PULMONARY TUBERCULOSIS AND RISK FACTORS OF MULTIDRUG-RESISTANT (MDR) AMONG MDR-TB PATIENTS REGISTERED AT LUMBINI ZONAL HOSPITAL

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RECOMMENDATION

This is to recommend that the thesis entitled **"Pulmonary Tuberculosis and Risk Factors of Multidrug-Resistant (MDR) among MDR-TB Patients Registered at Lumbini Zonal Hospital"** has been carried out by Sita Paudel for the partial fulfillment of Master's Degree of Science in Zoology with special paper Parasitology. This is her original work and has been carried out under my supervision. To the best of my knowledge, this thesis work has not been submitted for any other degree in any institutions.

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LETTER OF APPROVAL

On the recommendation of supervisor **" Dr. Mahendra Maharjan"** this thesis submitted by Sita Paudel entitled **"Pulmonary Tuberculosis and Risk Factors of Multidrug-Resistant (MDR) among MDR-TB Patients Registered at Lumbini Zonal Hospital"** is approved for the examination and submitted to the Tribhuvan University in partial fulfillment of the requirements for Master's Degree of Science in Zoology with special paper Parasitology.

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CERTIFICATE OF ACCEPTANCE

This thesis work submitted by Sita Paudel entitled **"Pulmonary Tuberculosis and Risk Factors of Multidrug-Resistant (MDR) among MDR-TB Patients Registered at Lumbini Zonal Hospital"** has been approved as a partial fulfillment for the requirements of Master's Degree of Science in Zoology with special paper Parasitology.

EVALUATION COMMITTEE

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ABSTRACT

Tuberculosis is still a major public health problem in developing countries like Nepal which has turned to a deadly form multidrug-resistant. A case-control study with 50 MDR-PTB patients as cases and 63 drug susceptible pulmonary tuberculosis patient as control was carried out to identify risk factors associated with multidrug-resistant tuberculosis (MDR-TB) at Lumbini Zonal Hospital. Irregularity in taking medicine (OR = 2.36), large family size (OR = 2.40), farming as occupation (OR = 2.83), past history of TB and bovine at home (OR = 6.5) were identified as risk factors. By screening 400 sputum samples from 200 TB suspected patients using Z-N staining method, 24 (12%) cases were found to be AFB positive. Prevalence of PTB in male and female was 14.50% and 7.25% respectively. Similarly, higher infection was found among the people of age group 41-50 years (16%). Most of the PTB patients had lower secondary level educational attainment (19.05%) and had involved in service (18.37%). In a questionnaire survey of same 200 TB suspected patients done to assess their knowledge, attitude and preventive practices for TB, knowledge regarding nature of disease, symptoms, route of transmission and prevention of TB was not adequate.

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LIST OF ABBREVATIONS

AFB	-	Acid-Fast Bacilli
AIDS	-	Acquired Immuno Deficiency Syndrome
BCG	-	Bacillus Calmette Guerin
CDC	-	Center for Disease Control
DoHS	-	Department of Health
DOTS	-	Directly Observed Treatment Short-Course
HERD	-	Health Research and Social Development Forum
HIV	-	Human Immuno-deficiency Virus
INH	-	Isoniazid
IGRAs	-	Interferon Gamma Release Assays
KAP	-	Knowledge Attitude and Practices
MDR-TB	-	Multidrug-Resistant Tuberculosis
NTC	-	National Tuberculosis Center
NTP	-	National Tuberculosis Programme
PCI	-	Project Concern International
PTB	-	Pulmonary Tuberculosis
RMP	-	Rifampicin
SAARC	-	South Asian Association Regional Co-operation
TB	-	Tuberculosis
WHO	-	World Health Organization
XDR-TB	-	Extensively Drug-Resistant Tuberculosis
ZN	-	Ziehl-Neelsen

1. INTRODUCTION

Tuberculosis is a specific infectious disease caused by *Mycobacterium tuberculosis*. The disease primarily affects the lungs and causes pulmonary tuberculosis. It can also affect intestine, meninges, bones, joints, lymph gland, skin and other tissues of the body (Park 2002). Pumonary tuberculosis is a common worldwide infection with medical and social problem causing high mortality and morbidity, especially in developing countries (Jeong 2008). About 9 million cases of active TB are reported annually; however one- third of the world's population are infected with *Mycobacterium tuberculosis* and remains asymptomatic but only 5-10% of these latent individuals develops active TB in their lifetime (Garra et al. 2013). TB incidence is falling at a rate of 2% per year and global TB deaths decreased from 1.4 million in 2011 to 1.3 million deaths in 2012 (WHO 2013).

Multi-drug-resistant tuberculosis (MDR-TB) is defined as tuberculosis that is resistant to at least isoniazid (INH) and rifampicin (RMP), the two most powerful first-line treatment anti-TB drugs. Mostly MDR-TB develops when the course of antibiotics is interrupted and the levels of drug in the body are insufficient to kill 100% of bacteria. This can happen for a number of reasons: patients may feel better and halt their antibiotic course, drug supplies may run out or become scarce, patients may forget to take their medication from time to time or patients do not receive effective therapy (Paul 2001). WHO estimates that 450,000 people were infected with MDR-TB in 2012 (WHO 2013). Drug resistance can be detected using special laboratory tests which test the bacteria for sensitivity to the drugs or detect resistance patterns which can be molecular in type (eg, Xpert MTB/RIF) or else culture-based (WHO 2015). China, India and the Russian Federation have the highest burden of MDR-TB followed by 24 other countries (WHO 2013).

1.1 Route of TB Transmission

When people with active pulmonary TB cough, sneeze, speak, sing or spit, they expel infectious aerosal droplets of 0.5 to 5.0 μm in diameter (Konstantinos 2010). A single sneeze can release up to 40,000 droplets (Cole and Cook, 1998). Each one of these droplets may transmit the disease, since the infectious dose of tuberculosis is very small (Nicas et al. 2005). Healthy people with prolonged, frequent or close contact with TB

patients are particularly at high risk of being infected, with an estimated 22% infection rate (Ahamed and Hasnain 2011). Transmission should occur from only people with active TB but those with latent infection are not thought to be contagious. The probability of transmission from one person to another depends upon several factors, including the number of infectious droplets expelled by the carrier, the effectiveness of ventilation, the duration of exposure, the virulence of the *M. tuberculosis* strain, the level of immunity in the uninfected person and others (Kumar et al. 2007).

1.2 Pathogenesis

TB infection begins when the mycobacteria reach the pulmonary alveoli, where tubercle bacilli are ingested by alveolar macrophages. The majority of tubercle bacilli are destroyed or inhibited but small number of bacilli multiply intracellularly and are released when the macrophages die (Houben et al. 2006). If alive, these bacilli may spread by way of lymphatic channels or through the bloodstream to more distant tissues and organs (including areas of the body in which TB disease is most likely to develop: regional lymph nodes, apex of the lung, kidneys, brain and bone) (ATS 1990).

