Treatment outcomes of patients with tuberculosis in war affected region of Khyber Paktunkhwa, Pakistan

CURRENT STATUS: UNDER REVIEW

BMC Infectious Diseases  ▶ BMC Series

TAUSEEF AHMAD  ➡️ Tauseef.ahmad@hu.edu.pk
School of Public Health, Southeast University, Nanjing, China
Corresponding Author
ORCiD: 0000-0001-8793-273X

Muhammad Ayub Jadoon
AUST

Muhammad Khan
Hazara University

Muhammad Mumtaz Khan
University of Haripur

Akbar Hussain
Dalian Medical University

Taha Hussain Musa
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GCMBDR

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Hui Jin
Southeast University
Haroon,
Northwest University

DOI: 10.21203/rs.2.9219/v2

SUBJECT AREAS Internal Medicine Specialties

KEYWORDS Tuberculosis, Treatment outcome, Pakistan
Abstract

Background: Globally, tuberculosis (TB) remains the leading cause of death from a single infectious disease. TB treatment outcome is an indicator for the effectiveness of a national TB control program. This study aimed to assess treatment outcomes of TB patients and its determinants in Batkhela, Khyber Pakhtunkhwa, Pakistan.

Methods: A retrospective cohort study was designed using all TB patients who were enrolled at District Head Quarter (DHQ) Hospital Batkhela, Pakistan, from January 2011 to December 2014. A multivariable logistic regression models were used to identify factors associated with successful TB treatment outcomes defined as the sum of cure and completed treatment. Results: A total of 515 TB patients were registered, of which 237 (46%) were males and 278 (53.98%) females. Of all patients, 234 (45.44%) were cured and 210 (40.77%) completed treatment. The overall treatment success rate was 444 (86.21%). Age 0-20 years (adjusted odds ratio, AOR= 3.47; 95% confidence interval, CI)= 1.54-7.81; P= 0.003), smear-positive pulmonary TB (AOR)= 3.58; 95% CI= 1.89-6.78; P= <0.001), treatment category (AOR= 4.71; 95% CI= 1.17-18.97; P= 0.029), and year of enrollment 2012 (AOR= 6.26; 95% CI= 2.52-15.59; P= <0.001) were significantly associated with successful treatment outcome. Conclusions: The overall treatment success rate is satisfactory but still need to be improved to achieve the international targeted treatment outcome. Type of TB, age, treatment category, and year of enrollment were significantly associated with successful treatment outcomes.

Background

Globally, tuberculosis (TB) remains the leading cause of death from a single
infectious agent (*Mycobacterium tuberculosis*), ranking above human immunodeficiency virus (HIV)/acquired immunodeficiency syndrome (AIDS) [1-2]. In 2018, an estimated 10 million (range, 9.0–11.1 million) incident TB cases were reported, and there were 1.2 million TB deaths in HIV negative people and 251,000 deaths among HIV positive people [1]. The magnitude of the disease varies from country to country with more prevalent in low-income countries [1-2]. Furthermore, 44% of total cases were from World Health Organization (WHO) region of South-East Asia, 24% from African region, 18% from the Western Pacific region (18%), 8% from the Eastern Mediterranean region, 3% from region of the Americas and 3 from Europe region [1]. In addition, India (27%), China (9%), Indonesia (8%), the Philippines (6%), Pakistan (6%), Nigeria (4%), Bangladesh (4%) and South Africa (3%) accounted for two thirds of the global total TB cases [1]. Increasing the rate of successful treatment outcome is one of the strategies for effective control of TB in the community. The End TB Strategy defines targets for 2030; to decrease the incidence rate by 80% (new cases per 100,000 population per year) and 90% reduction in the number of TB deaths compared with levels in 2015 [3]. However, successful treatment outcome has increased in several countries following the implementation of Directly Observed Treatment Short-Course (DOTS) program [4]. TB is still a major health problem in Pakistan, with an estimated 510,000 new TB cases and approximately 15,000 drug resistant TB cases reported every year [5]. Recently, a standardized TB prevention and control program that regularly monitors the incidence of TB and as well as drug susceptibility testing in the population has been launched at Hayatabad Medical Complex Peshawar, Khyber Pakhtunkhwa province [6]. In Khyber Pakhtunkhwa province of Pakistan several studies have been conducted on the prevalence of TB [7-12], however, there are
limited studies on the treatment outcome of TB [13]. Therefore, this study was undertaken to assess TB treatment outcome and its determinants in Batkhela, Khyber Pakhtunkhwa, Pakistan.

