Gender Disparity in Tuberculosis cases on Eastern and Western Fronts of Pakistan

Omara F Dogar¹*, Sarwat K Shah²*, Abrar A Chughtai³, Ejaz Qadeer³

¹ Research and Development Unit, Social and Health Inequalities Network, House 862, Street 13-C, E-11/4, NPF, Islamabad, Pakistan
² Research and Development Department, Health Services Academy, National Institute of Health, Chak Shehzad, Islamabad, Pakistan
³ National Tuberculosis Control Program, Zakia Aziz Plaza, Blue Area, Islamabad, Pakistan

*These authors contributed equally to this work
§Corresponding author

Email addresses:

OFD: omaradogar@hotmail.com
SKS: sarwatdopasi@hotmail.com
AAC: doctorahmad75@gmail.com
EQ: ntpmanagerpak@ntp.gov.pk
Abstract

Background
The male to female ratio (MFR) of new smear positive (NSS +ve) notified Tuberculosis (TB) cases is higher in all of the World Health Organization’s regions except of a few countries in Eastern-Mediterranean-Region, namely, Afghanistan, Lebanon, Iran and Pakistan where higher female cases are seen. Pakistan poses a rich ground for exploratory research to address the cross-cutting gender differences in TB cases, as it is bounded by India on East, with twice higher male cases than females, and, Afghanistan and Iran on West, with male cases approx. half of the female cases.

Methods
Cross-sectional analysis was carried out on secondary data of notified NSS +ve TB cases, obtained from National Tuberculosis Program. Disaggregated at provincial level, the sex-specific case notification rates (CNR) were calculated and trends over a 10-year span (2001-2010) were examined. Sex-specific differences in proportion of notified cases for the four provinces were analyzed using chi-square test and odds ratios with corresponding confidence intervals using cumulative countrywide sex-specific notification rates as the reference group.

Results
The trends in the western provinces of Pakistan show higher female case notification rate (CNR) opposed to those in the eastern provinces with higher male CNR. The proportions of female notified TB cases are approximately twice higher in the western provinces compared to eastern provinces, and Pakistan over all.
Conclusions
The gender disparity in TB case notifications on the two fronts of Pakistan is a rising public health concern that requires coordinated regional and international efforts to further explore the triggers and moderators of increased acquisition and progression of disease among females in this region, in order to guarantee effective TB control.
Background
Each year an estimated 8.8 million new cases of tuberculosis (TB) occur worldwide, out of which 81% are contributed by the 22 high burden countries, alone. Globally, the notification rates of TB cases vary across most of the countries, with males being predominantly greater than females [1]. The male to female ratio (MFR) of notified new sputum smear positive (NSS +ve) TB cases for various World Health Organization’s (WHO) regions range from 1:35: 1:00 in Africa, 1:49: 1:00 in Americas, and 2:03: 1:00 in South-East Asia to 2:16: 1:00 in Europe [2]. However, a few countries in Eastern Mediterranean Region (EMR) do not conform to the global MFR of notified NSS+ TB cases, including Afghanistan (MFR= 0:50: 1:00), Lebanon (MFR= 0:70: 1:00) and Iran (MFR= 0:90: 1:00) [1]. Pakistan falls among the five countries with highest TB burden in the world, with an estimated incidence of 231 new TB cases per 100 000 population, each year. About 47% of the pulmonary TB cases and 38% of all TB cases comprise of smear positive pulmonary TB cases [3]. It contributes about 63% of the TB burden in the EMR with 1Case Notification Rate (CNR) [4] of 60 per 100 000 population for NSS+ TB cases [1, 5, 6]. Pakistan shares similarities with the global MFR for notified NSS+ve TB cases, overall. However, when disaggregated by age and sex it presents a completely different picture showing a greater proportion of CNR contributed by the females in reproductive age groups (including 45 years of age), with an acute cross over, with older males predominating notified TB cases [5]. The estimated MFR for the general population of Pakistan is 1:07:1:00, in 2010, ranging from 1:05:1:00- 1:09:1:00 till the age groups 35-44 and dropping afterwards to around 0:93:1:00 for age groups of 65-69 years[7]. Still, disproportionately higher TB cases (20 – 30%) are notified among females compared to

1 CNR: The annual reported number of TB cases divided by the total population in the specified area per 100 000.
males in the reproductive age-group [8]. A study done in Zabol (Iran), adjacent to Pakistan and Afghanistan, shows a similar sex disparity with MFR of 1·00: 1·50 for the notified TB cases [2].