1.3 Symptoms of pulmonary tuberculosis

Patients with active pulmonary TB may be asymptomatic, have mild or progressive dry cough or present with multiple symptoms, including fever, fatigue, weight loss, chest pain, night sweats and a cough that produces bloody sputum.

1.4 Characteristics of *Mycobacterium tuberculosis*

The *Mycobacterium* responsible for tuberculosis was discovered in 1882 by Robert Koch. *M. tuberculosis* is an acid-fast, non-motile, gram-positive bacteria, measuring about 2-4µm in length and 0.2 - 0.6µm in breadth, has no capsule and spores (Skripkin and Milich 1981). It is an obligate aerobic, thus it can only survive in an oxygen containing environment. The cell envelope is composed of a core of three macromolecules covalently linked to each other (peptidoglycan, arabinogalactan and mycolic acids) and a lipopolysaccharide (lipoarabinomannan), which is thought to be anchored to the plasma membrane (Crick et al. 2001).

These bacteria express unique mycolic acids in the cell envelope that play a critical role in the structure and function of the cell wall (Barry et al. 1998). The waxy cell wall

confers many of the unique characteristics of this genus: acid-fastness, extreme hydrophobicity, resistance to drying, acidity/alkalinity and many antibiotics, as well as distinctive immunostimulatory properties (Daffe and Draper 1998). *M. tuberculosis* is a member of the slow-growing pathogenic mycobacterial species, characterized by a 12 to 24 hour division rate and prolonged culture period on agar of up to 21 days (Harshey and Ramakrishna 1977). *M. tuberculosis* is a member of the M. tuberculosis complex, which is defined as the etiologic agents of TB in distinct hosts and also includes *M. bovis*, *M. africanum, M. canetti,* and *M. microti*, with *M. caprae* and *M. pinnipedii* considered variants of M. bovis (Stead et al. 1995).

1.5 Risk factors of tuberculosis

A number of factors make people more susceptible to TB infections. The most important risk factor globally is HIV; 13% of all people with TB are infected by the virus (WHO 2011). This is a particular problem in sub-Saharan Africa, where rates of HIV are high (Chaisson and Martinson 2008). Tuberculosis is closely linked to both overcrowding and malnutrition, making it one of the principal diseases of poverty (Lawn and Zumla 2011).

Those at high risk thus include: people who inject illicit drugs, inhabitants and employees of locales where vulnerable people gather (e.g. prisons and homeless shelters), medically underprivileged and resource-poor communities, high-risk ethnic minorities, children in close contact with high-risk category patients, and health-care providers serving these patients (Griffith and Kerr 1996). Other disease states can also increase the risk of developing tuberculosis. These include alcoholism (Lawn and Zumla 2011) and diabetes mellitus (Restrepo 2007). Certain medications, such as corticosteroids and infliximab are becoming increasingly important risk factors, especially in the developed world (Lawn and Zumla 2011).

1.6 Vaccine for tuberculosis

Bacillus Calmette – Guerin (BCG) strain have been widely used as prophylactic TB vaccines. BCG vaccines are live attenuated bacterial strains that share a high degree of genetic and genomic homology with *M. tuberculosis* (Behr et al. 1999). BCG has proven to be highly efficacious against severe TB in children, including TB meningitis and milliary TB (Fine 1995).

1.7 Diagnostic method of tuberculosis

1.7.1 Microscopic sputum examination

As TB is mainly transmitted by sputum smear-positive patients, the DOTS strategy strongly promotes smear microscopy for the diagnosis of TB among symptomatic patients, the so-called TB suspects (Trebucq 2004). In high prevalence countries, TB case detection is largely based on microscopic examination of sputum for Acid-Fast Bacilli using Ziehl-Neelsen stain. The staining characteristics of *M. tuberculosis* allow its rapid identification in clinical specimens. The main value of AFB microscopy for diagnosis lies in its speed and extremely high specificity, while the main disadvantage is its low sensitivity (Duen 2001).

1.7.2 Radiological diagnosis

Radiology plays an important role in the diagnosis of pulmonary tuberculosis. Many medical practitioners believe on the chest x-ray for the diagnosis of pulmonary tuberculosis (Kumar et al. 2005). Chest x-ray is used in the diagnosis of milliary tuberculosis, smear negative pulmonary tuberculosis and extra-pulmonary tuberculosis (Chauhan and Arora 2004). There is a rule about radiological investigation in the National Tuberculosis Control protocol that “chest x-ray is used when the sputum samples are negative and the patients have no any sign from a good status after treatment by antibiotics for two weeks (Ayatollahi 2012).

1.7.3 Tuberculin skin testing

The Tuberculin Skin Test (TST) is one of the most common tests to determine if someone has been exposed to and become infected with the TB bacteria. A small amount of tuberculin (purified protein derivative) is injected intradermally and the skin reaction is measured two or three days later at a point of injection (Comstock et al. 1981).

1.7.4 Culture

A culture means that a sputum specimen is placed on some kind of medium (like jelly or both), either in a plate or tube, which favours the growth of TB bacilli (CDC 1995). The medium is then placed in an incubator (at body temperature) for some weeks. Bacteria take up to six weeks or more to grow (Konstantinos 2010).

1.7.5 Interferon gamma release assays

Interferon gamma release assays is one new tool developed to supplement or replace the TST (WHO 2008). Interferon gamma release assays (IGRAs) are blood tests that can aid in diagnosing *M. tuberculosis* infection but IGRAs do not differentiate latent tuberculosis infection from tuberculosis disease (Lange et al. 2009). IGRAs detect cellular immune responses to antigen (Wang et al. 2002) and results can be available within 24 hours (WHO 2008)

1.8 Treatment of tuberculosis (TB)

If TB is detected early and fully treated, people with the disease quickly become non-infectious and eventually cured (WHO 2008). Delays in second line drugs make multi-drug resistant tuberculosis more difficult to treat (Paul 2001). Isoniazid, Rifampicin, Pyrazinamide, Ethambutol and Streptomycin are the first line drugs that generally have the greatest activity against TB bacteria and they are core to any TB drug treatment program (WHO 2010). The unit cost for second line anti TB drugs, is much greater than for first line drugs (WHO 2012). MDR-TB requires longer duration of treatment (up to 2 years) to achieve cure, in comparison with 8 months treatment for drug susceptible TB. MDR-TB has much higher level of mortality than drug susceptible TB, lower cure rates and even higher default rates. The cost of drugs to treat MDR-TB cases can be up to 100 times more than the cost of treating a drug susceptible TB cases (NTC 2013).

