Adolescent Females are More Susceptible than Males for Tuberculosis

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**Abstract**

**Background and Objectives:** Published literature is silent about the gender gap in tuberculosis (TB) among adolescent (10–19 years) population despite extensive information on increased susceptibility of the male gender after 20 years. We analyzed the data from 1113 adolescent microbiologically confirmed TB cases using cartridge-based nucleic acid amplification test (CBNAAT) in 2019 in the State of Himachal Pradesh (HP), India. **Materials and Methods:** The data generated by 39 CBNAAT sites in HP were analyzed with an objective to describe the gender gap in TB among adolescents. **Results:** Among 983 patients with pulmonary TB (PTB), the male: female ratio was 1:1.5 ($P = 0.0001$), whereas in 130 patients with extra PTB (EPTB), the male: female ratio was 1:1.8 ($P = 0.0001$). This male: female ratio was seen to reverse after 20 years for PTB, and it persisted till 40 years for EPTB. Two main forms of TB that were significantly high in females during adolescence were PTB and lymph node TB ($P = 0.0001$). **Interpretation and Conclusions:** Significant gender difference with female susceptibility was seen for TB among adolescents, a fact that needs more research. Adolescent TB is a neglected area with little published data driven mainly by the fact that most countries report their TB population above and below 15 years, dividing the adolescent population into two halves. The world needs to acknowledge adolescents (10–19 years) as a separate important group for reporting TB statistics.

**Keywords:** Adolescence, gender, tuberculosis

**INTRODUCTION**

Pediatric tuberculosis (TB) is one of the ten major causes of mortality globally among children (population age <15 years). Globally, in 2018, an estimated 11 lakh children became ill with TB and 250,000 children died of TB (including children with HIV-associated TB).[1] TB India 2020 report says that about 342,000 incident cases of pediatric TB are estimated to occur every year, accounting for 31% of the global burden and 13% of the overall TB burden in the country.[2] Gender gap in adults with TB is universally acknowledged by researchers and public health experts. A recent meta-analysis of data from 1993 to 2016 (23 years) showed the overall random-effects weighted adult male: female TB prevalence ratio of 2.21 (95% confidence interval: 1.92–2.54; 56 surveys).[3] It is ironic that the same studies remain silent about the gender gap among adolescents (10–19 years) with TB due to a lack of reported data on this age group.[4] Adolescence is an important transitional phase of life where children often struggle with physical, hormonal, and emotional changes happening in their lives, and having to undergo an illness like TB may be associated with stigma and lower self-esteem. We present the analysis of the data on adolescent TB generated over 1 year in 2019 to look for gender distribution and type of TB adolescents are presenting with.

**MATERIALS AND METHODS**

**Study design**

This was a retrospective observational study.

**Objectives**

The objective of the study was to describe the gender gap in TB during adolescence.

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Himachal Pradesh (HP) is a state in the North of India located in Sub-Himalayan region. HP has bagged an award for best performance in TB control program in India, and it is one of the few states in India where all extrapulmonary TB (EPTB) and PTB samples are tested free of charge using the cartridge-based nucleic acid amplification test (CBNAAT) at 39 different sites in the state.[3] The data from all the CBNAAT testing sites are collated at a central repository with the state TB officer, which was accessed by us for analysis after getting necessary approvals and the institutional review board sanction.

Data processing
The raw data were obtained as a spreadsheet (65,701 entries), and it was cleaned to remove duplicate entries (1353 entries) and to exclude entries that had not reported the outcome of interest (CBNAAT result) or the cases where the outcome was reported as error or invalid (5525 entries). After cleaning the data, there were 58,823 sample entries tested using CBNAAT for presumptive TB in 1 year (2019).

Definitions
Cases where sputum, bronchoalveolar lavage, or gastric aspirate was tested were classified as presumptive PTB. All other samples tested were classified as presumptive EPTB.

Cartridge-based nucleic acid amplification test
CBNAAT is a rapid molecular test that diagnoses TB by detecting the presence of mycobacterium TB, as well as testing for resistance to the drug rifampicin during the same process.[4]

Ethics approval
The protocol was approved by the institutional ethics committee on January 4, 2020.

