The Impact of Directly Observed Therapy for Tuberculosis on Loss to follow-up in Baltimore City

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Abstract

We studied factors associated with loss-to-follow-up (LTFU) of reported cases of tuberculosis (TB) in Baltimore City from 1971 through 1995 to identify patterns in LTFU among individuals treated for TB in the city during this time. We also analyzed the spatial clustering of LTFUs to those who completed treatment. Demographic characteristics of individuals with confirmed TB were extracted from the records of the Baltimore City Health Dept. (BCHD) for every third year starting from 1971. Information on age, sex, race, ethnicity, place of birth, occupation, clinical status and place of residence were recorded. LTFUs represented a significantly higher proportion of individuals with TB prior to DOT (10.9%) than after DOT (4.7%) ($p<0.0001$). However, there were no differences in any of the demographic characteristics in LTFUs when compared to those who completed therapy for any of the years analyzed, except in 1992 when LTFUs were significantly younger. There were also no temporal patterns among LTFs. There was also no spatial clustering of the residences of LTFU relative to those completing therapy. We conclude that in Baltimore, DOT has successfully reduced the number of TB cases and has not resulted in an increase in or clustering of LTFU among any risk groups or geographical areas.

Introduction

Directly Observed Therapy (DOT) is recommended as the gold standard of care for treatment of Tuberculosis TB by the Centers for Disease Control and Prevention and the World Health Organization[i] [ii].DOT is predicated on the belief that directly observing a consume all required medications will reduce the risk of treatment failure and emergence of resistance. DOT was introduced as a treatment option for some cases of TB in Baltimore city in 1978 and has been offered as a universal program for all identified cases of TB in the city since 1981. Since then, rates of TB incidence in the city have maintained a decline despite a leveling-off and upswing in TB rates in most other big cities[iii].

Despite the empirically proven advantages of DOT for a chronic infectious disease such as TB, several points have been made against the use of the strategy. The most vocal argument revolve around the issues of individual rights versus public good especially if the program is made mandatory. The daily personal contact with one or several individuals that usually work for a government agency may cause infected individuals to avoid diagnosis and treatment or a high rate of dropout or loss of these individuals to follow up. So even though there is a high rate of sputum conversion and completion of treatment among those who choose to stay, it is postulated that certain groups may particularly be at risk to drop out, possibly affecting the positive impact of the strategy in the society.

In this study, we investigated factors associated with loss-to-follow-up (LTFU) of reported cases of TB in Baltimore City from 1971 to 1995. We wanted to determine if there were identifiable patterns of LTFU in people identified as TB cases in the city during this time. We primarily wanted to determine if the introduction of DOT in 1978 altered the pattern of LTFU individuals. We examined whether LTFU individuals differed from those who completed therapy demographically or geographically, we also examined if LTFUs identified prior to DOT (pre-DOT) differed from those following introduction of DOT (post-DOT) by these same parameters.

Methods

The Baltimore city TB control program is administered by the Baltimore City Health Department. It has an efficient multi-tier case identification program which is also involved in contact tracing and identification[iv]. The program also maintains confidential medical records for every case of TB identified in the city since 1956.

The study used archived administrative data gathered and maintained by BCHD, no informed consent from participants was required. The institutional review board of The Johns Hopkins University Bloomberg School of Public Health reviewed and approved the study.

The population studied included all patients with tuberculosis who were reported to BCHD every third year between 1971 and 1995, totaling nine data collection years. A case of TB was defined as a culture confirmed diagnosis of *M. tuberculosis* infection, a positive smear for *M. tuberculosis,* or response to therapy for tuberculosis. All of the data was abstracted from the records of BCHD by one person (OOO), between April and September, 1996. These records were abstracted from treatment summaries maintained by BCHD for every case of TB diagnosed or receiving treatment in the City. These summaries are abstracted directly from the case notes of every patient and each record includes all the information used in this study. An added asset was the fact that the individual who abstracted all the data from the original case notes of the patients for the summary records, was available during the period of data collection for this project and was able to help when certain information was unclear.