Patients and Methods

Study setting

Batkhela is the capital city of Malakand district and it is one of the popular business city in Khyber Pakhtunkhwa province. Malakand district is situated in Khyber Pakhtunkhwa province. The total population of the district is 720,295 (2017 census) [14]. The area is surrounded by district Dir (Lower) in the north, Swat district in the east, Mardan andCharsadda districts in the south east and south west respectively, Mohmand and Bajaur agencies are in the west (Fig. 1). The DHQ Hospital Batkhela, providing health care facilities to the local residence of Batkhela and district Malakand. The area has been providing humanitarian protection and shelter for a large number of refugees from different districts of Malakand division during flood and war.

Study population

All TB patients who were enrolled at DHQ Hospital between 1st January 2011 and 31st December 2014 were included.

Study design and data collection

A hospital based retrospective cohort study was conducted. Data were collected from patient medical records and TB registration books. The registration books contained basic information such as socio-demography and clinical profile of the patients, date of TB diagnosis and treatment outcome. The data was collected by trained unit healthcare personnel under supervision of principal investigator by
using self-designed performa and entered into Excel sheet.

**Laboratory procedure**

According to the standard protocol the sputum was collected from the suspected patients having symptom of TB in 5ml sterile bottle, after collection of sputum the bottle were kept in 15 ml sterile bottle to avoid the leakage of the infectious samples. The samples were labeled and further process by the laboratory technician of the hospitals. Smear microscopy with Ziehl-Neelsen staining and fluorescence microscopy are used in the Hospital for both the diagnosis and monitoring of TB [15].

**Standard definition**

TB treatment outcomes and clinical cases were defined according to the standard World Health Organization (WHO) definitions (Table 1). In this study, treatment success was defined as a sum of cured and treatment completed; and poor treatment was defined as the sum of treatment failure, death or lost to follow up. Table 1 Standard definition modified from WHO definitions [16]
| Treatment outcomes and clinical case | Definitions                                                                                                                                                                                                 |
|--------------------------------------|-------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| Cured                                | A patient who was initially sputum smear-positive and who finished treatment with a negative bacteriology result at the end of treatment or was sputum smear negative on two occasions at the end of treatment.                        |
| Treatment completed                  | A patient who completed treatment but did not meet the criteria for cure or failure; this definition applies to sputum smear-positive and sputum smear-negative patients with pulmonary TB and patients with EPTB. |
| Treatment failure                    | A patient who was initially sputum smear-positive and remained bacteriology or sputum smear-positive at month five or later during treatment.                                                                 |
| Death                                | A patient who died from any cause during the course of treatment.                                                                                                                                             |
| Lost to follow-up                    | A patient who has been on treatment for at least four weeks and whose treatment was unsuccessful for eight or more consecutive weeks.                                                                             |
| Transfer out                          | A patient who has been transferred to another recording and reporting unit and whose treatment outcome is unknown.                                                                                           |
| Successful treatment outcome         | A patient who was cured or completed treatment                                                                                                                                                             |
| Unsuccessful treatment outcome       | A patient who had treatment failure, lost to follow up, or death in other cases.                                                                                                                                 |
| Smear-positive pulmonary TB           | A patient with at least two sputum specimens which were positive for acid fast bacilli by microscopy, or a patient with only one sputum specimen which was positive for AFB and chest radiographic abnormalities consistent with active pulmonary tuberculosis. |
| Smear-negative pulmonary tuberculosis | A patient with symptoms suggestive of TB, with at least two sputum specimens which were negative for AFB by microscopy, and with chest radiographic abnormalities consistent with active pulmonary tuberculosis (PTB), or a patient with two sets of at least two sputum specimens taken at least two weeks apart and which were negative for AFB by microscopy and radiographic abnormalities consistent with active PTB and lack of clinical response to one week of broad spectrum antibiotic therapy. |
| Extra-pulmonary tuberculosis (EPTB)  | This included TB of organs other than the lungs, such as lymph nodes, abdomen, tract, skin, joints and bones, the meninges and others.                                                                          |

**Statistical analysis**

The collected data were checked for completeness by principal investigator. Data were entered, cleared and descriptive analyses were carried out using Statistical Package for Social Sciences (SPSS) version 20. Multivariable logistic regression model was used to analyze the association between treatment outcome and potential determinate variables at 95% confidence interval. P-value of less than 0.05 was considered as statistically significant.