The sex disparity seen in notified TB cases in these EMR countries raises concern for the global audience as well as the regional and local authorities and makes it eminent to pin down the factors contributing to higher rates of TB spread or activation in females if these differences are actually exist. Though the reasons for these disparities span a wide array of hypotheses, this study begins with looking at the geographic distribution of CNR of NSS+TB across administrative units of Pakistan. Thus, the aim of the study is to see whether these gender differences are evenly distributed across the country. Pakistan poses a rich territory for future research into the topic as it is bound by Afghanistan and Iran on the west, both having higher female notified TB cases than males (MFR: 0·50: 1·00 & 0·90: 1·00, respectively) compared to India on the east, where notified TB cases are higher in males than females (MFR: 2·30: 1·00) [1, 8].

**Methods**

Cross-sectional analysis was carried out on national data of notified NSS +ve TB cases that is not publicly available, and was obtained with permission from the National Tuberculosis Control Program (NTP), Pakistan. The case notification data is collected both from public (primary, secondary and Tertiary health care) and private health facilities by the NTP. The NTP is embedded in the health system infrastructure of the country at provincial, district, tehsil and union council levels. The private facilities were included for surveillance in 2007 after the Public Private Mix (PPM) launch. PPM was started as a pilot project with gradual scale-up that is being implemented in majority of districts in all four provinces. However, Khyber Pakhtunkhwa (KPK)
and Baluchistan have the least PPM coverage while administrative regions and tribal areas still have no coverage [9].

The case notification data is collected by NTP on a quarterly basis, through standardized recording and reporting tools. Sex-specific data on NSS +ve pulmonary TB cases reported in TB07 form (the quarterly reporting form) for the past ten years (2001-2010) were used for this analysis. Data for KPK for the year 2001 was not available, so the trends and statistical analysis for this province were restricted to years 2002 to 2010.

Population estimates were accessed from the database of Ministry of Population Welfare (Government of Pakistan), to calculate sex-specific notification rates of NSS +ve TB cases. The male-to-female sex-ratio of the general population for each province (1·05: 1·00- Punjab, 1·11:1·00- Sindh, 1·14:1·00 Baluchistan, and 1·04:1·00- KPK)) and Pakistan (1·07:1·00) was applied to the respective directly observed treatment short-course (DOTS) population for the given year to determine sex-specific CNR over a 10-year span (2001-2010) and trends were examined [10]. DOTS coverage is defined as the population living in administrative areas where DOTS services are available. This indicator serves as a proxy for people with access to DOTS [3].

Sex-specific differences in proportion of notified cases for the four provinces were further analyzed using Chi-square test and odds ratios with corresponding confidence intervals taking Pakistan as the reference. Data were analyzed using SAS version 9·2 (Cary, NC; USA).

This is a non-funded study. De-identified data for the study was provided by the NTP, Pakistan. None of the authors have been paid by any agency/company. Ethics committee approval was not required as data utilized for the purpose of this study were collected as part of routine TB surveillance by the NTP.
Results

Trends in TB case notification rates (2001-2010) of provinces and Pakistan

The study population consisted of 571958 notified new smear positive cases, from 2001 to 2010 reported from all over Pakistan to National TB Program. Out of these, 292551 were males and 279407 were females. In Pakistan, Case Notification Rates for NSS+ve are nearly equal for both males and females over the years (since 2001-2010). However, when disaggregated at province level, the proportions of female notified cases in the two western provinces are higher than male notified cases, opposite to that in the eastern provinces where male notified cases are higher than female (Figure 1). The gender pattern in notification rates remained consistent over time, both in Punjab and Sind with a slight predominance of male notified cases, over the period of ten years, which resembles overall trends in Pakistan. On the other hand, KPK and Baluchistan share similarities with regard to gender differences in CNRs where female notified cases are greater than that of males that is entirely opposite to the eastern provinces. These two provinces show a constantly widening gap in the male and female CNRs, since 2001, which plateaus after 2005 with approximately 20% difference between male and female notified cases. Overall, the CNRs of male and female cases show an increasing trend over time (2001 - 2010).

