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Full Length Research Paper

Burden of tuberculosis disease in South-East Asia: A statistical analysis

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ABSTRACT

The reports published by WHO on a daily basis suggest that tuberculosis (TB) remains the top infectious killer as in 2016 in South-East Asia, and hence considered a “burden” in these countries. Very few studies on the burden of TB in South-East Asia have been done. One cannot only hypothesize the causes of TB, but also try to venture what forms of medications have been implemented to eradicate the disease. Some of these possibilities have been looked into and analysed in the study of the patients suffering from TB in South-East Asian countries (as demarcated by WHO). It has been approximated that there is a total of 95602 TB suffering patients and among them just 1500 of them took different clinical tests to detect for the actual presence of the disease so that they can adopt treatment at the earliest. These patients were either immune to rifampicin or multi-drug treatment. Also, HIV test was done with their dried blood samples, but just a handful of them tested positive for HIV. So there was no reason to treat the HIV+ patients separately while carrying out the analysis. It is seen that women are more prone to running the risk of TB as compared to men. Further, we observe that the disease is not equally distributed in all the countries considered. For, instance there is hardly any new incidence of TB case in Singapore. At the same time, there is an unequal distribution among all the countries with respect to the processing of effective test detection for TB. Moreover, extensively drug-resistant TB has also been reported in Indonesia, Myanmar and Thailand.

Keywords: Rifampicin; HIV; Multi-Drug Resistant (MDR); Isoniazid; Epidemiology

INTRODUCTION

It has been observed that one-third of the world’s burden of tuberculosis, or about 4.9 million prevalent cases, are found in south-east Asia as per the report of the world health organization (WHO) **(**Nair et al., 2010 and *U.S. Department of Health and Human Services* – NNDSS. It is caused by the bacteria Mycobacterium tuberculosis that most often affects the lungs and spreads from person to person through the air when people infected by the virus cough, sneeze or spit, thus propelling the TB germs into the air. It mostly affects adults in their most productive years, although all the age groups are at risk. In 2006, TB caused India to lose an estimated 23.7 billion US dollars. In a region where one-fourth of the world’s poorest live, TB can lead to catastrophic out-of-pocket expenditure and cause patients to lose wages of an average of 3-4 months due to

Table 1. Frequency of Susceptible TB cases

Unaffected by	Frequency of cases	% of Cases
Rifampicin	77574	81.14
HIV	222	0.23
Multi-Drug	17806	18.63
Total	95602	100.00

illness-related absence from work.

TB associated with HIV infection is also an important concern in recent time. The age groups most affected by these diseases overlap, and over 50% of those dually affected die. As per WHO reports, among one million children (0-14 years of age) who fell ill with TB and 250000 children (including children with HIV associated TB) who died from the disease in 2016, 95% of them were from the South-East Asian countries. Multidrug-resistant TB still occurs in fewer than 3% of new cases and 18% of re-treatment cases in the region. However, the high TB incidence makes even these low percentages eventually translate into a large number of patients. Extensively, drug-resistant TB has also been reported in Indonesia, Myanmar and Thailand (Nair et al., 2010). It is estimated that at least one-third of TB patients goes undetected or gets treated outside national programmes, mostly with poor outcomes. These patients contribute to disease transmission and are at greater risk of developing drug resistance and dying from TB.

Further challenges arise from health systems constraints caused by staff shortages, inadequate laboratory facilities, and weak procurement, supply chains and surveillance systems. According to 2017 WHO reports, there are eleven TB affected South-East Asian countries **(**Nair N. et. al., 2010 and *U.S. Department of Health and Human Services* – NNDSS. These are namely

- Brunei Darussalam
- Cambodia
- Indonesia
- Lao People's Democratic Republic
- Malaysia
- Myanmar
- Philippines
- Singapore
- Thailand
- Timor-Leste
- Vietnam

METHODS AND MATERIALS

The study conducted by WHO is an exploratory investigation on a relatively small number of subjects and we have tried to extract a part of the data to study the burden of the disease in these eleven countries (as mentioned above). It is to be noted that the database is updated on a daily basis as countries notify WHO of corrections to previously submitted data. The entire work as of now is carried out on the basis of data available as on 13.10.2017. The study includes all the patients affected with TB, taking into account the susceptible TB cases (including incidence and prevalence cases) and the different laboratory tests
which have been used to detect TB (although just a handful of patients have been imposed to these tests) (*U.S. Department of Health and Human Services* – NNDSS and CDC WONDER). The population consists of 55592 males and 46944 females, summing up to 102536 incident or new cases of TB in the current year. Of these, 95602 cases who are susceptible to TB are sampled out. Table 1.

In this sample, there happens to be 93.24% of TB cases who are resistant to some agent, and only 6.76% of TB cases who are not resistant to any potential agent. A high percentage of TB patients who do not respond to the useful drugs (Rifampicin and Multi-drug) actually indicates that the burden of tuberculosis is tremendous in these countries.

Again throughout the analysis, this sample is not used. The main focus has been devoted to the different forms of laboratory methods and the number of patients whose sputum has been used to detect the presence or absence of the disease through those methods. So the second sample consists of 1500 susceptible TB cases, exposed to different methods of laboratory tests. The project thus aimed at looking into the different infectious agents which are mainly responsible for causing tuberculosis and the various clinical tests they are being exposed to for quicker detection of its presence. Xpert MTB/ RIF test can detect TB and its multidrug-resistant form with very high sensitivity and specificity in controlled studies, but no performance data exist from district and sub-district health facilities in the south-east Asian tuberculosis endemic countries (Park et al., 1998). The test simultaneously detects TB and resistance to rifampicin. Diagnosis is possible only in a short span of two hours and the test is now recommended by WHO as the preliminary diagnostic test in all persons with signs and symptoms of TB (Nair et al., 2010). Sputum smear microscopy is one of the most efficient tools for identifying people with infectious TB (Garduno, 2004).