**Results**
A total of 515 TB patients, registered and treated for TB at DHQ Hospital between January 2011 to December 2014, were included in this study. Of these, 278 (53.98%) were female and 185 (35.92%) were age less than 20 years (Table 2).

**Clinical characteristics of the patients**

Of the total patients, 252 (48.93%) were smear positive PTB, 82 (15.92%) were smear negative PTB and 181 (35.15%) were EPTB as shown in Table 2. Majority of the patients 493 (95.72%) were new TB cases, and 503 (97.7%) were treatment category I (CAT-I). The number of cases diagnosed with TB in the hospital was increased from 116 (22.52%) in 2011 to 161 (31.26%) in 2014.

**Table 2 Characteristics of TB patients attending the DOTS services**

| Characteristics          | Type of TB n (%) |
|--------------------------|-----------------|
|                          | Smear positive | Smear negative | EPTB       | Total n (%) |
| Sex                      | PTB             | PTB            |            |             |
| Male                     | 120 (50.63)     | 39 (16.45)     | 78 (32.91) | 237 (46.01) |
| Female                   | 132 (47.47)     | 43 (15.46)     | 103 (37.05)| 278 (53.98) |
| Age                      |                 |                |            |             |
| 0-20                     | 74 (40.00)      | 39 (21.01)     | 72 (38.91) | 185 (35.92) |
| 21-40                    | 100 (52.91)     | 23 (12.16)     | 66 (34.92) | 189 (36.69) |
| 41-60                    | 46 (56.09)      | 8 (9.15)       | 28 (34.14) | 82 (15.92)  |
| ≥61                      | 32 (54.23)      | 12 (20.33)     | 15 (25.42) | 59 (11.45)  |
| TB patient category      |                 |                |            |             |
| New                      | 234 (47.46)     | 79 (16.02)     | 180 (36.51)| 493 (95.72) |
| Relapse                  | 8 (80.03)       | 2 (20.00)      | 0 (0.00)   | 10 (1.94)   |
| Other                    | 10 (83.33)      | 1 (8.33)       | 1 (8.33)   | 12 (2.33)   |
| Treatment category       |                 |                |            |             |
| Category-I               | 243 (48.31)     | 79 (15.70)     | 181 (36.51)| 503 (97.66) |
| Category-II              | 9 (75.00)       | 3 (25.00)      | 0 (0.00)   | 12 (2.33)   |
| Treatment year           |                 |                |            |             |
| 2011                     | 50 (43.10)      | 26 (22.41)     | 40 (34.48) | 116 (22.52) |
| 2012                     | 59 (50.00)      | 17 (14.40)     | 42 (35.9)  | 118 (22.91) |
| 2013                     | 64 (53.33)      | 19 (15.83)     | 37 (30.83)| 120 (23.30) |
| 2014                     | 79 (49.11)      | 20 (12.42)     | 62 (38.5)  | 161 (31.26) |
| Total                    | 252 (48.93)     | 82 (15.92)     | 181 (35.14)| 515         |

Abbreviations: PTB: Pulmonary TB; EPTB: Extra-pulmonary TB

**Treatment outcomes**

The overall TB treatment success rate (i.e. cured and treatment completed) in
Batkhela was 444/515 (86.21%). Of all patients, 234 (45.44%) were cured, 210 (40.77%) completed treatment, 14 (2.72%) died, 20 (3.88%) lost to follow-up, and 3 (0.58%) were transferred out (Table 3). The treatment success rate was higher among female 243/278 (87.41%) than male 201/237 (84.81%) and increased over time.

Table 3 Trends of TB treatment outcome among TB patients attending the DOTS services

