

## Short Report: Gender Differences in Tuberculosis Notification in Pakistan

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### Abstract

Worldwide, the male to female ratio of new smear-positive tuberculosis (TB) cases is approximately two to one. However, in Pakistan, this is not the case. Rates of notified TB cases are 20-30% higher in young females compared with males, and female rates remain high regardless of increasing age. This is in stark contrast to neighboring India, which is characterized by an excess of male TB cases. It is currently unknown why rates of notified TB are so high in females in Pakistan, but it is clear that this epidemiology is a public health issue of importance that impacts transmission dynamics and disease control initiatives.

### Introduction

The global burden of 9.4 million annual cases of tuberculosis (TB) overwhelmingly falls on low-income countries, with 80% of cases occurring in just 22 high-burden countries.<sup>1</sup> Between 1998 and 2008, the average male to female ratio (MFR) of new smear-positive cases for the high-burden country bloc was 1.85 (range = 0.47-3.16).<sup>1</sup> These data are in line with the World Health Organization (WHO) global case notification estimated ratio of 1.81 over the same time period. Reasons for this excess of notified male cases are unknown; many hypothesize that female TB patients are subjected to greater stigmas and barriers that limit access to care. Although every country is unique, there are now reports that show that the gender differences observed in case notifications are often mirrored by gender differences in prevalent TB cases.<sup>2-4</sup> These studies indicate that inequitable access to healthcare facilities and reporting biases are not the root cause of observed differences in case notifications and that there are genuine gender

differences in the biology and epidemiology of TB.<sup>2</sup>

There are a handful of poorly understood exceptions where the MFR of cases for a country nears and dips below one. Many of these reports come from countries with small populations (frequently island nations) and/or a low incidence of TB. However, the high- and medium-burden countries of Afghanistan, Iran, and Pakistan, where in 2008, the MFRs of new smear-positive cases were 0.47, 1.03, and 1.05, respectively, are notable.<sup>1,5</sup> In countries where human immunodeficiency virus (HIV) prevalence exceeds 1%, there tends to be more females than males reported with active TB, 5 particularly in sub-Saharan Africa where HIV prevalence in women is higher than in men.<sup>6</sup> This results in more women with TB, because HIV-infected individuals are 20-30 times more likely to develop TB.<sup>7</sup> This association is unlikely to explain the low MFR of cases observed in Afghanistan, Iran, and Pakistan, where HIV prevalence is currently very low.<sup>8-10</sup>

Afghanistan, Iran, and Pakistan form a contiguous geographic land mass with many shared cultural practices that may be impacting the transmission and/or activation of latent TB. We used recent data to determine whether the observed differences in age-specific MFRs between Pakistani and Indian case notifications are real and whether they present a public health issue of importance that needs to be better understood. In addition, we analyzed case notification data from Karachi and data from the Indus Hospital TB control program to further develop an understanding of gender differences in TB notification in Pakistan.

### Methods

The WHO Global Tuberculosis Control 2009 report contains case notification data for new smear-positive TB cases over a 29-year span (1980-2008) for over 200 countries and territories worldwide (broken down by age and sex). These data, in conjunction with population estimates from the US Census Bureau International Database, were used to calculate age- and sex-specific rates of TB notification for the year 2008 for Pakistan and India. Age-specific differences in the proportions of female cases were analyzed using the  $\chi^2$  test, and odds ratios and 95% confidence intervals were calculated using

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the Indian population as the reference group. To ensure that 2008 did not represent an abnormal year for case detection efforts in either country, age- and sex-specific rates for Pakistan and India were calculated over a 10-year span (1999–2008), and trends were examined.

Karachi is the largest city and economic hub of Pakistan, with an estimated 18 million inhabitants in 2010. Currently, there are greater than 60 directly observed therapy shortcourse (DOTS) treatment centers located at government and non-governmental clinics and hospitals throughout Karachi. Annual reports of this data from 2006 to 2009 were accessed through the Provincial TB Control Program-Sindh and analyzed using SAS version 9.2 (Cary, NC). Because there are no reliable population estimates for Karachi, yearly totals of new smear-positive cases were broken down by age and sex, and a male to female ratio of cases was calculated for each age group; Indus Hospital patients were excluded from this dataset.

Indus Hospital is a 150-bed state of the art tertiary care facility located in a poor district of Karachi. All treatment at the hospital is free of charge, and it provides high-quality medical care to an ethnically diverse population of around 2.5 million. The Indus Hospital TB control program was started in November 2007 and has rapidly expanded

to include an internationally recognized program for the management of drug-resistant TB. Deidentified data from the Indus Hospital DOTS program was collected and also analyzed using SAS.