1.8.1 First-Line Drugs

Isoniazid

Isoniazid (INH) is a first-line agent for treatment of all forms of tuberculosis caused by *Mycobacteria* organisms. It has profound early bactericidal activity against rapidly dividing cells (Hafner et al. 1997). Because INH is the most commonly used antituberculosis drug, resistance to INH occurs more frequently among clinical isolates than resistance to any other agent (Karakousis 2009).

Rifampin

Rifampin (RIF) is also a first-line drug used for the treatment of all forms of tuberculosis. It has activity against organisms that are dividing rapidly and against semi-dormant bacterial populations, thus accounting for its sterilizing activity (Jindani et al. 1980). Rifampin is an essential component of all short-course regimens (Dickinson and

Mitchison 1981). Rifampin is a broad-spectrum antibiotic and the most widely used rifamycin to treat TB (Mitchison 1985).

Pyrazinamide

Pyrazinamide (PZA) is believed to exert greatest activity against the population of dormant or semidormant organisms contained within macrophages or the acidic environment of caseous foci (Girling 1984). Since the discovery of pyrazinamide (PZA) in 1952 (Yeager et al. 1952) and its routine use to treat TB, the duration of treatment required to achieve acceptable relapse rates has been reduced from 9–12 months to the current 6 months (Steele and Des-Prez 1988). Although its bactericidal activity is inferior to that of INH and rifampin (Jindani et al. 1980), the potent sterilizing activity and treatment-shortening potential of PZA has been attributed to the drug's unique ability to target semi-dormant populations of bacilli residing within an acidic environment (Mitchison 1985).

Ethambutol

Though ethambutol (EMB) is included in the initial treatment regimens, it is generally not recommended for routine use in children whose visual acuity cannot be monitored but if a child has adult-type tuberculosis or disease that is suspected or proven to be caused by organisms that are resistant to either INH or RIF, EMB should be used (Trebucq 1997). Like INH, EMB primarily actively multiplying bacilli and has very poor sterilizing activity (Mikusova et al. 1995)

Streptomycin

Streptomycin is most commonly used first line injectible drug. However, among patients likely to have acquired *M. tuberculosis* in a high-incidence country, the relatively high rate of resistance to SM limits its usefulness (Andrews et al. 1974).

1.8.2 Second line drugs

Fluoroquinolones

Of the fluoroquinolones, mostly levofloxacin, moxifloxacin, and gatifloxacin have the activity against *M. tuberculosis*. Levofloxacin is the preferred oral agent for treating drug-resistant tuberculosis caused by the TB bacilli or presumed to be sensitive when first-line agents cannot be used because of intolerance (WHO 2011). Cross-resistance has been

demonstrated among ciprofloxacin, ofloxacin, and levofloxacin (Sander 1991). Ofloxacin is an essential medicine as a reserve second-line drug for the treatment of MDR-TB (WHO 2011). Fluoroquinolones should not be considered first-line agents for the treatment of drug-susceptible tuberculosis except in patients who are intolerant of first-line drugs (Sander 1991).

1.9 Directly Observed Treatment Short Course (DOTS)

DOTS is a short course of chemotherapy given to tuberculosis patients under the direct supervision of the health workers that involves atleast six months antibiotic regimen. Patients should take TB drugs in front of health care workers making that sure patients have swallowed the drugs. This strategy can cure more than 90% of new smear positive patients and reduces spread of infection by breaking the chain of the transmission (WHO 1999). It has been found effective to cure TB and to prevent multidrug-resistance which prevents relapse and deaths. Countries around the world began applying DOTS in the early 1990s (WHO 1999).

Directly Observed Treatment Short Course (DOTS) based service are available through 1141 treatment centres, 3110 sub-treatment centre in the country, while 533 microscopy centres are providing TB diagnostic services (NTC 2012). DOTS was introduced first time in Nepal in April 1996 after a joint HMG/WHO review and is thus regarded as a cost effective and successful strategy (Bam 2002). NTP has consistently achieved both global targets of TB control including 73% case detection and nearly 90% treatment success rates (NTC 2012).

1.10 Objectives

1.10.1 General objectives

To determine the prevalence of pulmonary tuberculosis and risk factors of multidrug-resistant (MDR) among MDR-TB patients registered at Lumbini Zonal Hospital.

1.10.2 Specific objectives

- To determine the risk factors of MDR-TB.
- To determine the prevalence of pulmonary tuberculosis (PTB) among suspected patients visited at Lumbini Zonal Hospital.
- To assess knowledge, attitude and practices (KAP) of pulmonary tuberculosis suspected patients visited at Lumbini Zonal Hospital.

2. LITERATURE REVIEW

Tuberculosis is one of the most widespread infections in different parts of world and possess a serious threat to the health and development of the people. Pulmonary tuberculosis (TB) is one of the most common communicable and continue to be serious infectious disease in the world. TB is also called Koch's disease. Multidrug-resistant tuberculosis (MDR-TB) is an increasing global problem which arises as a result of several errors such as incomplete treatment, irregular taking of medicine, etc. In most part of the world *M. tuberculosis* has developed resistance against major first-line drugs.

Scenario of MDR-TB in World Context

Resistance against the primary drug of tuberculosis has been increasing globally. Development of the drug-resistance is a complex process which involves various risk factors, particularly interrupted treatment course. The phenomenon is basically due to the longer period of treatment.

In Asian Continent

Multidrug-resistant tuberculosis (MDR-TB) burden has been reported from almost all the Asian countries which are ranked as highest MDR-TB burden region. MDR-TB prevalence in South East Asia was estimated as 2.8% among new cases and 18.8% among previously treated cases (SAARC 2009). Half of the global MDR-TB cases (50%) occurs only in China and India (WHO 2011) which are the highly populated countries. The increasing MDR-TB cases has been reported from most of the Asian countries including Nepal, India, Hongkong, Bangladesh, Bhutan, etc. WHO (2008) has reported 2.8% of MDR-TB in new cases and 17.2% among previously treated cases in India while in Hongkong MDR-TB among new cases ranged from 1% to 7.2% between 2002 and 2007. WHO (2011) has isolated MDR-TB in 1.3% new patients with smear positive TB and 20% among retreatment cases in Bhutan.

The proportion of MDR-TB was significantly higher among the patients who had previously received anti-tuberculosis treatment (Shao et al. 2011, Barman et al. 2014) in

different region of Asia. Other statistically significant risk factors appeared to be non-permanent residents, frequent travel and young age (Flora et al. 2013, Laws et al. 2008). Ahmad et al. (2012) reported that a TB patients in the house or previous history of TB and male younger age with poor educational attainment was strongly associated with MDR-TB in Pakistan. MDR-TB was associated with inadequacy of treatment and patients who did not remain under directly observed treatment (Sharma and Mohan 2004, Amin et al. 2009, NTP 2009). TB contact was the strongest determinants of MDR-TB (Banu et al. 2010, Flora et al. 2013) in Bangladesh.