Statistical analysis
The data were analyzed using simple statistical methods in Microsoft Excel 2007. The continuous data were expressed as mean ± standard deviation, and the categorical variables were expressed as number (proportion). The comparison of the distribution of variables among various age groups (divided in 5-year groups) was done using Fisher’s exact for categorical variables and t-test for continuous variables. The results were considered statistically significant at $P < 0.05$.

Results
A total of 58,823 samples that were tested for presumptive TB using CBNAAT in 2019 in the State of HP were included in the analysis, out of which 10,939 (19%) samples were found positive for TB. The breakup of the samples received, and their positivity rate is given in Table 1. We classified the sputum, gastric lavage, and bronchoalveolar lavage samples into presumptive PTB samples (51,194 [87%]) and the rest of all sample types (7629 [13%]) were classified as presumptive EPTB samples. The positivity rate for PTB samples was 19% and that of EPTB samples was 13%. The samples that had the highest positivity rate were lymph node aspirate (30%), sputum (20%), pericardial effusion (18%), and pus (17%). Samples with the lowest positivity rate included gastric lavage (2%), ascitic fluid (3%), bone and joint samples (3%), pleural effusion (6%), cerebrospinal fluid (6%), and genitourinary samples (6%).

Gender gap in PTB and EPTB cases by age groups is shown in Figure 1a and b, respectively. In comparison to the males, females were more susceptible to develop PTB during adolescence, after which males were affected predominantly [Figure 1a].

In 2019, a total of 4665 patient samples (83% sputum and 17% extrapulmonary) were tested for TB using CBNAAT, out of which, 1113 (23.8%) samples were positive. Among adolescent PTB patients, males were 398 and females were 585 with a male: female ratio of 1:1.47 ($P = 0.0001$), whereas for adolescent EPTB, males were 46 and females were 84 with a male: female ratio of 1:1.8 ($P = 0.0001$). After the age of 19 years, however, the male: female ratio for PTB reversed and was 2.4:1.

Overall, irrespective of age, 3919 presumptive EPTB samples were received for males, resulting in 443 (11%) EPTB cases, whereas in females, 3709 presumptive EPTB samples resulted in 527 (14%) EPTB cases ($P = 0.0002$). The susceptibility to develop EPTB was disproportionately high among females during adolescence and throughout their reproductive period [Figure 1b]. Till 40 years of age, females had 405 EPTB cases compared to 284 in males giving a male: female ratio of 1:1.4.

Males and females both had a peak in PTB numbers at 20 years of age, but the peak persisted at the same level till 60 years of age for males, while in females, the number of cases started

### Table 1: Various samples that were tested for presumptive tuberculosis using cartridge-based nucleic acid amplification test in 2019 and their positivity rate

| Sample type                              | $n=58,823$ | Positive 10,939 (19%) |
|------------------------------------------|------------|----------------------|
| Presumptive pulmonary samples            | 51,194     | 9968 (19)            |
| Sputum                                   | 49,468     | 9880 (20)            |
| Gastric aspirate                         | 1229       | 29 (2)               |
| Bronchoalveolar lavage                   | 497        | 59 (12)              |
| Presumptive extrapulmonary samples       | 7629       | 971 (13)             |
| Pleural effusion                         | 2096       | 133 (6)              |
| Lymph node aspirate                      | 1529       | 455 (30)             |
| Pus samples                              | 1153       | 201 (17)             |
| Genitourinary samples                    | 664        | 37 (6)               |
| Ascitic fluid                            | 556        | 17 (3)               |
| Miscellaneous fluid samples              | 540        | 66 (12)              |
| Cerebrospinal fluid                      | 496        | 30 (6)               |
| Bone samples and joint fluid             | 340        | 11 (3)               |
| Miscellaneous tissue samples             | 184        | 10 (5)               |
| Gastrointestinal samples                 | 38         | 5 (13)               |
| Pericardial biopsies                     | 33         | 6 (18)               |
declining after 25 years. The male: female ratio for PTB was 2:1 at 30 years, 3:1 at 35 years, and 4:1 at 40 years of age [Figure 1a]. Peaking of EPTB cases occurs in males and females at the same time, i.e., 25 years, but numbers are higher for females till 40 years. The numbers decline for both genders and remain at comparably low levels thereafter [Figure 1b].

