to die during anti TB treatment than patients who are not HIV infected.[9,10]

With the growing HIV epidemic and high TB prevalence in Pakistan there is a serious threat of TB/ HIV co-infection with attendant high morbidity and mortality in the country. Currently there are no data available on the magnitude of TB/ HIV co-infection in Pakistan particularly the prevalence of HIV in TB patients. Determining the HIV status of TB patients is essential for optimal patient management.[11]

A multi centre study was conducted in Sindh province from April-June, 2008 to determine the prevalence of HIV among registered patients of TB including Multi

Drug Resistant TB cases and to assess acceptability of HIV testing among TB patients.

Methods

Study Design

This was a cross sectional study conducted at five different sites. A total of 729 study subjects participated in the study. The study was approved by ethical review board of BRIDGE. Informed consent was obtained prior to collecting information. All confirmed HIV positive study participants were transported and referred to the ARV (Anti Retro Viral) Center of Sindh AIDS Control Programme by one of the team members for further assessment and anti-retroviral treatment.

Study Sites

The study was conducted at three satellite clinics of Dow University of Health Sciences, Karachi which were Dr. Iqbal Yad Chest Clinic, MDR Clinic and Malir Chest Clinics. DOTS Centre of Liaquat University of Medical & Health Sciences Hospital, Hyderabad (LUMHS) and Civil Hospital Sukkur. Hyderabad and Sukkur are the two biggest cities of Sindh province followed by Karachi.

Sample size calculation

The sample size was calculated at 709. This takes into account a presumed proportion of 0.21 % HIV among TB subjects from a pilot study that could be detected with a precision of ± 0.03% and 95% confidence level (two-tailed) tests. To reduce the affect of drop outs and refusals 729 subjects were enrolled.

Sampling Method

All diagnosed TB patients registered with designated study sites for anti TB treatment, including sputum smear +ve, sputum smear -ve, MDR TB and extra pulmonary TB were explained the objectives of the study and invited to participate and those who consented were enrolled using a take all approach. Case definitions developed by WHO and National guidelines were followed to identify study participants.

Exclusion Criteria

TB patients under 16 year and those who did not give their consent were not included in the study.

Data Collection

Structured questionnaire developed in English & translated into Urdu (national language) was administered after getting informed consent. The questionnaire was administered by trained interviewers ensuring privacy and confidentiality.

Pre test HIV counseling was provided with the help of flip charts. Those that consented for HIV testing, provided blood samples. The blood samples were collected by finger prick under aseptic condition and were tested on rapid HIV testing kit Bioline SD HIV-1/2 3.0, manufactured by Standard Diagnostics, Inc. Korea.

Those cases which were non reactive on rapid testing were provided results with post-test counseling. While for reactive cases on rapid test, another specimen (5cc) of blood (venous blood) was drawn and sent to Referral Laboratory of Sindh AIDS Control Program for confirmation on ELISA and/or other tests according to WHO/Government of Pakistan diagnostic criteria. The guidelines require using three tests principle or three different antigens. Reactive samples were further tested on Abbott Determined ICP method, DAD Behring and Varonistika kits.

All confirmed HIV cases were provided post test counseling and were referred to ARV treatment Centre of Sindh AIDS Control Program for treatment assessment, while those cases which were not confirmed were provided results with post test counseling.

Data Management & Statistical analysis

All questionnaires were checked for completeness, and data was double entered using Epi data version 3.1. Once the data were cleaned, analysis was performed using SPSS version 13.0 qualitative variables like gender, occupation, household income, educational status, TB diagnosis, history of travel, blood transfusion, history of genital ulcer, history of drug, use, history of injecting drugs used sharing of needles/ syringes, injecting drug used of spouse, sharing of needles/ syringes, and history of imprisonment.

HIV screening test and HIV confirmatory tests were reported as percentages or proportions while the significant association between the risk factor and HIV confirmatory tests were assessed by using Chi-square independent test or Fisher exact where required. P-value <0.05 was considered as significant.

Ethical Considerations

The study proposal was approved by Ethical Review Committee of Bridge Consultants Foundation which is registered with the Office of Human Research Protection, National Institutes of Health, USA. Informed consent was obtained from the study participants before enrolment in the study and HIV testing confidentiality and privacy of the study participants was maintained.

Results

A total 729 study participants diagnosed with TB and registered with TB DOTS treatment centers at five designated study sites were included in the study. The demographic characteristics are described in Table 1. 55.3%

Table 1: Demographic characteristics of the patients.