Trained laboratory technicians look at sputum samples under a microscope to test for the presence of TB

Table 2. Frequency of cases undertaking Clinical tests for TB detection

Laboratory Test Technique	Number of patients exposed
Smear Microscopy	187
Culture	93
Drug Susceptibility Test	478
External Quality Assessment	188
Line Probe Assay	92
Xpert MTB/RIF	462
Total	1500

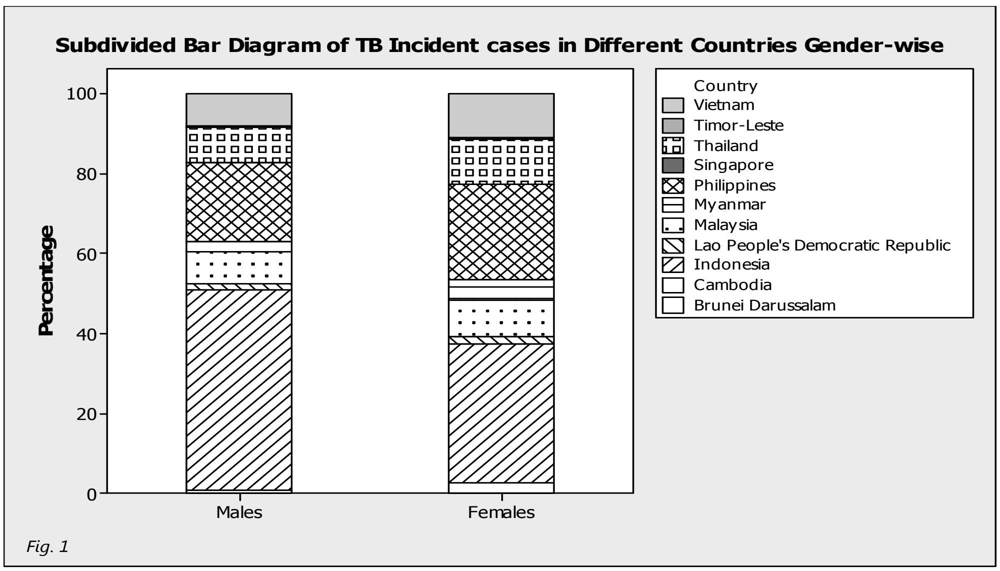

Figure 1. Subdivided Bar Diagram of TB Incident cases in Different Countries Gender-wise

bacteria. However this method can detect only half the number of TB cases and cannot detect drug-resistance (Nair et al., 2010). Drug susceptibility test is mainly used to cure MDR-TB where use of second-line drugs (Park et al. 1998; Telzak et al., 1995; Goble et al., 1993) will support clinical decision making and help to prevent the emergence of further drug resistance in patients with MDR-TB. External quality assessment has been used for comparison of a laboratory's testing to a source outside the laboratory. Line probe assay and culture tests have not been used to a large extent. Table 2.

Numerical values are available for each form of test separately
for males and females as well as separately for all the eleven countries. Also the reports provide the frequency of the susceptible TB cases separately for all these countries. First of all, a gender-wise comparison is made to see how many total incident cases of tuberculosis have occurred in the current year. This is shown through a subdivided bar-diagram as in Figure 1.

The first question that comes to our mind is that how many cases of tuberculosis are occurring under the influence of the different potential agents? This question answers our factor of incidence of TB by telling us whether the patient is resistant to the particular agent.

Here the resistance is against two different forms of agents i.e. (i) against the micro-organism HIV and (ii) against the treatment form Rifampicin (a reddish-brown antibiotic used to cure TB and leprosy) and multi-drug (i.e. the drugs Isoniazid and Rifampicin; however if the patient is resistant to (Rana et al., 2013) two drugs, other combination of drugs are used) (Caminero, 2010). Table 3.

Out of the total 95602 TB cases who are resistant to some form of agent, only 222 of them are free from HIV, i.e. this co-infection does not have any effect only on 0.23% of the total cases. This is a good sign, since as we know that the virus HIV is basically responsible for causing AIDS; and TB cure for an AIDS patient is a grievous task (Regional Response Plan for TB-HIV 2017-2021).

A country's TB burden can be described by saying how many cases of TB they have in a year. It can also be described by finding out how many cases of TB are prevalent at any given time point. The "burden" is also sometimes related to the population size (OECD 2017).

Table 3. Frequency and Percentage of TB cases resistant to drugs

Drug to which patient is Resistant	Frequency of cases	% of Cases
Rifampicin	77574	81.33
Multi-Drug	17806	18.67
Total	95380	100.00

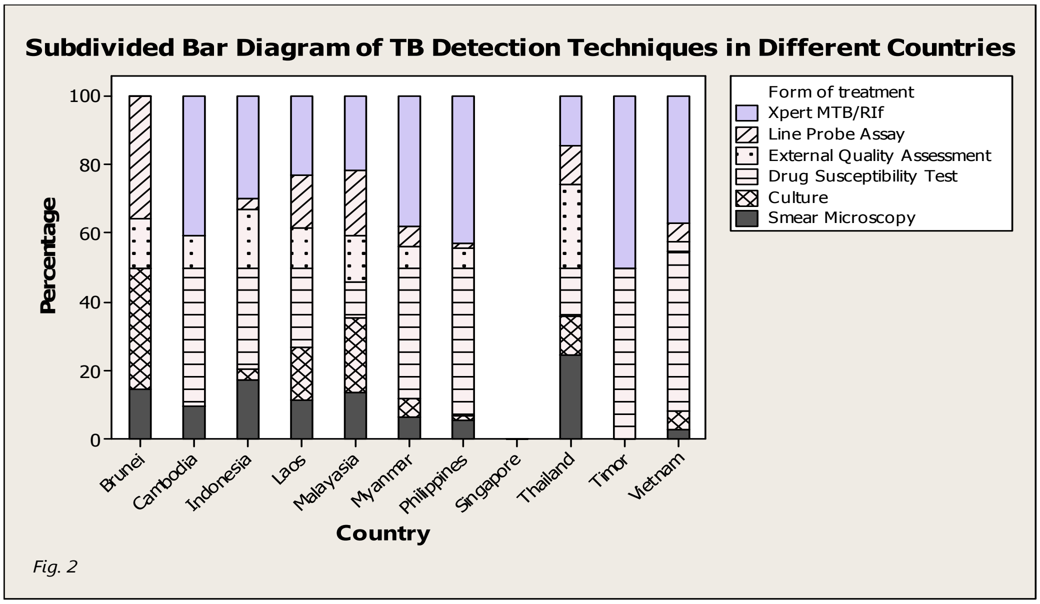

Figure 2. Subdivided bar diagram showing TB detection tests country-wise

For a country-wise comparison of the different forms of laboratory tests, we provide a subdivided bar diagram Figure 2.