| Treatment outcome/year | 2011 (n, %) | 2012 (n, %) | 2013 (n, %) | 2014 (n, %) | Overall outcome (n, %) |
|------------------------|-------------|-------------|-------------|-------------|------------------------|
| Cured                  | 46 (39.65)  | 57 (48.30)  | 60 (50)     | 71 (44.09)  | 234 (45.44)            |
| Completed              | 55 (47.42)  | 55 (46.61)  | 52 (43.33)  | 48 (29.81)  | 210 (40.77)            |
| Total success          | 101 (87.07) | 112 (94.91) | 112 (93.33) | 119 (73.91) | 444 (86.21)            |
| Died                   | 2 (1.72)    | 1 (0.85)    | 2 (1.67)    | 9 (5.59)    | 14 (2.72)              |
| Defaulted              | 0 (0.00)    | 2 (1.69)    | 3 (2.5)     | 15 (9.32)   | 20 (3.88)              |
| Transfer out           | 0 (0.00)    | 0 (0.00)    | 2 (1.67)    | 1 (0.62)    | 3 (0.58)               |
| Unrecorded             | 13 (11.21)  | 3 (2.54)    | 1 (0.83)    | 17 (10.56)  | 34 (6.60)              |
| Unsuccessful           | 15 (12.93)  | 6 (5.08)    | 8 (6.67)    | 42 (26.08)  | 71 (13.78)             |

Factors associated with treatment success

Table 4 shows factors associated with successful TB treatment outcomes. In the multivariate analysis, type of TB, age, and year of treatment commencement were significantly associated with successful treatment outcomes. Those patients with age group 0-20 years (AOR=3.47; 95% CI: 1.54-4.7.81) were more likely to have a successful treatment outcome than those patients with age group >=61 years. Similarly, those patients with age group 21-40 years (AOR=2.76; 95%CI: 1.26-6.03), and 41-60 years (AOR=2.82; 95%CI: 1.08-7.35) were more likely to have successful treatment outcomes than those patients with age group >=61 years. It was found that smear positive pulmonary TB patients were more likely to have successful treatment outcomes than extra pulmonary TB patients (AOR= 3.58; 95% CI: 1.89-6.78). Those patients with treatment CAT-I were more likely to have successful treatment outcomes than patients with treatment category II (CAT-II) (AOR = 4.71,
95%CI: 1.17-18.97).

Table 4: Predictor factors for successful treatment outcome among registered TB cases

| Character          | No. (%) of TB cases | Successful outcome, n (%) | COR (95% CI)       | P-value | AOR (95% CI)       |
|--------------------|---------------------|---------------------------|--------------------|---------|--------------------|
| Sex                |                     |                           |                    |         |                    |
| Male               | 237 (46.01)         | 201 (84.81)               | 0.08 (0.48-1.32)   | 0.39    | 0.93 (0.53-1.63)   |
| Female             | 278 (53.99)         | 243 (87.41)               | 1.00               | 1.00    |                    |
| Age                |                     |                           |                    |         |                    |
| 0-20               | 185 (35.92)         | 165 (89.19)               | 3.34 (1.61-6.93)   | 0.001   | 3.47 (1.54-7.81)   |
| 21-40              | 189 (36.69)         | 165 (87.30)               | 2.78 (1.37-5.65)   | 0.005   | 2.76 (1.26-6.03)   |
| 41-60              | 82 (15.92)          | 72 (87.80)                | 2.91 (1.22-6.95)   | 0.016   | 2.82 (1.08-7.35)   |
| ≥61                | 59 (11.45)          | 42 (71.18)                | 1.00               | 1.00    |                    |
| Smear positive PTB | 252 (48.93)         | 232 (92.06)               | 2.88 (1.60-5.16)   | 0.000   | 3.58 (1.89-6.78)   |
| Smear negative PTB | 82 (15.92)          | 67 (81.70)                | 1.11 (0.57-2.16)   | 0.762   | 1.18 (0.56-2.48)   |
| EPTB               | 181 (35.15)         | 145 (80.11)               | 1.00               | 1.00    |                    |
| Patient category   |                     |                           |                    |         |                    |
| New                | 493 (95.72)         | 426 (86.40)               | 0.57 (0.07-4.55)   | 0.603   | 0.57 (0.07-4.55)   |
| Relapse            | 10 (1.94)           | 7 (70.00)                 | 0.21 (0.02-2.46)   | 0.215   | 0.21 (0.02-2.46)   |
| Other              | 12 (2.33)           | 11 (91.67)                | 1.00               | 1.00    |                    |
| Treatment category |                     |                           |                    |         |                    |
| Category I         | 503 (97.66)         | 437 (86.87)               | 0.21 (0.06-0.68)   | 0.01    | 4.71 (1.17-18.97)  |
| Category II        | 12 (2.33)           | 7 (58.33)                 | 1.00               | 1.00    |                    |
| Year of treatment  |                     |                           |                    |         |                    |
| 2011               | 116 (22.52)         | 101 (87.06)               | 2.37 (1.24-4.54)   | 0.009   | 2.42 (1.22-4.82)   |
| 2012               | 118 (22.91)         | 112 (94.91)               | 6.58 (2.69-16.09)  | 0.000   | 6.26 (2.52-15.59)  |
| 2013               | 120 (23.30)         | 112 (93.33)               | 4.94 (2.22-10.98)  | 0.000   | 4.31 (1.88-9.86)   |
| 2014               | 161 (31.26)         | 119 (73.91)               | 1.00               | 1.00    |                    |

Abbreviations: PTB: Pulmonary tuberculosis; EPTB: extra-pulmonary TB; COR: Crude odds ratio; AOR: Adjusted odds ratio.