The tool for data collection was a form developed specifically for that purpose. The form recorded routine demographic data such as sex, age, race or ethnicity, occupation, country of birth and length of residence in Baltimore City. The form was also designed to record each patient's Baltimore City registration number and a unique number, which is the only link to the individual, and was the identification used during data analysis. All the data was collected and recorded by one individual (OOO). Cases were also coded as initial cases or relapses. Cases that had completed treatment previously and had a new record were considered relapse. Other specific information concerning TB included the date of initial report to BCHD, date of diagnosis and place of diagnosis. Information on criteria used for reaching diagnosis was also recorded, for example, if the patient had chest radiographs and sputum or other microbiology. The date that mycobacterial culture was positive was recorded, as was the date of the second consistently negative culture. This gave an indication of the duration on infectiousness of cases. The site of the disease (pulmonary viz. extra-pulmonary), medications used, reasons for ending therapy (close out) or subsequent relapse were also recorded.

Loss to follow up was defined as anyone identified as a case of TB in the BCHD TB records, but whose records did not indicate complete therapy and close out by a health care worker following sufficient therapy.

Analyses

We divided all cases into those who completed therapy and those who were LTFU, and used Chi square tests to determine if LTFUs differed significantly from those who completed therapy with regards to various demographic variables.We also used Chi-square trend tests on demographic variables to test the argument that DOT would lose "high risk" patients and LTFUs would increasingly have certain demographic characteristics. For these two analyses we used Statistix software package (1991, Analytical software, St. Paul MN).

Finally, we used a Geographic Information Systems (GIS) to determine if LTFUs were geographically clustered relative to those completing therapy, and if there were clustering of LTFUs or those completing treatment between pre- and post-DOT periods. This was done using the Edward and Cuzick case-control for spatial clustering. To study clustering of LTFUs over time, the abstracted data was entered in to the STAT software package (1994, Biomedware, Ann Arbor, MI). Losses to follow up were coded as "cases", while successful treatment, documented as sputum conversion and appropriate duration of treatment regimen from the data, were be coded as "controls".

The Edward-Cuzick case control test for spatial clustering was performed on individual years. The test statistic, $T_{k,}$ is the sum, over all cases, of the number of each cases k nearest neighbors that are also cases. When cases are close to one another, the nearest neighbor will tend to be another case and T_k will tend to be high. The p-values test the argument that cases and controls are sampled from a common point distribution and the occurrence of a value of T_k other than zero is due to chance[v]. It thus tested the hypothesis that following introduction of a DOT program, patients who were LTFU tended to occur in certain regions of the city more often than expected by chance alone It was expected that the value of the test statistic would increase the long DOT was in place, indicating that spatial clustering of LTFUs is occurring more often following the introduction of DOT. This particular approach was chosen as it controls for known and unknown confounders that may be present[v].

Results

A chi square test to determine a difference in proportion of LTFUs in all cases before 1978 compared cases after 1978, indicated that LTFU occurred more commonly prior to the 1978 (10.9% versus 4.7% p<0.0001). The Spearman's test for trend in the proportion of LTFUs over the study period was -0.6374 (p=0.09).

Table i. Summary of Demographic findings among TB cases in Baltimore city between 1971 and 1995

	1971			1974			1977		
	NLTF	LTF	p-value	NLTF	LTF	p-value	NLTF	LTF	p-value
Mean Age (years)	48	47	0.79	48	43	0.15	49	41	0.06
Sex (Male)	65%	70%	0.36	64%	47%	0.07	65%	81%	0.17
POB (Baltimore)	37%	35%	0.71	21%	17%	0.64	26%	13%	0.32
Occupation	38%	38%	0.9	16%	17%	0.79	35%	25%	0.42
Race (Black)	67%	57%	0.04	67%	58%	0.14	72%	88%	0.25
Case status	93%	92%	0.74	92%	97%	0.35	92%	100%	0.43