Now we try to find out how different laboratory tests for detection of TB are actually influencing the rate of tuberculosis. For this purpose, each individual who has been exposed to a laboratory test, we can denote the genres (different forms of test) undertaken by the individual using a vector. For example, the vector for genre combination of a patient who has been exposed to the tests Smear Microscopy, Culture and Drug Susceptibility Test may be represented by:- $(1\ 1\ 0\ 1\ 0\ 0)^T$

The above vector is 6-component vector. The i^{th} component is 1 or 0 according as the individual has been exposed to the i^{th} form of test or not, respectively; $i = 1,2,3,4,5,6$. So for this group, we will have $\binom{n}{2}$ pairs of vectors. If d_i denotes the distance between the i^{th} pair of vectors, then a measure of variability in the genres between the n individuals of this group called Average Genre Variability (Rana F. et. al., 2013) may be defined, which is given by the average of d_i's i.e.

$$AGV = \frac{1}{\binom{n}{2}} \sum_{i=1}^{\binom{n}{2}} d_i$$

To make AGV dimension free, we define Average Standardized Genre Variation (ASGV) as $ASGV = \frac{AGV}{\sqrt{6}} \times 100\%$

We provide a multiple bar diagram (Figure 3 below) representing the ASGV for the various countries. Also, in each country, the ASGV has been calculated separately for males and females.

Multidrug-resistant tuberculosis has emerged as a possible threat to global tuberculosis control efforts in recent years. It is a challenge not only from public health point of view but also in the context of global economy, especially in the absence of treatment for MDR-TB at national level programmes in the South-East Asian countries (Atre and Mistry, 2005). Anti-TB medicines have been used for decades; drug resistance evolves when anti-TB medicines are used inappropriately, through incorrect prescription by health care providers, poor quality drugs and patients stopping to take the requisite medicines before completion of the doses (Nair et al., 2010).

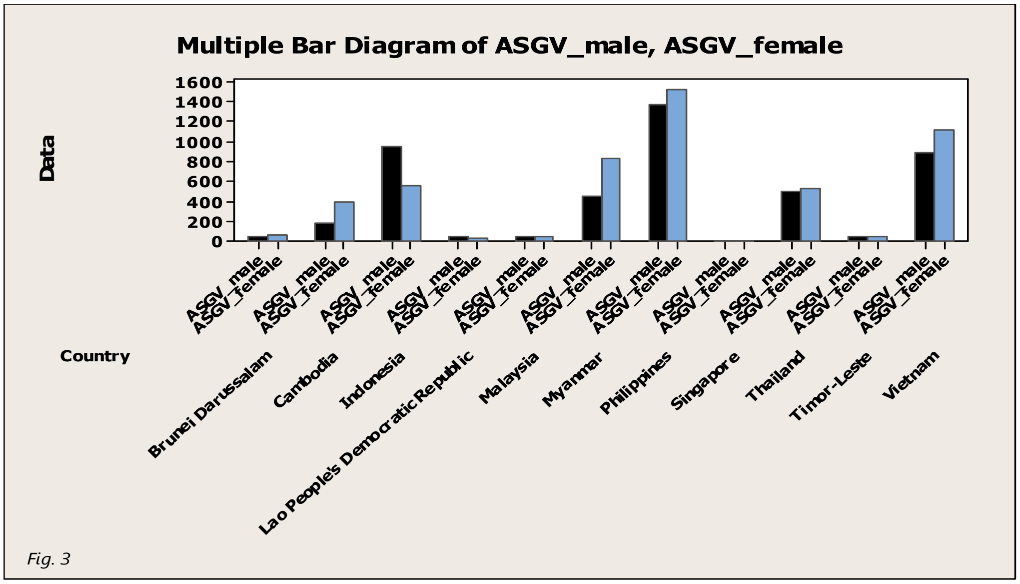

Figure 3. Average Standardised Genre Variation with respect to the detection test exposed to

Table 4. Frequency of Agent-Resistant TB cases detected through Clinical Tests

Laboratory Test Form	Rifampicin	HIV	Multi-Drug	Total
Smear Microscopy	152	0	35	187
Culture	75	1	17	93
Drug Susceptibility Test	388	2	89	479
External Quality Assessment	152	0	35	187
Line Probe Assay	75	0	17	92
Xpert MTB/RIF	375	1	86	462
Total	1217	4	279	1500

We first try to find out if there is any association between the different forms of tests used to detect TB and the agents the patients are resistant to. Here both the variables are nominal in nature. Table 4.

We use Pearson's Chi-square test to find the degree of association between the two variables by treating both the variables as nominal. Higher the value of Pearsonian Chi-square test statistic, higher is the strength of association between the two variables.

Several studies of TB patients have shown a high prevalence of HIV infection in some parts of south-east Asian countries. Now, detection of HIV cannot be done by any form of clinical test. HIV serologic surveys in TB clinics providing clinical services to TB patients are needed to assess the local prevalence of HIV infection in TB patients and the consequent need for public health intervention to prevent further spread of HIV and TB infection, although HIV-TB cases are very small in our case (McCray et al., 2017). High value of correlation coefficient between any pair of tests would indicate that those two laboratory tests are to some extent inter-related or in a more appropriate form, work in parallel with each other.

Tests for homogeneity of males and females (Welch, 1938) have been done in order to judge whether the proportion of the levels of each form of test used for detection of tuberculosis, are significantly different in these two groups with respect to the different forms of laboratory tests the patients are exposed to. Our test of hypothesis in this case is $H_0: The\ tests\ are\ NOT\ significantly\ different\ against\ H_1: Not\ H_0.$

t- test is performed for each form of the test and decision is taken at 5% level of significance.

Also, we try to test if each form of TB detection test is different or not for the different resistant agents. More precisely, our claim is that females are exposed to greater number of test forms than males for early detection of the disease, so we consider that as our alternative hypothesis. First of all, we test for the Normality of each form of test for both male and female populations. If for at least one group of laboratory technique, the normality test stands rejected, we cannot apply the usual ANOVA technique. We choose the test hypothesis to be

H_0: *Laboratory Test (Males) follows a Normal Distribution against* H_1: *Not* H_0.