Discussion

In this study, the overall TB treatment success rate is higher from previous published studies in different countries; studies from India reported the overall treatment success rates were (81%) [17], (83%) [18], (84.21%) [19], and (86%) [20], in Thailand the success rate was (78.5%) for patients in the TB Case Management cohort, while the success rate is high (87.5%) for patients in the National Health Security Office cohort [21], Iran (83.1%) [22], Uzbekistan (83%) [23], Denmark (80.5%) [24], Malaysia (67.26%) [25], Ethiopia (85.6%) [26], Somalia (81.8%) [27], Nigeria (83.1%) [28], in Afghanistan the treatment success rates were
(77.5%) in male and (84.4%) in female patients [29], and (77.7%) [30]. However, the treatment success rate was lower than that reported in the previous studies in Pakistan [13,31]. Type of TB, age, and year of treatment commencement were significantly associated with successful treatment outcomes.

In this study, patients with age less than 60 years were nearly three times more likely to get successful treatment outcome as compared to patients with age greater than 61 years. These results are consistent with previous studies conducted in Ethiopia [26]. This may be due to the fact that older age patients are at a higher risk of death due to ageing. Another reason for low treatment outcome in older age patients could be because older age patients might be at higher risk of having chronic comorbidities such as cardiovascular diseases, hypertensions, and cancers. Low socio-economic status, poor adherence to treatment, and difficulty of traveling and arriving early at health facilities for DOTS could be also other reasons for low treatment outcomes in older age patients. These findings highlight the importance of providing close follow up for older age patients to increase their successful treatment outcome.

The other important finding is that smear positive pulmonary TB patients were more likely to have a successful treatment outcome than other types of TB patients. This result is consistent with previous studies conducted in Ethiopia [26]. This could be explained by the fact that smear positive pulmonary TB patients might be diagnosed easily and started the treatment promptly and may have close follow by health professionals. All TB diagnosed patients were treated at DOTS clinics using regimens recommended by WHO. Two types of treatment category were set CAT-I and CAT-II. Results of the current study show that patients with treatment CAT-I was more likely to have successful treatment outcomes than patients with treatment
Our study also showed that patients who started treatment before 2014 were more likely to have successful treatment outcomes than patients who started treatment in 2014. The finding indicated that successful treatment outcomes were decreased overtime from (87.0%) in 2011 and (94.9%) in 2012 to (73.9%) in 2014. This may be related to the desaturation of health care systems and TB treatment services of country because of the war. It could be also due to increased number of multidrug-resistant tuberculosis (MDR-TB) which is defined as TB that is resistant to the two most powerful first-line TB drugs (i.e. isoniazid and rifampicin). We also found that the overall prevalence of smear positive PTB was high among reported cases, which concurs with previous studies showing that majority of patients taking TB treatment were smear positive PTB [31]. The smear positive PTB patients are dangerous and can easily spread the infection in the community. Early diagnosis and treatment of such cases are very important and necessary to reduce the progression of TB. The overall case fatality rate was (2.72%) which is high from previous published studies [32]. The high rate of mortality among TB patients could be attributed to less access to hospitals, at door step availability of least health diagnostic facilities, no early diagnosis and treatment of the disease, poverty, and poor nutritional status in our society.

This study has several limitations. Firstly, since the study was based on secondary data, some important clinical variables such as HIV, diabetes mellitus, and other co-morbidities as well as behavioral factors such as alcohol drinking and smoking were not available in the registers and therefore were not included in our study.

Secondly, in this study those patients who had documented evidence of completion were counted as having a successful treatment outcome, whereas they may have
undetected failure of therapy. This may lead to overestimation of the treatment outcome rate in our study. Third, as the study used data reported between 2011 and 2014, we have not assessed recent treatment outcomes, and a longer follow-up period will be required to assess longer-term trends in treatment outcomes.