Sex-specific TB case notifications - comparison of provinces with Pakistan

Table 1 presents the MFR of notified cases in each province, for the respective year, and the year-wise comparison of proportions of male and female notified cases. Pakistan’s aggregate data on notified TB cases was taken as the reference for statistical comparisons with the provincial male and female proportions of TB cases. Over a ten year period, the MFR of notified cases for two Eastern provinces remained, on average, 1.27:1.00 (range: 1.13 – 1.35) and 1.12:1.00 (range: 1.01- 1.16) for Sind and Punjab, respectively; however, for the two Western
provinces, the average MFR was 0.74:1.00 (range: 0.68 – 0.78) and 0.70:1.00 (range: 0.57 – 0.75), for KPK and Baluchistan, respectively. The geographic distribution of these differences is remarkably noticeable.

The proportion of female notified TB cases exceeds male cases, from 36% up to 99% (range of OR: 1.36-1.99), in Baluchistan (Table-2). Similarly in KPK the proportion of female notified TB cases are 30% to up to 50% (range of OR: 1.32-1.50) higher than males when compared to reference group, over ten years period. The differences in proportions, for both the western provinces are statistically significant. In the two eastern provinces, male and female CNRs are proportionate, as evident from the Odds ratio. These findings strongly suggest that females are particularly affected by TB disease burden in these parts.

**Discussion**

We present CNR as a measure of disease burden in this study because true incidence of TB for Pakistan is currently not available. Although CNR under-represents the disease burden for any country [4], it is often a good approximation of incidence in settings where health care system, diagnostics and reporting of tuberculosis is of reasonable quality [9]. If CNR for all types of TB was used instead as an indicator for disease burden, the numerator (number of total TB cases) might have been influenced by the capacity to diagnose extra-pulmonary and sputum smear negative pulmonary cases (availability of diagnostic methods, skill of physician to interpret chest X-ray abnormalities etc) [4]. Therefore, only NSS+ve TB cases were used to derive CNR as it uses a single objective method (sputum microscopy) [4]. Overall, the CNRs of male and female cases show an increasing trend over time (2001 - 2010) consistent with the significant increase in the coverage of DOTS population [3]. An indicator used for the quality assurance of sputum smear microscopy is the percentage of supervisory visits of laboratories at district and sub-
district levels by the reference laboratory officers out of the planned for each province [3]. The percentage of supervisory visits was more than 90% for Punjab and Sindh, while it was 86% for KPK and 62% for Balochistan, in 2010 [3].

Women’s risk of disease may be increased by differential exposure to tubercle bacilli which might be attributable to sexual division of labor, cultural seclusion practices and socialization patterns. Women also tend to be the lone caretakers of the sick and spend more time indoors than outside, being exposed to a higher infectious dose [11, 12]. Increased rates of progression might be one of the reasons as women generally have worse health than men in terms of nutrition. Evidence also exists for higher prevalence of TB disease among strict vegetarians compared to those who take mixed diet [13, 14].

Tobacco smoking and other smoke exposures like biomass fuels used for cooking fire and air pollution from coal fires have been associated with TB [12]. Khyber Pakhtunkhwa and Balochistan are comprised of predominantly rural population (83 and 76 percent, respectively) in comparison to Punjab and Sindh (69 and 51 percent, respectively) [15]. Women are disproportionately exposed to cooking fire, passive smoke and habitual tobacco smoke in the form of huqa in rural parts of Pakistan that may partly explain female excess in TB cases in west parts of the country but this need to be established with evidence from future research [16]. The development of active disease and the progression of latent to active tuberculosis are also noted to be higher in females [17-19]. Changes in host immunity and altered physiologic and metabolic state in pregnancy may increase susceptibility to infection; pregnancy also increases the risk of reactivation of latent infections [20]. It might be a possibility that early marriages and higher fertility rates can partly explain the observed gender disparity in west parts of the country.
However, same sex differences in TB notification rates were also observed in Norway, Denmark, England and Wales in mid-20th century leading one to think of reasons other than socio-cultural, life-style and ethnicity factors that might impact the observed sex differences in CNR [17]. One can argue the linkage of Human immunodeficiency virus (HIV) infection with this disparity as HIV infected persons are 20 – 30 times more liable to develop TB than non-infected persons but the estimated HIV prevalence is less than 0.1% for Pakistan (also very low for both Iran and Afghanistan) making it very unlikely to associate. Similarly the mid 20th century sex disparity in Europe cannot be explained by HIV infection as the epidemic hardly existed at the time. If we look across geographies and time of occurrence of this sex disparity, we find a common point of ponderance: all of these regions are or were subject to wars and/or conflicts leading to mass displacements of populations!