In this testing problem, Kolmogorov-Smirnov test for Normality (Austin and Gurland, 1975) is applied to get suitable results. Let Med_M and Med_F be the population medians corresponding to the Male and Female populations undergoing the detection tests respectively. We apply Mann-Whitney Test for equality of medians for males and females exposed to TB detection tests. Our test of hypothesis in this case will be $H_0: Med_M = Med_F \ against \ Med_M > Med_F$

Then we carry out Kruskal-Wallis Test for the equality of the medians for different forms of laboratory tests. The basic purpose behind this test is to judge whether there exists any differential effects of different forms of tests in the detection of TB. This will also provide an idea about which techniques are more effective in general. Here we do not perform the test separately for males and females. There is a fundamental difference between treating countries as groups and treating the different forms of laboratory techniques as groups.

Now we are interested in a direct relationship between the test genre and different forms of tests, or relationship among the test forms within the group itself. Therefore testing separately for males and females is unnecessary for this purpose. Our test of hypothesis may be framed as H_0: *Medians of different test forms for all techniques are equal against* H_1: *Not* H_0.

After scrutinizing the data on the agent-resistant TB cases and discarding the cases of non-tests (although having symptoms of tuberculosis), we perform our analysis with a sample of size $n = 1467.$ Corresponding to each test form, we perform Kolmogorov-Smirnov test for Normality of Percentage of Laboratory Tests (Lilliefors, 1967). Here our test of hypothesis is

H_0: *Tests (in %) do not follow a Normal distribution against* H_1: *Not* H_0.

Finally we carry out Bartlett's test for homoscedasticity (Garduno et al., 2004) of percentage of test forms for different countries. This means we are to test $H_0: \sigma_1^2 = \sigma_2^2 = \cdots = \sigma_{11}^2 \ against \ H_1: Not \ H_0$ where σ_i^2 denotes the population variance of percentage of the different forms of tests for the i^{th} country, $i = 1(1)11$

RESULTS

Here we try to summarize our findings obtained from the different tests and hypotheses carried out so far. The results are based on only the incident cases of TB for the year 2017.

A positive result here is that only 0.23% of TB affected population in South-East Asia have been tested positive for HIV. Since HIV and TB form a lethal combination thus speeding up each other's progress, this is indeed a good sign. Among the eleven countries considered, we see that there are no new TB cases in Singapore. Also during this period, Brunei showed a very slight increase in the percentage of TB cases, whereas in Timor, the percentage is slightly more than the former two countries. Further, except in Indonesia and Malaysia, the females are at greater risk of getting affected by TB as compared to the males. Over and above, the most important eye-catching point is that Myanmar and Timor follows exactly similar tests for detection of TB. Then there are some countries like Cambodia which work more or less parallel with Indonesia, Philippines and Myanmar. Brunei presents completely a different scenario – its detection mechanism is not related with any of the countries (since, high negative correlation with all countries except Malaysia, where also the association is not that much significant). Thus it can be said that the different countries exhibit significant differential patterns when it comes to conducting tests for detection of presence of tuberculosis. Table 5.

Next, we observe that drug susceptibility test and Xpert MTB/ RIF are the two tests which have been widely carried out among the patients. Culture and Line Probe Assay are hardly being used or are hardly able to detect the presence of TB. Smear Microscopy and External Quality Assessment are more or less working parallel. A subdivided bar diagram can well represent our findings. Figure 2.

We have used AGV to reflect the variation in the rate of detection of TB within a group (country) with respect to the form of laboratory test. The ASGV i.e. the standardised AGV for the different countries is shown by a multiple bar diagram for the males and females separately figure 3. It clearly demonstrates that the overall ASGV will be slightly higher for females than for males because except in Cambodia and Indonesia, the ASGV is higher for females.

The large value of Pearsonian Chi-square shows that there is a very strong association between the two variables under consideration i.e. between the agents to which the TB patients are resistant to and the different forms of laboratory tests carried out on the patients to detect the degree of severity of the disease. Further using partial correlation coefficients within different test forms, we find that the pairs (Smear Microscopy, External Quality Assessment) and (Culture, Line Probe Assay) are used at the same extent, so they are perfectly related with each other. Other test forms like (Drug Susceptibility Test, Xpert MTB/RIF), (Smear Microscopy, Culture), (Smear Microscopy, Line Probe Assay), (Culture,

Table 5. Correlation Coefficient within different countries subject to TB detection cases

(Pair)	R^2
(Brunei, Cambodia)	-0.916
(Brunei, Indonesia)	-0.997
(Brunei, Laos)	-0.564
(Brunei, Malaysia)	0.374
(Brunei, Myanmar)	-0.812
(Brunei, Philippines)	-0.855
(Brunei, Thailand)	-0.329
(Brunei, Timor)	-0.803
(Brunei, Vietnam)	-0.755
(Cambodia, Indonesia)	0.946
(Cambodia, Laos)	0.847
(Cambodia, Malaysia)	-0.219
(Cambodia, Myanmar)	0.978
(Cambodia, Philippines)	0.991
(Cambodia, Thailand)	-0.076
(Cambodia, Timor)	0.974
(Cambodia, Vietnam)	0.948
(Indonesia, Laos)	0.629
(Indonesia, Malaysia)	-0.407
(Indonesia, Myanmar)	0.857
(Indonesia, Philippines)	0.895
(Indonesia, Thailand)	0.251
(Indonesia, Timor)	0.849
(Indonesia, Vietnam)	0.805
(Laos, Malaysia)	0.142
(Laos, Myanmar)	0.940
(Laos, Philippines)	0.910
(Laos, Thailand)	-0.594
(Laos, Timor)	0.945
(Laos, Vietnam)	0.953
(Malaysia, Myanmar)	-0.085
(Malaysia, Philippines)	-0.135
(Malaysia, Thailand)	-0.597
(Malaysia, Timor)	-0.075
(Malaysia, Vietnam)	-0.142
(Myanmar, Philippines)	0.997
(Myanmar, Thailand)	-0.284
(Myanmar, Timor)	1.000
(Myanmar, Vietnam)	0.986
(Philippines, Thailand)	-0.208
(Philippines, Timor)	0.996
(Philippines, Vietnam)	0.977
(Thailand, Timor)	-0.298
(Thailand, Vietnam)	-0.354
(Timor, Vietnam)	0.987

External Quality Assessment) and (External Quality Assessment, Line Probe Assay) are also highly associated with one another, i.e. the tests (taken two at a time) for TB detection are working in parallel to a significantly high extent. The remaining pairs are not that much associated, or in other words those test forms are not much dependent on each other in detecting the presence of TB. Table 6, we have computed the correlation coefficient within different clinical tests which are carried out in the laboratory for the early detection of the disease.