Chen et al. (2013) found that low family income was significantly associated with MDR-TB in China. According to Baghaei et al. (2013), link of diabetes mellitus and TB is more prominent in the developing countries where TB is endemic and the burden of diabetes mellitus is increasing but significant association between MDR-TB and diabetes was found in a study conducted by Rifat et al. (2014) in Bangladesh. Changing trend of number of family members (Barman et al. 2014), presence of smoking history (Barman et al. 2014, Rifat et al. 2014) and bussiness as occupation (Rifat et al. 2014) were statistically significant risk factors for the development of MDR-TB. In China, Illiteracy or primary level school education, low income and lack of proper diet were associated with the development of MDR-TB (Li et al. 2015).

In a study conducted by Bhatt et al. (2012), in Ahamedabad city, males and females MDR-TB patients were 68.5% and 31.5% respectively with 90% reproductive age group (16-45 years) having maximum literacy rate (86.4%), of which 61.4% had primary education and 65.4% patients were belonging to nuclear family. There was significant association between prior treatment and age < 45 years with MDR-TB in a survey conducted by Farazi et al. (2013) in Iran.

In African Continent

Drug-resistant tuberculosis imposes a tremendous health burden throughout Southern Africa. Several factors may have resulted in an increase of MDR-TB in Africa in recent years. South Africa has the second highest number of diagnosed MDR-TB cases (Churchyard et al. 2014). WHO (2012) estimated that the number of MDR-TB patients in Ethiopia in the year 2012, was below 1% of new and 4% of retreatment cases while 7% of

new TB patients and 12% of previously treated patients had MDR-TB in Ethiopia in 2013 (WHO 2013).

Previous exposure to TB treatment was found to be the most significant risk factor reported in Ethiopia (Hirpa et al. 2013, Biadlegene et al. 2014). Inadequate quality of anti-TB drugs and low drug exposure (WHO 2010, Pasipanodya et al. 2013), exposure to a known TB cases (Diande et al. 2009, FMOH 2012) contribute to the development of drug-resistance tuberculosis. Yimer et al. (2011) and Abebe et al. (2012) reported HIV to be a risk factor for MDR-TB in Ethiopia. Male gender, employment, history of TB contacts and having a positive smear to AFB on admission were concluded as risk factors for developing MDR-TB in a case-control study conducted by Akl and Mahalli (2012) in Egypt.

In South Africa, more females (63.6%) than males (36.4%) were infected with MDR-TB and 64% patients were HIV positive in the study conducted by Ukanwa and Madiba (2013). Lienhardt et al. (2003) demonstrated that as children get older they are more likely to become infected with TB due to increasing duration of exposure to more potential source cases and more interaction with the community in addition to household exposure, in the survey conducted on risk factors for tuberculosis infection in children in contact with infectious tuberculosis cases in the Gambia, West Africa. Amor et al. (2008) indicated that the retreatment failure rate was the most predictive indicator for MDR-TB in Africa.

In European Continent

Emergence of excessive drug-resistant tuberculosis has been a major threat in most of the countries. In 2011, the prevalence of MDR-TB was 13.2% among new cases and 46.4% among previously treated cases, in the European region (WHO 2013). The high proportion of new cases and drug resistant TB suggest an increased role of ongoing transmission in the community (Skrahin et al. 2013). The overall drug resistance ranged from 0% (Iceland), 1.4% in Bosnia and Herzegovina to 49.2% in Georgia, 51.2% in Tashkent, Uzbekistan and 56.3% in Baku City, Azerbaijan, respectively (WHO 2008).

Migration from high MDR-TB prevalence countries (Sotgiu et al. 2009, Van-Zyl-Smit et al. 2009), previous treatment for TB (Espinal 2001, Suarez et al. 2009), alcoholism (Antunes et al. 2000, Skrahina et al. 2013) and diabetes (Torres et al. 2000) had been

identified as the strongest risk factors for MDR-TB in Europe. According to Faustini et al. (2006) the risk of MDR-TB was found to be statistically co-related with younger than 65 years, HIV positive patients and male gender in Europe but female gender was significantly associated with MDR-TB development in the study conducted by Mdivani et al. (2008) and Lomtadze et al. (2009) in Georgia.

The most significant risk factors identified in European continent includes previous tuberculosis with pulmonary location, prison, known tuberculosis contact, health care worker and acquired immunodeficiency syndrome in a case-control study conducted by Casal et al. (2005) in four European countries: France, Germany, Italy and Spain. Arevalo et al. (1996) demonstrated that hepatic cirrhosis and age 45 yrs and older were considered as risk factors associated with drug-resistant tuberculosis. MDR-TB is associated with poor treatment outcomes (Grzybowski and Enarson 1978, WHO 2006, WHO 2013). According to Antunes et al. (2003) in Portugal, social factors such as poverty and homelessness induces treatment failure and fascililates the emergence of MDR-TB.

According to Vander-Werf et al. (2012), risk factors include close contact to a patient with MDR-TB, migration, HIV infection and young age. In Lithuania, TB contact and previous imprisonment showed an increased risk for XDR-TB in patients with MDR-TB (Balabanova et al. 2012). Skrahina et al. (2013) in Belarus demonstrated that smokers were statistically associated with MDR-TB. Although previous treatment for TB and contact with persons infected with drug-resistant strains had been reported as strong risk factors for MDR-TB, the role of HIV infection, young age, sex and previous imprisonment were less clear in the study conducted by Lange et al. (2014) and Kliiman et al. (2009) in Europe.

In American Continent

The percentage of MDR TB cases increased slightly from 1.2% (86 cases) in 2012 to 1.4% (95 cases) in 2013 (CDC 2013). In Brazil, there were an estimated 1,056 patients of MDR-TB in 2007 (WHO 2009). Moonan et al. (2013) reported 168 cases of MDR-TB in USA from January 2007 to December 2008 and concluded that many individuals acquire MDR-TB before entry into the USA. Argentina showed a slight but not statistically significant increase in MDR-TB among new patients from 1.8% in 1999 to 2.2% in 2005 (Migliori et al. 2009). MDR-TB has increased in USA from 2.4% in 1996 to 5.3% in 2006 (WHO 2008).

The factors significantly associated to MDR-TB occurrence were lack of sanitary infra-structure (sewer system) at home, alcoholism + smoking, number of previous treatments, irregular treatments and lung cavities in USA (Barroso et al. 2003, Kritski 2003). Among patients with a history of previous tuberculosis, being 19 years or younger was the only factor associated with multiple drug-resistance but female sex, being 20 to 39 years of age and foreign birth were risk factors for resistance among patients with no history of previous tuberculosis along the Mexico-Texas border (Taylor and Suarez 2000).