## Results

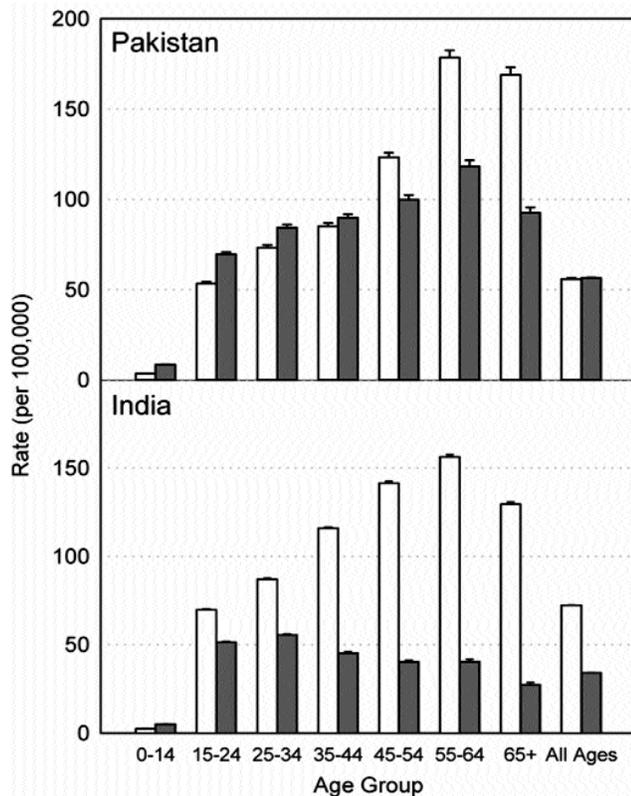
The male to female rate ratio for all ages often masks marked differences in age-specific rates. In Pakistan, notification rates are roughly equal in males and females when examined in aggregate (Figure). However, age-specific notification rates are higher in females compared with males aged less than 45 years, and female notification rates in Pakistan peak at a much higher level and later age than in India. An excess in females is not seen in India, except in those under 15 years of age, which is when TB notification is consistently higher in females across cultures, countries, and continents. The proportions of notified female cases in Pakistan are significantly higher in every age group examined compared with India (Table); the highest odds ratios are seen in the 45–54 and 55–64 age groups, indicating that Pakistan does not record a large excess of male cases in older age groups like India.

Case notification rates have increased, potentially because of intensified case detection efforts in both

Table-1: TB case notification by gender and age group in 2008.

Age group (years)	Pakistan	Pakistan MFR	India	India MFR	P value	OR (95% CI)
< 15						
Male	1,213	0.45	4,648	0.56	< 0.00001	1.24 (1.15–1.34)
Female	2,696	0.45	8,319	0.56	< 0.00001	1.24 (1.15–1.34)
15–24						
Male	10,521	0.82	77,121	1.5	< 0.00001	1.83 (1.78–1.88)
Female	12,838	0.82	51,485	1.5	< 0.00001	1.83 (1.78–1.88)
25–34						
Male	9,889	0.94	83,798	1.68	< 0.00001	1.78 (1.73–1.84)
Female	10,489	0.94	49,887	1.68	< 0.00001	1.78 (1.73–1.84)
35–44						
Male	8,428	1.03	90,498	2.69	< 0.00001	2.60 (2.51–2.69)
Female	8,146	1.03	33,664	2.69	< 0.00001	2.60 (2.51–2.69)
45–54						
Male	8,284	1.3	78,815	3.67	< 0.00001	2.83 (2.73–2.93)
Female	6,387	1.3	21,486	3.67	< 0.00001	2.83 (2.73–2.93)
55–64						
Male	6,890	1.45	56,928	3.95	< 0.00001	2.72 (2.61–2.84)
Female	4,750	1.45	14,407	3.95	< 0.00001	2.72 (2.61–2.84)
? 65						
Male	5,959	1.68	36,079	4.32	< 0.00001	2.57 (2.45–2.70)
Female	3,547	1.68	8,357	4.32	< 0.00001	2.57 (2.45–2.70)
All ages						
Male	51,184	1.05	427,887	2.28	< 0.00001	2.18 (2.15–2.21)
Female	48,853	1.05	187,605	2.28	< 0.00001	2.18 (2.15–2.21)

CI = confidence interval; OR = odds ratio.