A cluster comprised of Western Provinces of Pakistan with a huge refugee influx from Afghanistan, Afghanistan itself and parts of Iran adjacent to Afghanistan, share a common pattern of MFR of notified TB cases, leading us to hypothesize that these areas share some common risk factors. These risk factors range from all of the above discussed that can be modified in the long run, to the risk factors that might be difficult to change like mass population displacements and ethnicity. Ethnic groups in Pakistan comprise approx. 45% Punjabi, 15% Pakhtun, 14% Sindhi and 3.6% Balochi [21]. Balochistan is comprised of 55% Balochs and 33% Pakhtuns while KPK is predominantly Pakhtun in origin [22]. The proximities of Durand line are inhabited predominantly by Pakhtun and Baloch ethnic people. Afghanistan in addition to other ethnic groups hosts some 42% Pakhtuns and 2% Balochs [21]. It is of utmost importance to explore the triggers and moderators of disease, particularly responsible for increased female CNR in this region, in order to guarantee effective TB control.
Pakistan shares similarities in socio-cultural, life-style and ethnicity, with Afghanistan and Iran that needs further exploratory research to infer linkages with the observed sex disparity. In general, socio-economic and cultural factors seem to play an essential role in determining overall gender differences in rates of infection and progression to disease. Women in Western parts of Pakistan are less likely to seek health-care due to the set socio-cultural norms and practices which is contrary to the observed pattern of increased female CNR in these parts.

**Conclusions**
The results show higher TB case notifications among females in the West of Pakistan compared with the Eastern fronts which is in accordance with the CNR of the bordering countries, Afghanistan and Iran on the West and India on the East. Either the difference in proportions is due to the exposure of females to certain factors predisposing them to increased acquisition and/or progression of latent to active disease in comparison to males, or it is the confounding effect of increased notification of female cases, or increased proportions of females in specific age groups, in general population of these provinces. This needs further exploration and evidence-based research that can be translated into policy leading to effective implementation of TB control measures to address this gender disparity.

**Competing interests**
There are none.

**Authors' contributions**
OFD- 1) Conceived the idea and contributed to conception, analysis and interpretation of data, 2) Drafted the main sections of the manuscript, and, 3) Approved the version to be published.

S.K.S- 1) Substantially participated in conception and design, acquisition and interpretation of data 2) drafting the results and methods (in parts) section of the manuscript and revising other
parts of the paper critically for important intellectual content, and, 3) Final approval of the version to be published.

AAC- 1) Substantially contributed to data acquisition and interpretation, 2) Revising it critically for technical programmatic content, and, 3) Final approval of the version to be published.

EQ- 1) Provided the data, 2) participated in revising the manuscript critically for important intellectual content, and, 3) final approval of the version to be published.
References

5. TB Situation in the Region: Regional Profile [http://www.emro.who.int/stb/tbsituation-regionalprofile-epidemiology.htm]
Figures

Figure 1 - Trends of CNR by Sex for Provinces and Pakistan (2001-2010)

* Data is from 2002 – 2010
† Data includes the North-western Regions in addition to the Provinces
CNR: Case notification rate