Characteristics	n= 729 (%)
Gender	
Male	403 (55.3)
Female	326 (44.7)
Marital Status	
Married	421 (57.8)
Unmarried	300 (41.2)
Mean Age	31
Average Age	
Males	32
Females	29
Present Occupation	
Unemployed	245 (33.3)
Overseas worker	11 (1.5)
Air crow/Sea man	1 (0.1)
Driver	27 (3.7)
Police/Military	10 (1.4)
Showbiz	3 (0.4)
Health care providers	8 (1.1)
Industrial worker	72 (9.9)
Office worker	28 (3.8)
Others	324 (44.4)
House hold monthly income	
Mean income	4369
Educational status	
No formal education	381 (52.3)
Upto five years schooling (Primary)	175 (24.0)
Upto ten years schooling (Secondary)	124 (17.0)
Upto 12 years schooling (Higher Secondary)	30 (4.1)
Graduate	19 (2.6)

(403/729) were males and 44.7% (326/729) were females. 57.8% (421/729) subjects were married. Mean age of participants was 31 years. Average age of males was 32 and females 29 years. 44% (324) study subjects were employed while 33.3% (245) were unemployed. 52.3% (381) subjects were not literate while 24.0% (175) had received education up to five years of schooling. Average monthly income was Rs. 4369 (US$ 58).

69.5% (507) were sputum smear + ve, 18.9% (138) were sputum-ve, 10.6% (77) had extra pulmonary and 1% (7) had MDR TB (table 2). 27 (4%) study subjects had history of travel abroad including 20 (3%) who traveled abroad with their spouse. 105 (14%) had a history of blood transfusion or dialysis. 132 (18.1%) had history of genital ulcer, urethral or vaginal discharge. 78 (10.7%) had a history of sexual contact with other than wife/husband including rape (Table 2). 56 (8%) had history of drug (narcotic) use and 33 (5%) reported history of imprisonment (Table 3).

Table 2: TB Diagnosis.

Variables	n= 729 (%)
T.B Diagnosis	
Sputum Smear +ve	507 (69.5)
Sputum Smear -ve	138 (18.9)
Extra Pulmonary	77 (10.6)
MDR T.B	7 (1.0)

Table 3: HIV Risk Factors & History of Drug Use.

History of Travel Abroad	n= 728 (%)
Yes	27 (3.7)
No	708 (96.3)
History of Travel Abroad of Spouse	
Yes	20 (2.7)
No	708 (97.3)
History of Receiving Blood Transfusion/ Dialysis	
Yes	105 (14.4)
No	623 (85.6)
History of Genital Ulcer/Urethral/Vaginal Discharge	
Yes	132 (18.1)
No	589 (80.9)
Don't know / No reply	7 (1.0)
History of Sex with other than wife / husband, including Rape	
Yes	78 (10.7)
No	648 (89.0)
Don't know / No reply	2 (0.3)
History of Drug use (Narcotic)	
Yes	56 (7.7)
No	672 (92.3)
History of Injecting Drug Use (Sharing of Needles / Syringes)	
Yes	5 (0.7)
No	719 (98.8)
Don't know / No reply	4 (0.5)
History of Injecting Drug Use of Spouse (Sharing of Needles / Syringes)	
Yes	10 (1.4)
No	699 (96.0)
Don't know / No reply	19 (2.6)
History of Imprisonment	
Yes	33 (4.5)
No	695 (95.5)

Table 4: HIV Voluntary offer, Screening and Confirmatory tests.

Variables	n= 728 (%)
Voluntary HIV Testing Offer	
Accepted the offer	726 (99.7)
Declined the offer	2 (0.3)
Result of HIV Screening test	
Reactive	5 (0.7)
Non - Reactive	719 (98.8)
Indeterminate	4 (0.5)
Result of HIV Confirmatory tests	
HIV + ve	4 (0.5)
HIV -VE	724 (99.5)

Seven hundred and twenty seven (99.7%) patients accepted the voluntary HIV testing offer. Out of 729 study subjects 0.7% (5) were reactive on initial HIV

screening while 4 study subjects were confirmed HIV positive (Table 4).

Significant association was found in confirmed HIV +ve study subjects and history of blood transfusion, history of genital ulcer, urethral/ vaginal discharge, sexual contact with other than wife/husband and history of injecting drugs, sharing of needles/syringes and history of imprisonment as given in (Table 5,6).

Table 5: Risk factor associated with HIV and Confirmatory results.