In Australian Continent

Tuberculosis is not a major problem in Australia. Tuberculosis (TB) is estimated to infect a third of the world's population but the possibility of TB as a diagnosis may be forgotten in Australia where the overall incidence is low; about 1,000 cases are diagnosed nationally each year and the incidence is 5-6 per 100,000 population (Barry and Konstantinos 2009). In Australia, 2 to 3% of cases are resistant to at least isoniazid and rifampicin (Lumb et al. 2011). The rate of TB notifications has remained relatively stable since 1986 and in 2009, there were 1,322 cases (6.0 per 100,000 population) of TB reported in Australia (Barry et al. 2012). Almost 40% of Australian notifications in 2007 were extra-pulmonary infections (Barry and Konstantinos 2009).

Scenario of MDR-TB in National context

Multidrug-resistant tuberculosis has been raisen in the alarming rate in the recent years in Nepal. Multi Drug Resistance prevalence was 1.0% in 1999, 1.3% in 2001 and 2.9% in 2006 among new cases (NTP 2011). Drug-resistance in new TB cases has not increased but remained stable at a low level (1.3%) in the recent years (NTC 2013). In 2009, with WHO support National TB Center conducted surveillance of XDR-TB among the registered MDR-TB patients and the study showed a prevalence of 5% of XDR-TB cases among MDR-TB cases registered.

Poor housing, overcrowding and homelessness were associated with MDR-TB in Terai region of Nepal (DoHS 2008). In a study conducted by Marahatta et al. (2010) with 55 MDR patients as case and 55 non-MDR-TB patients as control among the patients attending National Tuberculosis Centre, Bhaktapur, significant association was found between history of prior TB, smoking habit, knowledge on MDR-TB and knowledge on DOTS Plus with the development of MDR-TB. According to HERD (2012), low wealth

category, smoking habit, alcohol consumption, past history of TB and travel outside the country were stastistically associated with the development of MDR-TB and the highest proportion of respondents (62% cases and 55% controls) were in the productive age group (20-40 years) and greater than half of respondents were males in Nepal. Previous TB treatment, male sex, poverty, migration to India, Illiteracy and smoking habit also had been observed in a majority of MDR-TB patients in the study conducted by Pant et al. (2009) in Bhairahawa.

Scenario of Pulmonary TB in World Context

Tuberculosis (TB) is a leading public health problem particularly in the developing countries. There were about 9 million new cases of tuberculosis with 1.4 million deaths recorded worldwide in 2011 (WHO 2012) while mortality rate due to tuberculosis has been slightly decreased (1.3 million deaths) in 2012 (Glaziou et al. 2015).

In Asian Continent

South Asian Association for Regional co-operation (SAARC) region bears 22% of the global population with 29% of the global burden of tuberculosis and it is estimated that SAARC region has 2.5 million new cases and 0.6 million death per year due to tuberculosis (SAARC 2003). The increase in the incidence of tuberculosis was more predominant amongst the socio-economically deprived population (Noridah et al. 2003). In 2001, tuberculosis was the second most commonly notified communicable disease in Malaysia (Dony et al. 2004). The prevalence of PTB was 3.9% among the inmates in Pakistan (Shah et al. 2003).

The overall prevalence of pulmonary tuberculosis was significantly higher among male patients (Bhat et al. 2009, Iqbal et al. 2011, Rao et al. 2012). Males were greater sensitive to TB (Jetan et al. 2010, Myneedu et al. 2011, Afroz et al. 2012) and people in the urban areas were affected more (Maiti et al. 2010). About 48% of foreign born single males and 71% of married females had a greater percentage of tuberculosis infection in Malaysia (Nissapatorn et al. 2005). Bhat et al. (2009) in Madhya Pradesh had concluded that the prevalence of tuberculosis had increased with age. Nayak et al. (2013) in a tertiary care institute in Ahmadabad diagnosed 13.17% of the patients as PTB positive by Ziehl-Neelsen staining with maximum numbers of TB patients (40.91%) from age group 25-34

years followed by age group 35-49 years (36.36%). Similarly, in the study conducted by Afroz et al. (2012) in Bangladesh the working youth group (25-34 years) and older people (above 64) were found most vulnerable to PTB infection.

In India, Sarin et al. (2001) diagnosed 92.2% and 24.9% sputum positive patients out of 3,738 and 4,189 new chest symptomatic from the year 1998 and 1999 respectively. Myneedu et al. (2011) collected sputum samples from 330 TB suspected patients from New Delhi and were stained by Ziehl-Neelsen stain, which showed 18.48% smear positivity. In a cross-sectional survey conducted by Rao et al. (2012), overall prevalence of PTB was found to be 255.3 per 100,000 population in Central India. Among 3,355 household contact, 9.27% had PTB, among which 46 were asymptomatic in China (Jia et al. 2014).

The overall prevalence of latent tuberculosis infection among health care workers was 10.6% in Malaysia (Rafiza et al. 2011). Lisha et al. (2012) conducted a study on morbidity and mortality at five years after initiating category I treatment among 224 patients with new sputum smear positive pulmonary tuberculosis and found that 81% of patients were male, smoking and alcoholism were prevalent in 136 patients (61%), treatment success rate at six months was 94.2% and at the end of five years, 124 patients (57.9%) were symptomatic, relapse in 10 patients (4.5%) and mortality in 12 (5.4%) patients was found.

Nearly 52% of tuberculosis cases had secondary education in a survey conducted by Narwani and Naing (2004) in Kota Bharu Hospital, Kelantan. Age, sex, occupation, tobacco use, perceived health status and discrimination due to tuberculosis positive status were significantly associated with alcohol use and concluded that high prevalence of alcoholism was found among tuberculosis patients in India (Thapa et al. 2014).

In African Continent

South Africa was listed eighth amongst the 22 high tuberculosis burden countries in the world in 1997, with an estimated incidence rate of 392 per 100,000 population (Dye et al. 1999). South Africa has the highest estimated incidence and prevalence of TB (Churchyard et al. 2014). In 2003, South Africa had an estimated incidence of 218 new smear positive tuberculosis cases per 100,000 population (WHO 2005). There were more

than 500,000 cases of active TB in South Africa, of whom an estimated 330,000 cases also had HIV infection in 2011 (WHO 2011). Africa carried the greatest proportion of new cases per population with 280 cases per 100,000 population (WHO 2013).

The number of female TB cases were higher than males within the age group 0-14 years in the survey conducted by Dim and Dim (2013) in Nigeria. Male patients within the age group of 21- 40 years had statistically significant ($P<0.05$) higher proportion of tuberculosis in humans with mean prevalence of 12.9% in Southeast Nigeria (Nwanta et al. 2011). The prevalence of smear positive pulmonary tuberculosis was high (14.2%) and statistical association was observed between age, family size, history of contact with chronic coughers, smoking habit and alcoholism with pulmonary tuberculosis in eastern Ethiopia (Yohanes et al. 2012).