**MALE**  
**FEMALE**
Table 1: TB (NSS+ve) Case Notification by sex, from 2001-2010

<table>
<thead>
<tr>
<th>Years</th>
<th>*Pakistan</th>
<th>Punjab</th>
<th>‡OR († 95% CI)</th>
<th>Balochistan</th>
<th>OR (95% CI)</th>
<th>Sindh</th>
<th>OR (95% CI)</th>
<th>KPK</th>
<th>OR (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>2001</td>
<td>Males</td>
<td>3258</td>
<td>106</td>
<td>150</td>
<td>2280</td>
<td>1684</td>
<td>0.84 (0.77-0.91)</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td></td>
<td>Females</td>
<td>2865</td>
<td>(1-14)</td>
<td>262</td>
<td>(1-35)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>MFR</td>
<td>306</td>
<td>(1-01)</td>
<td>1.12 (0.95-1.33)</td>
<td>1.99 (1.62-2.44)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>2002</td>
<td>Males</td>
<td>6521</td>
<td>1011</td>
<td>347</td>
<td>3029</td>
<td>2372</td>
<td>0.76 (0.71-0.81)</td>
<td>1720</td>
<td>1.35 (1.24-1.46)</td>
</tr>
<tr>
<td></td>
<td>Females</td>
<td>6725</td>
<td>(0-97)</td>
<td>512</td>
<td>(0-68)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>MFR</td>
<td>917</td>
<td>(1-10)</td>
<td>0.87 (0.80-0.97)</td>
<td>1.43 (1.24-1.65)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>2003</td>
<td>Males</td>
<td>9820</td>
<td>1985</td>
<td>391</td>
<td>4634</td>
<td>3431</td>
<td>0.76 (0.73-0.81)</td>
<td>1907</td>
<td>1.35 (1.26-1.44)</td>
</tr>
<tr>
<td></td>
<td>Females</td>
<td>9504</td>
<td>(1-03)</td>
<td>585</td>
<td>(0-67)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>MFR</td>
<td>1720</td>
<td>(1-15)</td>
<td>0.90 (0.83-0.96)</td>
<td>1.55 (1.36-1.76)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>2004</td>
<td>Males</td>
<td>13113</td>
<td>3962</td>
<td>783</td>
<td>6851</td>
<td>5224</td>
<td>0.79 (0.76-0.83)</td>
<td>2465</td>
<td>1.45 (1.37-1.53)</td>
</tr>
<tr>
<td></td>
<td>Females</td>
<td>14520</td>
<td>(1-04)</td>
<td>1076</td>
<td>(0-73)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>MFR</td>
<td>3459</td>
<td>(1-15)</td>
<td>0.91 (0.86-0.96)</td>
<td>1.43 (1.30-1.57)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>2005</td>
<td>Males</td>
<td>23661</td>
<td>9039</td>
<td>1168</td>
<td>8915</td>
<td>7140</td>
<td>0.82 (0.79-0.85)</td>
<td>3473</td>
<td>1.50 (1.43-1.57)</td>
</tr>
<tr>
<td></td>
<td>Females</td>
<td>23086</td>
<td>(1-02)</td>
<td>1552</td>
<td>(0-75)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>MFR</td>
<td>7986</td>
<td>(1-13)</td>
<td>0.91 (0.87-0.94)</td>
<td>1.36 (1.26-1.47)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>2006</td>
<td>Males</td>
<td>33461</td>
<td>16188</td>
<td>1367</td>
<td>10646</td>
<td>8166</td>
<td>0.82 (0.80-0.85)</td>
<td>4278</td>
<td>1.45 (1.39-1.51)</td>
</tr>
<tr>
<td></td>
<td>Females</td>
<td>31126</td>
<td>(1-08)</td>
<td>1976</td>
<td>(0-69)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>MFR</td>
<td>13998</td>
<td>(1-16)</td>
<td>0.93 (0.90-0.96)</td>
<td>1.55 (1.45-1.67)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>2007</td>
<td>Males</td>
<td>45123</td>
<td>25405</td>
<td>1564</td>
<td>12006</td>
<td>9582</td>
<td>0.85 (0.82-0.87)</td>
<td>5029</td>
<td>1.45 (1.39-1.50)</td>
</tr>
<tr>
<td></td>
<td>Females</td>
<td>42442</td>
<td>(1-06)</td>
<td>2094</td>
<td>(0-75)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>MFR</td>
<td>22523</td>
<td>(1-13)</td>
<td>0.94 (0.92-0.96)</td>
<td>1.42 (1.33-1.52)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>2008</td>
<td>Males</td>
<td>50587</td>
<td>30374</td>
<td>1519</td>
<td>12253</td>
<td>10030</td>
<td>0.86 (0.83-0.88)</td>
<td>5308</td>
<td>1.42 (1.37-1.48)</td>
</tr>
<tr>
<td></td>
<td>Females</td>
<td>48341</td>
<td>(1-05)</td>
<td>2040</td>
<td>(0-74)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>MFR</td>
<td>27558</td>
<td>(1-10)</td>
<td>0.95 (0.93-0.97)</td>
<td>1.41 (1.31-1.50)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>2010</td>
<td>Males</td>
<td>51974</td>
<td>31199</td>
<td>1368</td>
<td>12517</td>
<td>10193</td>
<td>0.86 (0.83-0.88)</td>
<td>5547</td>
<td>1.44 (1.39-1.49)</td>
</tr>
<tr>
<td></td>
<td>Females</td>
<td>49354</td>
<td>(1-05)</td>
<td>1908</td>
<td>(0-72)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>MFR</td>
<td>27963</td>
<td>(1-12)</td>
<td>0.94 (0.92-0.96)</td>
<td>1.47 (1.37-1.58)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

† CI= Confidence Interval
‡ OR= Odds Ratio
* Pakistan has been taken as the reference, for comparison
M= Male-to-female ratio of notified TB cases