**Figure:** Rates of new smear-positive case notification by age and sex in 2008. White columns represent male rates, and grey columns represent female rates. Error bars are 95% confidence intervals.

Pakistan and India during the 10-year window that was examined; however, the gender patterns in notification rates remained consistent over time. Regardless of the year examined, in Pakistan, the rates of notification are higher in females compared with males in the young age groups (aged < 45 years), whereas the rates in those aged > 45 years are higher in males. In India, rates of TB are higher in males in both the young and old age groups.

Over a 4-year period (2006-2009), the MFR of cases for the National TB Control Program data from Karachi was 0.97, indicating that slightly more females than males presented with new smear-positive TB cases. These findings confirm those from the national WHO data for Pakistan. Similarly, the MFR of cases becomes more exaggerated when broken down by age. In the 0- to 14-years age group, there were almost four times as many females as males (MFR = 0.27). The 15- to 24-years age group shows a similar but less exaggerated excess of females (MFR = 0.74).

The Indus Hospital data again show a similar pattern in the age frequency distributions, with an overall MFR of 0.71. Like the Provincial TB Control Program Karachi data,

the young age groups are characterized by a huge excess of female cases, whereas the older age groups are characterized by an excess of male cases. The MFR of cases in the 15- to 24-years age group is 0.45, suggesting that young females in the immediate catchment population of the Indus Hospital are particularly affected by TB.

## Discussion

We have shown that, in Pakistan, rates of new smear-positive TB notification are significantly higher in young (45 years) females than males compared with India and that notification rates do not skew heavily to males in older age as they do in India. These findings run counter to the accepted epidemiology of male predominance in TB around the globe, and because gender may impact control strategies, this needs to be better understood.

The data from Pakistan are particularly troubling, because TB is highly prevalent, translating into thousands of excess female cases per year. Although there have been prior isolated reports,<sup>11</sup> no systematic attempts have been made to discover the scale of this problem in Pakistan. Young women are vulnerable, because they are often socially and economically marginalized in Pakistani society. In poorer communities, women often care for the young, elderly, and sick in the home, creating the potential for sustained transmission of the mycobacteria. There is also evidence that females in Pakistan delay seeking healthcare and will seek out low-quality care compared with males.<sup>12</sup> However, many of these facts are true of females living in India, and therefore, they cannot explain the underlying mechanisms of exposure and/or activation of disease. We do not know how these females are becoming infected and why they are succumbing to TB.

Interestingly, the gender profile of the Karachi city TB data is similar to TB data collected from European countries at the start of the 20th century.<sup>13</sup> In Denmark,<sup>14</sup> Norway,<sup>15</sup> and England and Wales,<sup>16</sup> rates of TB in women were 10-35% higher than in men for ages 15-24 years. Only after the age of 40 years did rates become higher in men. Today, this pattern is no longer seen in the West. These observations and others of the role of women in disadvantaged communities lead us to believe that a complex of sociocultural factors and nutritional status in young women may underline these high rates.<sup>17</sup> It is possible but unproven that vitamin D deficiency caused by poor diet and inadequate exposure to sunlight may play a role. Several studies indicate that Pakistani women have low levels of vitamin D,<sup>18,19</sup> and there is growing evidence of an association between TB infection and vitamin D deficiency.<sup>20-22</sup>

The data used to prepare portions of this report represent national case notifications that may not accurately reflect the true burden of disease in each country. The case detection rates for Pakistan and India were 60% and 67%, respectively, in 2008, far below internationally accepted goals. It is unknown but possible that case detection rates are biased to one gender. Based on over 700,000 TB cases reported in Pakistan and India in 2008 and evidence from community-based prevalence surveys, it seems unlikely that the gender differences in calculated rates will change significantly.

Understanding these aberrant observations is likely to be important for control of TB transmission in some cultures. It is well-understood that improvements in public health and living standards effectively control TB in the long term. In the shorter term, however, understanding the key factors contributing to infection and disease in women will be of great importance to TB control.

### Acknowledgments

This work was supported by National Center on Minority Health and Health Disparities (NCMHD) Grant MD000170 P20, the University of Texas Houston Health Sciences Center, National Center for Research Resources (NCRR) Center for Clinical and Translational Science Center for Clinical and Translational Science Center for Translational Science Award 1U54RR023417-01, and Centers for Disease Control Award R01 DP000210-01.

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