In case of homogeneity among males and females, it can be inferred that each of the tests imposed on the patients do not vary to a great extent for males and females, although we have already mentioned that females are running the risk of being affected by TB more as compared to males and a good sign is that in these countries the detection tests used are actually far more imposed on women before men irrespective of gender discrimination, even if the entire scenario represents just

Table 6. Correlation Coefficient within different Clinical tests to detect TB

(Pair)	R^2
(Smear Microscopy, Culture)	0.884
(Smear Microscopy, Drug Susceptibility Test)	0.330
(Smear Microscopy, External Quality Assessment)	1.000
(Smear Microscopy, Line Probe Assay)	0.887
(Smear Microscopy, Xpert MTB/RIF)	0.359
(Culture, Drug Susceptibility Test)	0.264
(Culture, External Quality Assessment)	0.884
(Culture, Line Probe Assay)	1.000
(Culture, Xpert MTB/RIF)	0.238
(Drug Susceptibility Test, External Quality Assessment)	0.330
(Drug Susceptibility Test, Line Probe Assay)	0.270
(Drug Susceptibility Test, Xpert MTB/RIF)	0.983
(External Quality Assessment, Line Probe Assay)	0.887
(External Quality Assessment, Xpert MTB/RIF)	0.359
(Line Probe Assay, Xpert MTB/RIF)	0.244

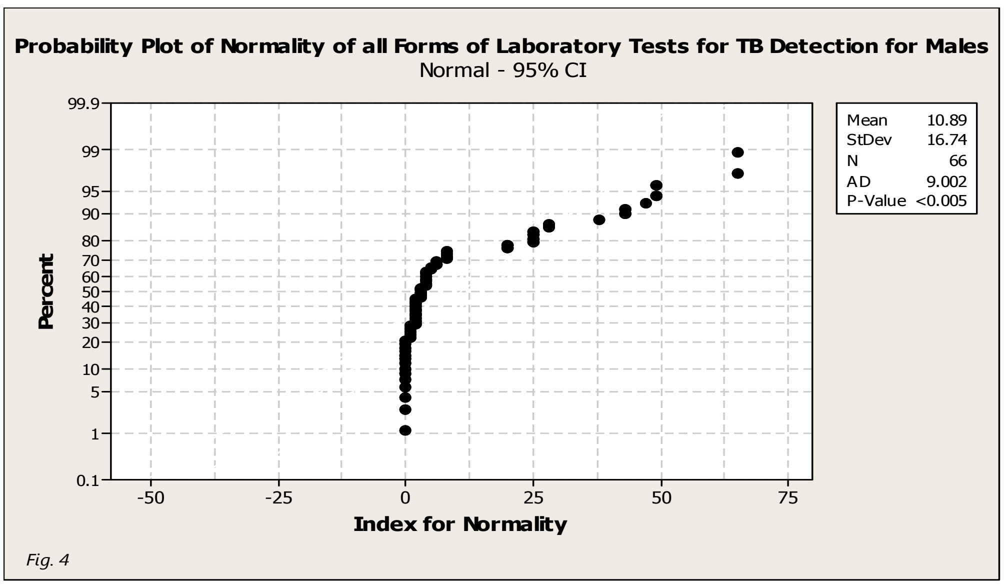

Figure 4. Normality plot showing all forms of laboratory tests for TB detection in males

a handful of patients actually receiving any treatment (after the disease has been detected). In other words, both the sexes are receiving the same level of "attention" for detecting TB. The normality plot for test detection forms used has been drawn for males. Figure 4. The fit is a highly positively skewed one, i.e. far different from normal distribution and hence non-parametric tests can be adopted as confirmatory tests, i.e. to validate our findings.

Next, Mann-Whitney test for checking the equality of medians for males and females exposed to a particular test form and Kruskal-Wallis test for testing equality of medians of different test forms have been done in parallel. Table 7.

For Mann-Whitney test, we discover that in each case $\mathrm{p-value} > 0.01$ or even > 0.05. Hence H_0 is strongly accepted at 1% or even at 5% level of significance. Thus the medians corresponding to the male population is not significantly greater than that for the female population; or in other words the medians for both the different forms of tests used are more or less equal for both the sexes. Also for Kruskal-Wallis test, $\mathrm{p-value}\ (= 0.434)$ which is significantly greater than 0.05. This implies that there does not exist significant difference in the different treatment forms as well.

The Kolmogorov-Smirnov test and the Bartlett's test for homoscedasticity of percentage of test forms reveals that $\mathrm{p-value} > 0.05$ for each test form, which is a clear

Table 7. Results of Mann-Whitney and Kruskal-Wallis test for different laboratory tests for TB detection

Mann-Whitney Test			**Kruskal-Wallis Test**		
Variable	Sample Median	p-value	Median	Average Rank	Z
Smear Microscopy	53.0	0.6437	93.00	2.0	-0.88
Culture	56.5	0.8156	478.00	6.0	1.46
Drug Susceptibility Test	60.5	1.0000	187.00	3.5	0.00
External Quality Assessment	56.0	0.7915	92.00	1.0	-1.46
Line Probe Assay	59.5	0.9733	187.00	3.5	0.00
Xternal MTB/RIF	58.0	0.8951	462.00	5.0	0.88
Overall	-	-	-	2.5	

Table 8. Results of different Statistical tests

S. No.	**Test**	**Test-Statistic value**	**p-value**	**Decision**
1.	Pearson's Chi Square χ^2 for association between different forms of laboratory detection tests and agent resistant to	360062	-	-
2.	Test for Homogeneity of males and females with respect to the forms of laboratory detection tests	-	-	Accepted for all forms at 5% level of significance
3.	Normality test for laboratory detection test form	-	-	Rejected at 1% level of significance.
4.	Kruskal-Wallis test for equality of medians for different forms of laboratory tests	-	0.434	Accepted for all forms at 5% level of significance
5.	Kolmogorov-Smirnov test for normality of percentage of laboratory detection tests patients are exposed to	-	-	Accepted at 5% level of significance
6.	Bartlett's test for homoscedasticity of percentage of laboratory test forms for different countries	2.38	0.993	Accepted at 5% level of significance