Okutan et al. (2003) reported positive smear in 61% and positive cultures in 31% of gastric lavage specimens obtained from patients with suspected TB who were unable to provide specimen. El-Sony et al. (2003) reported 963 as TB cases in Sudan from March 1998 to March 1999, out of which 763 were pulmonary cases and 166 were extra-pulmonary cases. Out of 4,762 recorded new cases among outpatients attendes presenting to the Tamale Teaching Hospital in the Northern Region of Ghana, 620 were sputum smear positive yielding positivity rate 13% and the positivity rate on a year basis was 15.7% (2004), 15.8% (2005), 13.4% (2006), 12.7% (2007), 20.6% (2008), 10% (2009) and 6.3% (2010%) (Acquah et al. 2012).

Amare et al. (2013) collected sputum samples from 225 TB suspected diabetic patients from Ethiopia and the prevalence of smear positive PTB was found to be 6.2% in TB suspected diabetic patients and concluded that patients with a previous history of contact with TB patients, as well as those who had prolonged diabetes were more prone to have PTB. Higher prevalence of smear positive pulmonary tuberculosis was reported from the survey conducted by Tulu et al. (2014) in South East Ethiopia. The prevalence of smear positive pulmonary TB among patients with cough lasting 2 or more weeks was significantly higher as compared to those patients with cough lasting less than 2 weeks (Eliso et al. 2015).

In European Continent

Fifteen of the 27 high MDR-TB burden countries worldwide are in the European Region (WHO 2015). WHO (2007) reported that European Region constitutes less than 10% of worldwide TB notifications. Notification rates of TB in the European region had been increased from 74.4 cases/100,000 population in 1997 to 104/100,000 population in 2004 (Walls and Shingadia 2007). In 2003, EU countries reported 62,743 tuberculosis cases, of these, 76% were previously untreated and 30% were foreigners (Falzon and Belghiti 2007). Tuberculosis notification rates in the European Union had been declining at a mean annual rate of 4.4% since 2006 and in 2010 there were 73,996 TB cases (WHO 2012). About 510,000 TB cases were notified in 2012 (WHO 2013). In 2011, 89,877 new TB cases and 3,129 previously treated TB cases were identified (WHO 2011).

The resurgence of TB mortality in Eastern European countries during 1990 was explained by the major political, economic and social disruption associated with the breakup of the Soviet Union 1991 and related failures in TB control and provision of health care (Shilova and Dye 2001). Sex workers, alcoholism and previous TB were potentially affecting the period of sputum conversion but not statistically significant in the study conducted by Dominguez-Castellano et al. (2003) in Spain.

In American Continent

Lifson et al. (1999) stated that the risk of TB was greater in areas of residence characterized by crowding, poverty and lower education. A total of 9,582 TB cases were reported in the United States in 2013 and a total of 65% of reported TB cases occurred among foreign born persons (CDC 2014). In 2014, a total of 9,412 new tuberculosis cases were reported in the United States, with an incidence rate of 3 cases per 100,000 persons , a decrease of 2.2% from 2013 (CDC 2015). Enarson et al. (1979) reported that morbidity rates were highest among persons born in Asia and lowest among those born in Europe and the United States. In 2012, the reported number of TB cases (9,945) and case rate (3.2 cases per 100,000) both decreased; these represented declines of 5.4% and 5.9% respectively, as compared to 2011 (CDC 2013). A total of 25.5% of persons had been previously diagnosed as having TB and only 13.2% had prescribed treatment (Bennet et al. 2008).

In Australian Continent

Annual risk of TB infection was 3.1% for continuously detained prisoners (Levy et al. 2007). In 2011, almost 1,385 tuberculosis cases were notified representing a rate of 6.2 cases per 100,000 population and the incidence in the Australian born Indigenous population was 7.5 per 100,000 population which was 11 times the incidence in the Australian born non-Indigenous population of 0.7 per 100,000 population in 2010 (Bareja et al. 2014). Tuberculosis cases were 5.8 per 100,000 population in 2012 and 5.5 per 100,000 population in 2013 (Tom et al. 2015).

Scenario of Pulmonary TB in National context

Tuberculosis is a major public health problem in Nepal. Nepal is among the poor developing countries in SAARC region with population of 23 million and it gets 201 tuberculosis cases per 100,000 populations of which 90/100,000 are smear positive tuberculosis (SAARC 2003). Almost 45% of total population are infected with TB, 40,000 people get TB every year with 20,000 new sputum positive cases and 5000-7000 people die each year from TB (NTC 2013).

Smith (1994), Joshi et al. (2005), Sharma (2008), Amgain et al. (2013) found the higher prevalence of TB infection in males than in females. Highest prevalence of TB was found among age group of 20-30 years (Dhungana 2002, Joshi et al. 2005, Sharma 2008) but Amgain et al. (2013) reported the highest prevalence of TB infection (36.89%) among age group 30-40 years in Chitwan. Sharma (2008) revealed 4.14% AFB positive cases in Gorkha but prevalence rate of pulmonary tuberculosis was found to be 9% in the study conducted by Amgain et al. (2013) in Chitwan. A study done by Verma et al. (2012) on prevalence of pulmonary tuberculosis among HIV infected persons in Pokhara found prevalence of tuberculosis to be 5.97%.

Tiwari et al. (2012) found higher prevalence of tuberculosis (32.4%) among HIV infected people and concluded that the participants with tuberculosis were significantly more likely to have lower CD4 counts, diarrhoea and parasitic infections in Kathmandu. Prevalence of pulmonary tuberculosis among 242 HIV positive patients attending HIV clinics of Sunsari, Morang and Jhapa district of Eastern Nepal was found to be 27.3% (Yadav et al. 2011). The isolation rate for extra-pulmonary samples was three fold higher in culture in comparison to AFB Smear and the confirmation rate of extra-pulmonary

tuberculosis was approximately 1/8th of the pulmonary tuberculosis by conventional bacteriological diagnostic methods (Rijal et al. 2004).

Knowledge, Attitude and Practices (KAP) of Pulmonary TB in World Context

Drug-resistant tuberculosis has been increasing in the alarming rate in the recent years, although every TB burden countries in the world have launched TB control projects such as DOTS. Most of the TB cases have been reported from Asian region (India and China). Lack of proper knowledge on causative agent, route of transmission, symptoms, preventive and control measures might be the reasons for higher TB burden. Knowledge, attitude and perceptions of the health care workers as well as individuals about tuberculosis play an important role in the reduction of burden of tuberculosis in the world. Several KAP surveys have identified knowledge gaps, cultural beliefs or behavioural patterns that facilitate understanding and action as well as create barriers for TB control efforts.