	1980			1983			1986		
	NLTF	LTF	p-value	NLTF	LTF	p-value	NLTF	LTF	p-value
Mean Age	47	42	0.49	50	46	0.57	55	49	0.39
Sex (Male)	66%	50%	0.48	60%	50%	0.83	63%	100%	0.06
POB (Baltimore)	28%	25%	0.82	28%	33%	0.71	18%	38%	0.31
Occupation	3%	25%	*	22%	42%	0.13	20%	38%	0.39
Race (Black)	73%	75%	0.81	74%	92%	0.3	70%	86%	0.4
Case status	87%	88%	0.65	92%	83%	0.52	93%	100%	*

	1989			1992			1995		
	NLTF	LTF	p-value	NLTF	LTF	p-value	NLTF	LTF	p-value
Mean Age	52	51	0.97	51	37	0.03	49	33	0.24
Sex (Male)	62%	57%	0.72	58%	50%	0.82	66%	100%	*
POB (Baltimore)	7%	14%	*	10%	0%	*	0%	0%	*
Occupation	13%	14%	0.65	5%	0%	*	6%	0%	*
Race (Black)	88%	100%	0.4	82%	100%	*	78%	67%	*
Case status	94%	100%	*	97%	100%	*	96%	100%	*

Expected values in cells include values <1, chi-square not calculable

When we examined differences between LTFUs and those who completed therapy, we found that LTFUs did not differ significantly from those who completed therapy in any of the variables analyzed except for age in 1992. LTFUs were younger (p=0.03) (Table i) than those who completed therapy in 1992. In all other years, age, race, place of birth, occupation and clinical status were not significantly different between LTFUs and those who completed therapy. TB cases were increasingly reported to be female and to report an employment (Table ii). Among LTFUs, the only significant temporal trend was for them to be increasing reported as being of black race, though there was no trend in LTFU pattern when we analyzed gender and report of employment. There were no trends seen in the race or clinical outcomes of the cases (Table i).

Table ii. Results of the Spearman's test for trend in proportions of demographic factors among TB cases and LTFU in Baltimore city between 1971 and 1995

	trend (p-value) Total Cases	Trend (p-value) LTFUs
Sex (Male)	-0.01 (0.09)	0.004(0.86)
POB (Baltimore)*		
Occupation	-0.04(<0.001)	-0.047(0.1)
Race (Black)	-0.01(0.33)	0.128(0.0006)
Case status	0.00(0.9)	0.9

*Values not calculable, zero values in several cells

ANOVA and Pearson test for trend tests of age revealed that there was no statistically significant difference or trend among the mean ages of those who completed therapy or LTFUs in all the years analyzed Table iii. Edwards and Cuzick's test statistic and p-values for spatial clustering of treatment failures, 1971-1995.

A summary of the results of the models used to examine the clustering losses to follow-up (Table 3) indicates that in all the years analyzed, there was no spatial clustering of LTFU relative to those who completed therapy.

Table iii. Edwards and Cuzick's test statistic and p-values for spatial clustering of treatment failures, 1971-1995

Year	NLTFU No tx	LTFU failed tx	T_1 k=1	T_2 k=2	T_3	T_4	T_5	p
1971	676	101	17 (0.3430)	36 (0.2259)	58 (0.1145)	74 (0.1491)	88 (0.2089)	0.2439
1974	467	36	2 (0.6296)	4 (0.6669)	7 (0.6024)	8 (0.7050)	9 (0.7692)	0.5774
1977	356	16	0 (0.7421)	0 (0.8121)	1 (0.7027)	2 (0.6213)	2 (0.7021)	0.8807
1980	184	8	0 (0.6755)	0 (0.7379)	0 (0.7778)	0 (0.8088)	0 (0.8355)	0.8770
1983	116	12	1 (0.5480)	2 (0.5656)	3 (0.5798)	3 (0.7331)	4 (0.7287)	0.5472
1986	142	8	0 (0.6996)	0 (0.7676)	2 (0.2739)	2 (0.3966)	2 (0.4968)	0.6472
1989	131	7	0 (0.6773)	2 (0.0851)	2 (0.2011)	2 (0.3100)	2 (0.1918)	0.5107
1992	133	4	0 (0.5958)	0 (0.6331)	0 (0.6622)			0.6622
1995	92	3	0 (0.5804)	0 (0.6144)				0.6144