The description of various forms of TB among adolescent males and females is given in Table 2. PTB and lymph node TB were the two forms of TB that were significantly higher in female compared to male adolescents ($P = 0.0001$).

**Discussion**

Adolescents, defined by the United Nations, are those between the ages of 10 and 19. Their number in the world is 1.2 billion, making 16% of the world’s total population. Most of the adolescents live in the low- and middle-income countries, which have a high burden for TB. Adolescence is the transitional phase of life when physical and hormonal changes predispose the children to TB. Although the World Health Organization (WHO) does not give specific data for adolescent TB, we can draw estimates from the childhood TB that represents 10% of the TB population, i.e., 1 million children every year. In the last decade, worldwide, organizations have realized the need to work in the area of TB among children and adolescents, and therefore, a special side event was dedicated to this cause during the 73rd UN General Assembly, UNICEF, WHO, and the Stop TB Partnership.

Meta-analysis of 56 surveys from all over the world published between 1993 and 2016 shows that most countries record their data on TB in a way that splits the adolescents into two halves below and above 15 years of age. This has unintentionally led to the neglect of TB research on the adolescent population. The TB control policies adopted by various countries have largely been focused on adult TB since they are presumed to be the prime spreaders of TB. Childhood and adolescent TB is given only a passing reference in the published reports. A recent systematic review published in January 2020 on adolescents with TB found only 11 published studies that reported data for 10–19-year-old patients with TB.

The gender gap in TB among adolescents has gone unnoticed, while the literature is abundant in the gender gap among adults. The WHO document on “Gender and Tuberculosis,” the meta-analysis of studies between 1993 and 2016, and the systematic review of adolescent TB in 2020 are all silent about the gender gap in TB among adolescents.

Recognizing the gap in literature on adolescent TB, we analyzed our database of 10,939 bacteriologically confirmed cases by CBNAAT in 2019, out of which, 1113 (10.2%) were adolescents, 444 (40%) males, and 669 (60%) females with a male: female prevalence ratio of 1:1.5 ($P = 0.0001$).

The community-based data on adolescent TB ($n = 5961$) from Gauteng Province in South Africa had a higher female proportion (57.5%). The TB gender assessment from India published in 2018 had 234 (29%) males and 576 (71%) females having TB in the population below 15 years of age with a male: female prevalence ratio of 1:2.5 in the State of Maharashtra, India ($P = 0.00001$). A small hospital-based study from Iran ($n = 143$ adolescents with TB) had 62.9% of females.

Adolescents are also more likely to present with EPTB that is difficult to diagnose due to its paucibacillary nature. Now, with the universal availability of CBNAAT in our state, a higher number of EPTB cases are now being detected among adolescents.

Looking at the high adolescent population worldwide and increased female susceptibility at a very crucial stage in their life has not only physical and psychosocial repercussions but also this is a major cause for infertility among females in low- and middle-income countries. Adolescents with TB have a higher loss to follow-up than children or adults, and educational interventions are suggested to minimize stigma, social isolation, and dropping out of schools. More efforts
are needed to understand the pathophysiological basis of this significant reverse gender gap in adolescents with TB.

**Conclusions**

The review of the limited data available from South Africa and our study shows that females, during adolescence, have a higher predisposition for TB compared to the males. This gender gap is reversed for PTB after 20 years, but it persists to 40 years for EPTB. Most of the available data on TB are dichotomized into below and over 15 years of age, which cuts the adolescent age into two halves. Need for further research in high TB burden countries focusing on the adolescent age group (10–19 years) as a separate entity is again emphasized. This is a susceptible population, and higher susceptibility among females in this age group has far-reaching consequences.

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**Conflicts of interest**

There are no conflicts of interest.

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