Conclusions

The overall treatment success rate is satisfactory but still need to be improved to achieve the international targeted End TB Strategy milestones. Type of TB, age, treatment category, and year of enrollment were significantly associated with successful treatment outcomes. Successful treatment outcomes were decreased over time which is an alarming signal for MDR-TB.

Abbreviations

TB: Tuberculosis; DHQ: District Head Quarter; AOR: Adjusted Odds Ratio; CI: Confidence Interval; HIV: Human Immunodeficiency Virus; AIDS: Acquired Immunodeficiency Syndrome; DOTS: Directly Observed Treatment Short-Course; WHO: World Health Organization; AFB: Acid Fast Bacilli; PTB: Pulmonary Tuberculosis; EPTB: Extra-pulmonary Tuberculosis; SPSS: Statistical Package for Social Sciences; CAT-I: Category-I; CAT- II: Category-II; COR: Crude Odds Ratio; MDR-TB: Multidrug-resistant Tuberculosis.

Declarations

Acknowledgements

We acknowledge the support of Department of Microbiology, Hazara University Mansehra and DHQ Hospital Batkhela during the current study.
Authors’ contributions
TA: Study design, data collection and extraction, paper writing and analysis; MAJ: Study design and critical review; MK, H: Help in data collection and paper writing; MMK, AH, MW, HJ: Technical assistance and literature search; EE: Help in statistical analysis. MAJ, MK, H, MK, KAA: Critical reviewed and edited the final manuscript. All authors have read and approved the final manuscript for publication.

Funding
This study was supported by Chinese National Natural Fund (81573258), Jiangsu Provincial Six Talent Peak (WSN-002). The funder had no role in study design, data collection, analysis, interpretation of data, and manuscript writing.

Availability of data and materials
The datasets used, generated and/or analyzed in this study are available free of cost from the principal author/corresponding author on reasonable request.

Ethics approval and consent to participate
This study was reviewed and approved by the ethical research committee (Advanced Studies and Research Board) of Hazara University Mansehra, Khyber Pakhtunkhwa Pakistan [No. HU/R&P/ASRB/2015/1995]. The study was conducted in accordance with approval guideline and prior permission was granted by the higher authority of DHQ Hospital Batkhela. To ensure confidentiality of the information collected from TB registration books, name or identification number of TB patient was not included in the data collection sheet.

Consent for publication
Not applicable.

Competing interests
The authors declare that they have no competing interests
Author details

1Department of Epidemiology and Health Statistics, School of Public Health, Southeast University, Nanjing (210009), China

2Key Laboratory of Environmental Medicine Engineering, Ministry of Education, School of Public Health, Southeast University, Nanjing (210009), China

3Department of Microbiology, Hazara University Mansehra (21300), Khyber Pakhtunkhwa, Islamic Republic of Pakistan

4Department of Microbiology, Abbottabad University of Science and Technology Abbottabad, Khyber Pakhtunkhwa, Islamic Republic of Pakistan

5Department of Genetics, Laboratory of Human Genetics, Hazara University Mansehra (21300), Khyber Pakhtunkhwa, Islamic Republic of Pakistan

6College of Life Sciences, Northwest University, Xian (710069), China

7Department of Public Health, University of Haripur, Khyber Pakhtunkhwa, Islamic Republic of Pakistan

8Department of Medical Microbiology, Dalian Medical University, 9 Western Section Lvshun South Road, Lvshunkou District, Dalian, Liaoning, China

9Genome Centre for Molecular Based Diagnostics and Research Centre, Cl-25 Block B Al-Sudais Plaza Abdalian Cooperative Society, Lahore, Islamic Republic of Pakistan

10Department of Medical Laboratory Sciences, College of Health Sciences, Wollega University, Nekemte, Ethiopia

11Modeling of Noncommunicable Diseases Research Center, Department of Epidemiology, School of Public Health, Hamadan University of Medical Sciences, Hamadan, Iran
Faculty of Health Sciences, Curtin University, Perth, Western Australia, Australia

Wesfarmers Centre of Vaccines and Infectious Diseases, Telethon Kids Institute, Perth, Western Australia, Australia

Research School of Population Health, College of Health and Medicine, The Australian National University, Canberra, Australian Capital Territory, Australia

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Figures

Figure 1
Map of study area (highlighted as green)

Supplementary Files
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