Tk represents the test statistic measuring the number of LTFU among the k nearest neighbors of each LTFU and the number of LTFU's nearer than the k nearest NLTFU. For example, T3 in 1971 is the measure of 3rd nearest neighbor of each LTFU in that year and the number of LTFUS's nearer than the 3rd nearest NLTFU. The value in brackets represents the p value measuring the probability that this measurement of clustering is due to chance. The final p value is the total probability of clustering among LTFUs in each year

This finding supported earlier epidemiologic evidence that indicated that LTFUs were a random sample of all cases and did not differ significantly from those who completed therapy (Table 2). We observed no spatial clustering of losses to follow-up at anytime during the period studied.

Discussion and Conclusion

In this study, we found that the number of TB cases decreased with the introduction of DOT and that the decrease was not associated with a geographical clustering or a concentration of LTFUs among a particular risk group. These results indicate that the DOT was successful in providing treatment to patients without regard to obvious biases. There was a substantial reduction in the proportion of people LTFU following DOT although a fraction (4.7%) of the cases remained unaccounted. In addition to the reduction in LTFU, there was a a reduction in the total number of cases after DOT.

There has been a secular trend in cases of TB in Baltimore city since the study began and they are increasingly female and report a form of employment, though there was no similar pattern among LTFUs. If analyzed against the backdrop of a successful program, then this finding is intuitive. Prior to the introduction of DOT, TB was concentrated among high-risk groups, which tend to be unemployed males. A successful program will lead to low numbers of TB cases with epidemiological distributions resembling the general population.

Hence, percentage of women and employed TB patients should rise but then stabilize. We postulate that since the program is achieving its aim, the background level of infection would be expected to involve people of all risk levels, hence a higher percentage of women and employed people will be expected though the actual numbers will be expected to remain low. Women and employed people, generally, have a lower probability of LTFU[vi] [vii], so even though the risk of new infection begins to approach equality between men and women, and employed and unemployed, a successful TB treatment program should see less incidence of LTFU among women and those employed.

An interesting finding was the significant increase in the proportion of LTFUs that were black even though the proportion of total patient that were black did not increase with any statistical significance. This finding suggests that socio economic disparities among different ethnic groups may not affect the development of new disease but affect follow up. BCHDs efforts at community involvement in case identification, contact tracing and patient appear to be highly successful, but there is a changing ethnic milieu in Baltimore like most other big cities. Recent migrants may bring new isolates with them. The results of our study go counter to the arguments against DOT that suggest the personal nature of the approach may lead to increase in absconding from therapy. There are certain qualities of the Baltimore city DOT program that contribute to its success and may explain the findings. This system consists of the several layers of case reporting including physicians, laboratories and pharmacies, it also includes case contact tracing, and work in coordination with the treatment of cases.

Screening programs are part of the surveillance system. Patient reporting, though an integral part of this system, is not the main or only form of patient identification. The main thrust of the program is surveillance with case identification using community resources and contact tracing. The success of the Baltimore city TB control program also derives from its approach to patients as individuals and to the community as a whole as the entity of interest. The clinic staffs are recruited from the community and undergo orientation and continuing education through in-service workshops and external conferences.

In conclusion, the sustained reduction in new TB cases as well as the reduction in LTFUs along with the lack of any epidemiologic pattern in LTFUs suggest that a mandatory DOT program for all TB cases is effective in reducing TB cases among all risk groups, and that DOT does not contribute to a higher attrition rate among any risk group. The study also suggests that targeting DOT programs to only high-risk individuals is not advisable as their risk of LTFU is similar to all others infected with the disease.

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