In Asian Continent

Due to several socio-economic factors and lack of knowledge on TB, individual in Asia are more prone to PTB infection. As a result, one-third of the world's burden of tuberculosis (TB), or about 4.9 million prevalent cases are found in the South-East Asia Region (WHO 2009). Higher prevalence of TB in the Asian region might be due to insufficient awareness about disease. The average knowledge of migrants regarding tuberculosis was low among 509 labour migrants in Tajikistan (Glipin et al. 2011). In a survey conducted by Christina et al. (2009) among treatment partners of pediatric patients seen at the OPD of Tarlac Provincial Hospital, Tarlic city, 57% scored "good" in their overall knowledge on TB. According to Paul et al. (2015), more than half (53%) of the key community members (KCMs) had good knowledge regarding TB in Bangladesh.

Only 1.6% of sand stone quarry workers in Jodhpur knew that tuberculosis was caused by germs (Yadav et al. 2006). Nearly 48% were aware of correct etiology i.e. infective organism in India (Khali et al. 2011). Correct answer on cause (infection) was responded by 16.81% of general patients of Tertiary Care Hospital of Bengal in the study conducted by Das et al. (2012). Most of the University students of Malaysia were not sure about the main cause of TB (Mokhtar et al. 2012).

Majority of the key community members (KCMs) were aware about the transmission pathways of TB and believed that smoking and addiction were the prime causes of transmission of TB in Bangladesh (Paul et al. 2015). According to Khali et al. (2011), in India 96.6% were aware about the transmission of PTB but only 31.47% of general patients gave correct response on mode of spread of TB (Das et al 2012). The study conducted by Glipin et al. (2011) among 509 labour migrants in Tajikistan showed that misconceptions were frequent. About 45% of sand stone quarry workers had misconception that TB was a hereditary disease (Yadav et al. 2006).

According to Khali et al. (2011), in India majority of the pulmonary TB patient (80.7%) were aware of symptoms of tuberculosis. About 62.07% correctly answered that cough was the commonest symptom (Das et al. 2012). In the study conducted by Mokhtar et al. (2012), 78% of University students of Malaysia gave the correct answer about the mechanism of the spread of TB (i.e. cough)

The treatment of TB in Kerala was initiated through DOTS but majority of the people who were infected for the first time were not aware about the DOTS (Sukumaran et al. 2002). Nearly 7% of sand stone quarry workers in Jodhpur knew about the need of treatment (DOTS) for 6-8 months (Yadav et al. 2006). According to Khali et al. (2011) majority of PTB patients in India (95.5%) believed that tuberculosis is curable and (6 – 9 month) duration was correctly known to only 32.9% of patients. Almost 90% of general patients of Bengal knew about curability of the disease in the study conducted by Das et al. (2012).

Only 0.8% of sand stone quarry workers in Jodhpur knew about the use of BCG vaccine for the prevention of tuberculosis (Yadav et al. 2006) but 9.1% of PTB patients were aware about BCG vaccination as mode of prevention for tuberculosis in India (Khali et al. 2011). In the survey conducted by Christina et al. (2009) in Tarlic city, 61% of the treatment partners of pediatric patients had acceptable practices and attitude towards the disease. Nearly 73% of sand stone quarry workers in Jodhpur opined to isolate TB patients from the family and 80.6% opined to avoid sharing food with these patients (Yadav et al. 2006). Isolation of patient (8.62%) and avoidance of sharing of food (6.03%) were reported as preventive measures in the study conducted by Das et al. (2012) in Bengal.

In African Continent

According to Bati et al. (2013), 58% of community people of Itang district of Southwest Ethiopia had good level of knowledge about TB (Bati et al. 2013). Among 614 household heads of Ethiopia interviewed by Kura et al. (2010), 31.0% of the respondents knew that TB is caused by germs. Almost 25% of the HIV patients of Addis Ababa, Ethiopia reported that bacteria/germ causes TB (Abebel and Demissie 2012). In sudan, 19.6% of TB patients had knowledge on cause of TB (Kenyi et al. 2014) but only 3.3% of community people of Itang district of Southwest Ethiopia, mentioned bacteria/germ as a cause of pulmonary TB (Bati et al. 2013).

Out of the 636 HIV patients of Addis Ababa, Ethiopia, majority of the patients (95.4%) knew that TB is infectious disease and 91.2% knew that it has aerosol transmission. According to Esmael et al. (2013), among PTB suspected patient and retreatment cases in DOTS in Ethiopia, inhaled droplets through coughing and sneezing were recognized as the common source of TB infection (79.9%). Agho et al. (2014) reported that in Nigeria 63.1% of the nationally representative sample of household believed that TB spreads from person to person through the air by coughing or sneezing. Among 102 TB patients interviewed in Sudan, knowledge on correct means of TB transmission was 80% i.e. coughing (Kenyi et al. 2014).

In a community-based cross-sectional survey conducted by Legesse et al. (2010) involving randomly selected healthy individuals in pastoral communities of Afar region, Ethiopia, majority of the interviewers (74.3%) reported that persistent cough as the main symptom of PTB. Productive cough, cough for longer than two weeks, weight loss were highly mentioned as symptoms/signs of TB by 65.3%, 52.2% and 39.0% of HIV patients of Addis Ababa, Ethiopia respectively (Abebel and Demissie 2012). According to Esmael et al. (2013), the most commonly recognized symptoms of TB mentioned by the PTB suspected patient and retreatment cases in DOTS in Ethiopia was coughing (65.6%) but only 9.9% of community people of Itang district of Southwest Ethiopia mentioned cough for at least two weeks as the sign of TB (Bati et al. 2013). According to Kenyi et al. (2014) 52.0% of TB patients in Sudan were knowledgeable about correct symptoms of TB.

The majority of the TB patients in Namibia, Africa (78.2%) had a high level of knowledge on prevention (Musasa 2011). Nearly 15% of household heads mentioned that ventilating the living room as a means to prevent TB (Kura et al. 2010) but about 40% of healthy individuals in pastoral communities of Afar region mentioned ventilation as a method of prevention of TB (Abebel and Demissie 2012). According to Esmael et al. (2013), among PTB suspected patient and retreatment cases in DOTS in Ethiopia, 66% respondents considered covering their mouth and nose as the most commonly used method for preventing the spread and transmission of TB. Out of 422 community people of Itang district of Southwest Ethiopia, 45.9% had good practices (Bati et al. 2013).

Esmael et al. (2013) and Agho et al. (2014) reported that in Ethiopia and Nigeria 80% of the respondents believed that TB can be cured. According to Kenyi et al. (2014), 94% of the respondents believed that TB disease is curable. Most of the HIV patients of Addis Ababa, Ethiopia (95.4%) said that TB is curable disease (Abebel and Demissie 2012). Out of 422 community people of Itang district of Southwest Ethiopia, 40.8% had favourable attitude towards TB (Bati et al. 2013).