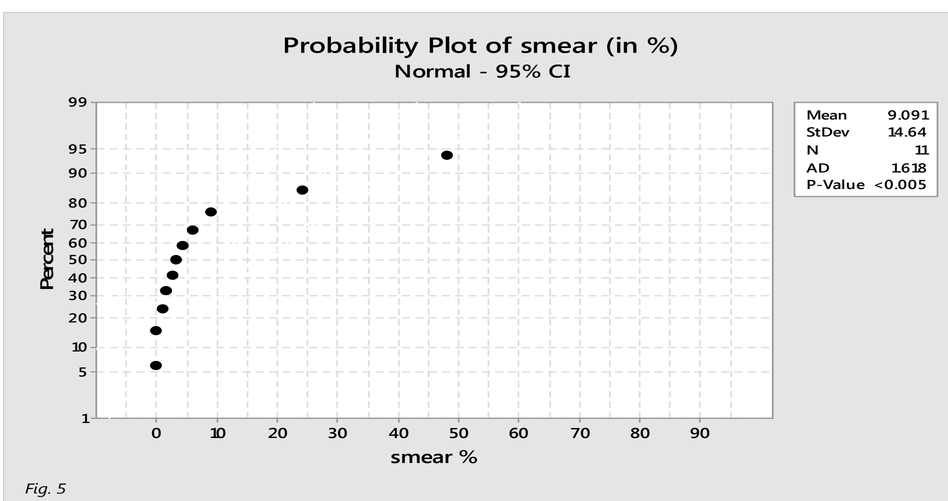

Figure 5. Probability Plot for the % of TB cases detected through Smear Microscopy

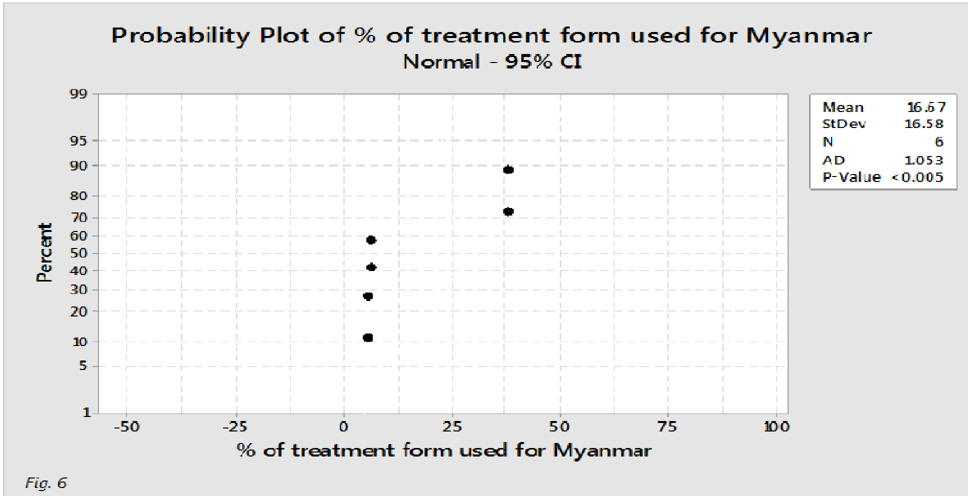

Figure 6. Probability Plot of Percentage of Clinical tests used for TB detection in Myanmar

evidence of the fact that there does not exist a significant difference in the variance of the different test forms used for detecting TB. Further results which have been obtained through different statistical measures have been tabulated above.

Also we display in Figure 5 the probability plot for one form of clinical test, say Smear Microscopy as an example.

The probability plot gives a highly positively skewed fit. Similar fits are obtained for other tests (when expressed in percentage). Hence it is evident that the Percentage of Different Test Forms does not follow a Normal Distribution.

95% Bonferroni Confidence Interval has been used to obtain the standard deviations of the testing forms for the different countries. We obtain an Individual Confidence Level of 99.5455% for Bartlett's test. Figure 6. The probability plot for Myanmar has been shown as an illustration.

Among the eleven countries, Myanmar is shown because the distribution of percentage of the different forms of tests is strikingly different for Myanmar as compared to other countries. For Myanmar, a straight distribution curve cannot be fitted, while in other countries this is possible. (Here we ignore the case of Singapore as no form of treatment has been used in this country).

Main cause of tuberculosis disease in South-East Asia region

A lower than expected case detection rate indicates that tuberculosis cases in the community are not being adequately identified and treated (which we see is happening in our case) - this obviously results in ongoing transmission of TB infection. The risk of transmission increases with the closeness of contact and the degree of infectiousness of a TB case as determined by the positivity of sputum smear microscopy of acid-fast bacilli and the degree of lung field involvement in the chest X-ray. Close contacts to a TB case such as those living in the same household are at a higher risk of getting infected than causal contacts (Nair et al., 2010).

Among infected persons, children below the age of five years and patients suffering from immunodeficiency (such as HIV infected) are at a greater risk of developing TB, usually within two years following infection.

Poverty in South-East Asia

- A large section of South-East Asia is characterised by harsh environmental conditions, overcrowding, poor ventilation and poor nutrition. Under these circumstances they are more vulnerable to tuberculosis, resulting in further financial and social insecurity (Getahun et al., 2010).

We observe that 81.14% of the total number of TB cases is resistant to Rifampicin, which is a very useful drug for curing TB. So the only option for them is to go for multi-drug treatment. However, it is seen that 18.63% is also resistant to multi-drug (where one drug used is Rifampicin). Hence the need for new combination of drugs arises. Again, it is quite likely that all the patients will not respond to the same drug combinations. So the biochemists have to go for testing effectiveness on patients with different drugs.