TB Diagnosis	HIV Confirmatory Test +ve	HIV Confirmatory Test - ve	P-value
Sputum Smear + ve	4 (0.8)	502 (99.2)	0.623
Sputum Smear -ve	0	138 (100)	
Extra pulmonary	0	77 (100)	
MDR TB	0	7 (100)	
History of Travel Abroad	**HIV Confirmatory Test +ve**	**HIV Confirmatory Test - ve**	
Yes	1 (3.7)	26 (96.3)	0.141
No	3 (0.4)	698 (99.6)	
History of Receiving Blood transfusion / Dialysis	**HIV Confirmatory Test +ve**	**HIV Confirmatory Test - ve**	
Yes	3 (2.9)	102 (97.1)	0.010
No	1 (0.2)	622 (99.8)	
History of Genital ulcer/ Urethral/Vaginal Discharge	**HIV Confirmatory Test +ve**	**HIV Confirmatory Test - ve**	
Yes	3 (2.3)	129 (97.7)	0.012
No	1 (0.2)	588 (99.8)	
Don't Know	0	7 9100)	

Table 6: Risk factor associated with HIV, Screening and Confirmatory results

History of Sex with other than wife/husband	HIV Confirmatory Test +ve	HIV Confirmatory Test - ve	P-value
Yes	2 (2.6)	76 (97.4)	0.04
No	2 (0.3)	646(99.7)	
Don't Know	0	2 (100)	
History of drug (Narcotic)	**HIV Confirmatory Test +ve**	**HIV Confirmatory Test - ve**	
Yes	3 (5.4)	53 (94.6)	0.0001
No	1 (0.1)	671 (99.9)	
History of injecting drug use (sharing of needles/ syringes)	**HIV Confirmatory Test +ve**	**HIV Confirmatory Test - ve**	
Yes	2 (40)	3 (60)	0.0001
No	2 (0.3)	717 (99.7)	
Don't Know	0	4 9100)	
History of injecting drug use of Spouse (sharing of needles/ syringes	**HIV Confirmatory Test +ve**	**HIV Confirmatory Test - ve**	
Yes	1 (10)	9 (90)	0.0001
No	3 (0.4)	696 (99.6)	
Don't Know	0	19 (100)	
History of Imprisonment	**HIV Confirmatory Test +ve**	**HIV Confirmatory Test - ve**	
Yes	3 (9.1)	30 (90.9)	0.0001
No	1 (0.1)	694 (99.9)	

P value <0.05 is considered significant.

Discussion

The prevalence of HIV among TB patients was less than one percent (0.5%). Although the present study has documented a low prevalence of HIV in high risk population of TB patients but estimated prevalence of HIV among general population is 0.1%, which is much less than 0.5%. The TB patients who were found to be positive for HIV had known risk factors for HIV. Only two patients declined to be tested for HIV. This high acceptability could be due to proper pre test counseling of the study participants by a trained counselor.

Tuberculosis is endemic in Pakistan since its inception and presently it is responsible for 5.1% of total national disease burden. The total number of persons living with tuberculosis is estimated at 1.5 million in Pakistan, a country with a population of 161.37 million. There are 1108 TB diagnostic centers actively involved in sputum smear examination for Acid Fast Bacilli (AFB) and reporting to the National Tuberculosis Program (NTP). During the first three quarters of 2008 these centers examined 454,854 sputum samples and detected 54,704 AFB positive cases.[12] Tuberculosis is quite common in HIV infected persons and several HIV infected persons seek medical advice for symptoms of tuberculosis. HIV infected individuals are screened for tuberculosis in endemic countries but TB patients are generally not offered HIV test and the infection

may go unrecognized resulting in treatment failure, prolonged morbidity and prolonged propagation of infection in the community.[13] The studies conducted in India, a neighboring country with similar cultural and socio-economic characteristics has documented 0.4 to 27% of HIV prevalence among TB patients.[14] While recently, HIV infection is evolving as a concentrated epidemic among IDUs, MSM & HSWs.[1-3] This low prevalence of HIV among TB patients is probably because the epidemic has not matured to the level it is in India and is still restricted among certain high risk groups. However, in many HIV affected countries the epidemic starts from vulnerable groups and spreads to the general population through bridging populations.

Treating two diseases instead of one i.e. TB and HIV together will be very challenging in a country where the healthcare system is fragile and several front line general practitioners or family physicians are not trained to deal with co-infection. To prevent such a situation it is imperative that HIV screening be included in DOTS program. HIV screening also requires pre and post test counseling, provision of HIV and STI testing facility and referral to ARV treatment centers. This study clearly calls for inclusion of HIV/STI prevention to be included in counseling of tuberculosis patients as an integral component of DOTS program.

Although HIV prevalence among TB patients is low (0.5%) but considering an evolving epidemic in the country it is highly likely that the prevalence of HIV in TB patients will increase with the maturation of HIV epidemic in Pakistan. Therefore it is necessary to include risk assessment for HIV in the DOTS protocol.

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