Accessing the presence of TB in a patient is a difficult task. Finding the poor and testing if they are suffering from the disease involves both cultural and socio-economic concerns for TB programmes – this happens because most of the section is either unaware of the

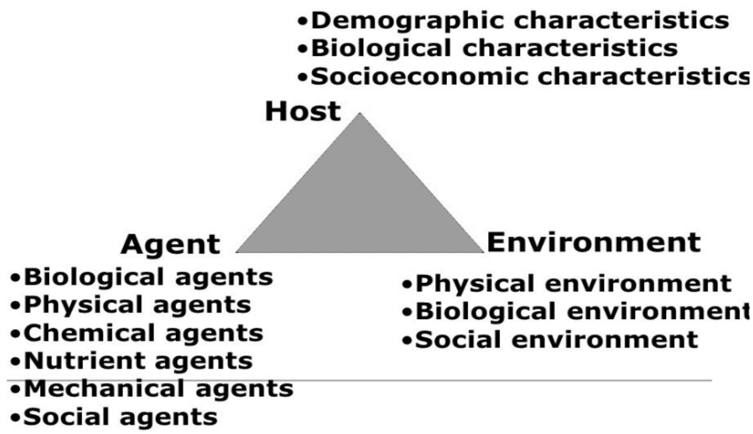

Figure 7. The Epidemiologic Triad of Tuberculosis Disease

consequences of the disease or cannot be persuaded to go for treatment (the latter due to superstitious norms) (Global Tuberculosis Report 2017).

Tuberculosis in children

• Detection of TB in children can be difficult. This is because children under the age of 10 years usually cannot cough up enough sputum to be sent for laboratory investigations to confirm the infection of tuberculosis. The diagnosis is thus largely based on the clinical features of cough, weight loss, with a history of close contact with an infectious adult TB patient. With increasing coverage of BCG vaccination, the tuberculin skin test is no longer considered a confirmatory test. Chest X-rays of children are difficult to interpret as the typical shadow is rarely seen (Tuberculosis control in the South-East Asia Region).
• Isoniazid Preventive Therapy (IPT) which has proved to be quite efficient in preventing TB disease in infected and uninfected child contacts is recommended for children below five years of age. However, this therapy is rarely provided. This is so because when IPT is prescribed, poor adherence is another problem that is likely to reduce the effectiveness of this intervention (Getahun et al., 2010).
• The prevalence of TB infection among children is in most of the cases the result of variations due to uncontrollable epidemiology features in the south-east Asian countries such as cases of pulmonary TB inherited from their parents or suffocation due to lack of proper ventilation in houses (Triasih et al., 2010).

The epidemiologic triat of tuberculosis in South -East Asia

The epidemiologic triad (Gordis and Park, 2013) is the product of an interaction of the human host, an infectious or other type of agent and the environment that promotes the exposure. It may be diagrammatically represented as shown above. Figure 7.

Now, let us study the epidemiologic triad in the context of tuberculosis. We shall restrict ourselves only to our sample, i.e. the case of the eleven south-east Asian countries, considered so far.

Host

Host refers to the organism, say human being that is capable of being infected by a specific agent.

Demographic characteristics

• The proneness of an individual to TB depends on the geographical locations of the country. This is because the geographical characteristics of the place determine the health and living conditions of the natives.
• For example, Indonesia has the maximum population among all the eleven countries. However the country is said to comprise more than 17000 islands which are occupied by the tribal people. These tribes are mostly unaware of the ways to control TB or are ignorant about the consequences of the severity of the disease. As a result, the detection tests available are also less in number which is being undertaken by the civilised people.
• Maritime south-east Asian countries including Malaysia, Singapore, Philippines and Brunei are characterized by the seas themselves. The regions as a whole are free of hurricanes and typhoons. But there are many active volcanoes and the islands are vulnerable to earthquake activities. As a result, the air is contaminated with harmful gases which contain an active form of bacteria causing tuberculosis. In these regions, the TB

patients are resistant to any useful potential substance that causing an alarming rate of infected persons. The laboratory test forms are again few in numbers, not reaching out to the entire population.

- Timor has the least population. The deep jungles here were home to the maximum population, which are now being urbanised. The less number of TB affected patients usually go undetected.

Biological characteristics

- As is known, TB is caused by a type of bacterium called Mycobacterium tuberculosis. It gets spread from one person to another when a person with active TB disease in their lungs coughs or sneezes and someone else inhales the expelled droplets, which contain TB bacteria.
- The immunological diagnosis of TB has been historically performed by the Mantoux test or tuberculin skin test and the introduction in the last decade of the line probe assay examinations. The majority of the population is unaware of the immunization programmes available or are reluctant to undertake them because of the costs involved.
- The patients having AIDS usually feel hesitant to go to doctors and undergo the test for detection of TB. Although such cases are few in number, yet the figures cannot be completely ignored.

Socio-economic characteristics

- The different laboratory techniques just for detection of the disease are usually quite expensive. Even if not costly, they are not within the reach of the lower sections of people. Also inadequate funds being provided by the government or nation-wide health organizations to the local residents for their treatment do not actually meet the needs of the huge population.
- The tribal people usually are of the opinion that supernatural powers or herbs and leaves of some trees would cure them – hence there are several cases where the people have not seen a doctor in their lifetime.
- Also, TB is such a disease which cannot be detected easily; or even when detected its stage or extent of severity goes unfathomed. Further it is such a disease which cannot be cured easily by medicines alone. One has to undergo some form of therapy, about which most of the people do not show interest or are unable to afford.
- Even undertaking the laboratory techniques for detection of TB in the south-east Asian countries is a grievous job because the scientific and technological aspects are not that much advanced. As a result, the treatment policy is such that either one has to pay and get the treatment, or die untreated.

Agent

Agent refers to entity or micro-organism as well as the physical and chemical components capable of causing the disease.

In this case, it is meaningless to segregate the agents into different categories like physical, chemical or mechanical. So we combine the biological and chemical components into one and name them as bio-chemical agents. The different forms of tests may be kept under mechanical agents and other factors can be summed up under physical or social agents.

Bio-chemical agents

- The potentially useful agents to which the patients are resistant to (in our study) – Rifampicin, HIV and Multi-drug, are nothing but biological agents. The group which is resistant to these agents run a much higher risk of not recovering than the complimentary group.
- It is seen that a huge proportion of individuals in south-east Asia are running the risk of being exposed to TB. However since they are also resistant to the biological agents, the technological therapies cannot be applied for them. As a result, there is little chance for the patients to recover.

Physical agents

- The physical environments like unhealthy living areas, unhygienic living conditions are an obvious cause of TB in south-east Asia.
- Most of the countries being coastal, the water supply is adequate. But this water which is not suitable for most of the purposes, is being supplied to houses (mostly without being filtered) and WHO evidences have reported that leaked pipes are causing both incoming and outgoing water to flow through the same passage, thus polluting even the fresh water on its way.
- Limited evidence exists that the food habits in these countries are safe and hygienic.

Mechanical agents

- It is worthwhile to note how the laboratory techniques for early detection of TB are affecting the rate of the disease.
- From all the tests and hypotheses being done above, it is seen that Smear Microscopy is the most widely adopted technique followed by others.

- The mechanical agents in this case, i.e. the different laboratory methods are not affecting a huge population as only a small sample is exposed to the tests. The agents are effective for those individuals who are not resistant to the biological agents mentioned above.

Environment

The environment is all that is external to the host.

Physical environment

- The extent to which a patient is prone to getting TB depends on the type of environment where he/ she is residing. The physical environment includes the drinking water facilities, sanitation facilities, food storage techniques followed by him/ her.
- Sometimes it is not within the hands of an individual to control his physical surroundings. When food or water is contaminated globally, it goes out of control to maintain a healthy physical environment.

Biological and Social Environments

Can be clubbed into a single case. The social norms prevalent in the south-east Asian countries are usually not that sound. There is no suitable family planning methods adopted or no proper treatment is adopted to cure any disease. Most of the things are left in the hands of nature and to some superstitious beliefs. Hence no remedial measures are taken to prevent the outbreak of water-borne diseases. Thus eventually outbreak of tuberculosis is a common cause especially in the tribal areas and no suitable remedial measures being followed, adds to the increase in its intensity.

DISCUSSION

It has been observed that there is an effective drug treatment for tuberculosis and there has been good progress since the introduction of the directly Observed Therapy Strategy (DOTS) of the WHO in 1995 which aims in treating up to 85% of the TB cases across the globe. It is estimated that at least one-third of TB patients goes undetected or get treated outside national programmes, mostly with poor outcomes. These patients contribute to disease transmission and are at greater risk of developing drug resistance and dying from TB. Further challenges arise from health systems constraints caused by chronic staff shortages, inadequate laboratory facilities, and weak procurement, supply chains and surveillance systems. As expected, there are significant differential patterns in the adoption of different forms of laboratory tests when different countries are considered; however there is not much significant differential effect when just the different forms of tests are considered. Also, there is not much difference in the tests received by the male and the female populations. Inspite of the availability of detecting the presence of the disease in patients, its availability is limited only to some particular regions and not throughout the nations, thereby curbing the anti-tuberculosis therapy and preventive therapy (Mehta et al., 1991).

Tuberculosis is a curable disease. Active, drug-susceptible TB is treated with a standard six-month course of four antimicrobial drugs that are provided with information, supervision and support to the patient by a health worker or trained volunteer. Without such support, treatment adherence can be difficult and the disease may take the form of an epidemic. A 12-component approach of collaborative TB-HIV activities is recommended by WHO, including actions for prevention and treatment of infection and disease to reduce deaths. In some cases, more severe drug resistance can develop such as extensive drug-resistant TB (XDR-TB) is a more serious form of MDR-TB which is caused by bacteria that do not respond to the most effective second-line anti-TB drugs, often leaving patients without any further treatment options thus increasing the “burden” of the disease in these developing countries (Nair et al., 2010). Currently, MDR-TB is estimated to be 2.2% among the new incident cases and 16.7% among re-treatment cases based on WHO modelling – the result of a small-scale TB drug-resistance study with Xpert MTB/ RIF was in conformity with the estimation. Presently, most patients with drug resistance tuberculosis are diagnosed and managed by regional/ provincial and some private hospitals, which provide local resources such as the Government Pharmaceutical Organization (Tuberculosis control in the South-east Asia region, Annual Report 2015).

Based on the data and analyses being carried out, numerous statistical analyses can be performed in the future. Methods can be adopted how to tackle with the agents which are responsible for causing tuberculosis. Regarding the analyses concerning different test procedures, one can construct a more sophisticated model incorporating a concomitant variable say “Treatment Form Index (TFI)” (Dyer and Keating, 1980), along with the relevant categorical factors like countries or antigens or diagnostic methods. To know the effect of different treatment forms in antigen-resistant TB in a more rigorous manner, one can try to fit a theoretical distribution to TFI. As the epidemic of TB infection differently impacts in the various parts of the nation, awareness of the regional variation is highly crucial in understanding the changing epidemiology and the clinical picture of tuberculosis. The realization of these local differences in demographics and the epidemiology of tuberculosis will assist physicians and TB program workers in the mission of tuberculosis elimination from these nations (Austin and Gurland, 1975). Further HIV services implementing TB screening and Isoniazid Preventive Therapy should embrace standardized TB screening and IPT indicators – prevention of the disease in this region will contribute to the overall target of reducing global TB burden and improving the quality of life of the suffering patients (Getahun et al., 2010).

CONCLUSION

The analyses and the testing of various hypotheses regarding the population being done, we now proceed to the final step i.e. conclusion. On the basis of the data at hand, we first conclude the following about the different test forms adopted.

(i) The six different forms of laboratory tests or techniques carried out on patients to detect TB, have less differential patterns for different countries as well as for different genders.

(ii) The different forms of laboratory techniques do not follow a Normal distribution.

(iii) Females are suffering comparatively more than males; and so the different tests are provided more to females than males for detecting the level of illness.

(iv) Considering males and females separately or together, there is no significant difference in the median of the test forms imposed on them.

Now in the light of the given data, we conclude the following about the burden of TB in different countries.

(i) The laboratory techniques are not available equally in all the eleven countries. The inequality occurs mainly of socio-economic constraints, although geographical demarcations like size of the countries also play a role to some extent.

(ii) Myanmar, Timor and Singapore do not undertake any form of test. Although Singapore does not have much TB affected patients, but in the other two countries, the figures of patients suffering are significant.

(iii) There exists significant differential effect in the forms of tests with respect to different countries. This is clear from the epidemiologic triad considered above.

Hence in a nutshell, it can be said that there are significant differential patterns in the adoption of different forms of laboratory tests when different countries are considered; however there is not much significant differential effect when just the different forms of tests are considered. Also, there is not much difference in the tests received by the male and the female populations.

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