In European Continent

Most of the immigrants of Somalian ethnic origin in London were aware of the infectious nature of TB (Shetty et al. 2004). According to Nikovaska et al. (2014), 93.5% of the general population in Macedonia were aware that TB is contagious disease, nearly 50% of the population had correctly identified blood in sputum and coughing more than three weeks as possible symptoms for TB, only 49.8% of the respondents knew that TB can be spread through air when a person with TB coughs or sneezes, only 37.3% of the respondents knew that TB is vaccine preventable disease and 89.3% knew that TB is curable.

In American and Australian Continent

According to PCI (2010), 82.1% of the general public in Mexico stated that coughing as a symptom, 87.8% mentioned that a patients that coughs or sneezes can be an agent of transmission, 91.2% and 86.3% of the respondents believed that covering the nose and mouth when sneezing and getting immunized can avoid contracting TB respectively. A higher proportion of prison workers (63.5%) than public health workers (29.8%) in Brazil

had received information about TB (Junior et al. 2013). No surveyed was done on KAP relating to pulmonary tuberculosis in Australia.

Scenario of Knowledge, Attitude and Practices (KAP) of Pulmonary TB in National context

A KAP survey gathers information about what respondents know about TB, what they think about people with TB and perform several actions related to TB. Only 17.5% of DOTS patients in Chitwan were known about the causative organism of TB (Amgain et al. 2014). Among community people, people living with TB and family members of TB infected people from 10 districts representing all five developments and three ecological regions, only 20% of community people, TB infected people and their family members knew about main causative agent of TB (HERD 2011).

Most of the respondents had proper knowledge on curability of disease (Bhatt et al. 2010 and Yadav et al. 2012). About 60% of local people were well known about TB transmission (HERD 2011). In a survey conducted by Tiwary (2008), 37.51% of local people in Dhanusa knew that TB transmits through cough and direct contact with patients (18.75%). According to Joshi (2004), 75.86% of the DOTS patients visiting Patan Hospital knew that TB is an infectious disease.

Regarding the symptoms of TB, 25.49% of the DOTS patients (Joshi 2004) and 66% of local people (HERD 2011) stated coughing as a major symptom. According to Yadav et al. (2012), in Eastern Nepal 85% of HIV/AIDS patients were aware that cough for more than 2 weeks was suggestive symptom of TB and 84% knew of haemoptysis. Blood in sputum (80.7%) was reported as the most common symptoms of TB in the study conducted by Amgain et al. (2014) in Chitwan district among the patients of Pulmonary TB undergoing treatment with DOTS therapy including those who had completed the treatment.

Majority of the respondents had positive attitude towards the TB prevention and control in the study conducted by Amgain et al. (2014) in Chitwan district. According to Bhatt et al. (2010), 82% of the TB patients were found to be conscious about duration of treatment. Most of the participants (68.4%) had strongly agreed that DOTS is an effective treatment and the treatment should not be discontinued during the course of treatment

(Amgain et al. 2014). In the survey conducted by Yadav et al. (2012) in Eastern Nepal, majority of the respondents had good knowledge on DOTS.

3. MATERIALS AND METHODS

3.1 Study area

The study was carried out at DOTS Plus Clinic of Lumbini Zonal Hospital which lies in Butwal, Rupandehi from March-September 2014. Butwal is a small city of about eight thousand hector square in area, situated on the low-altitude land (Terai) near the border side to India. It is situated at the latitude of 2741'60.000"N and longitude of 8327'0.000"E.

3.2 Materials

3.2.1 Apparatus Required

Microscope	Spirit lamp
Disposable containers	Slide stand
Forceps	Iron rod
Glass slides	Cotton
Marker	Slide box
Diamond pencil	Staining pan or rack
Bamboo sticks	Laboratory register book

3.2.2 Chemical Required

Carbolfuchsin	0.1% Methylene Blue Solution
20% Acid alcohol	Immersion oil
Distilled water	

3.3 Study design

The study was divided into three phases to fulfil the objectives.

(i) Case-control study among the MDR and drug susceptible patients to determine the risk factors associated with MDR-TB.

(ii) General screening of TB suspected patients visiting DOTS Plus Clinic to determine the prevalence of PTB.

(iii) Questionnaire survey to assess the knowledge, Attitude and Preventive Practices (KAP) of the TB suspected patients towards TB.

3.3.1 Case-control study to determine risk factors associated with MDR-TB

Selection of cases

Altogether 61 multidrug-resistant (MDR-TB) patients were registered in the DOTS Plus Clinic of Lumbini Zonal Hospital in the fiscal year 2014/2015. But, only 50 MDR-TB patients were selected as cases for the study by observing the hospital record.

Selection of controls

Age and sex matched 63 drug susceptible pulmonary tuberculosis (PTB) patients undergoing DOTS Plus Clinic for the treatment were selected as controls. In case of dissimilar ages of cases and controls, sex was firstly matched and 2 or more than 2 controls were selected for single case.

Inclusion and exclusion criteria

Only the pulmonary MDR-TB patients from Lumbini zone registered at Lumbini Zonal Hospital were included in the study as cases. Patients unwilling to participate in the study, extra-pulmonary patients and patients not turning up at the hospital during the study period were excluded. Some patients of Gandaki Zone registered in the DOTS Plus Clinic of Lumbini Zonal Hospital were excluded.

Major variables assessment

Multiple variables under demographic factors, TB contact, previous treatment status, income, knowledge on DOTS, family size, number of rooms and presence of bovine at home were studied as major variables assessment.

Questionnaire pre-testing, testing and application

An structured questionnaire was firstly pre-tested among the colleagues and was modified where the patients felt uneasy to answer the questions. It also was again tested among the

pulmonary tuberculosis patients (those are not included in the final questionnaire) and modification was done. Finally, questionnaire was applied to the study population.

Data collection, analysis and Interpretation

Data collection was done through structured interviews with the patients during visits to the DOTS Plus Clinic. After data collection, data were checked for the completeness. Statistical Package for Social Sciences (SPSS) version 21 for windows was used to analyze the data. Then, the association between categorical variable was assessed by chi-square ($\chi 2$) test (Marahatta et al. 2010). A result was considered significant at a P value < 0.05. Odd ratio (OR) were calculated to evaluate the magnitude of association between risk factors and MDR-TB (Marahatta et al. 2010).

3.3.2 General screening of TB suspected patients

TB suspected patients with the clinical history of two or more weeks continuous cough, haemoptysis, fever and marked weight loss visiting Lumbini Zonal Hospital were included in this study. Sputum samples of two consecutive days were collected from 200 TB suspected patients. The samples were examined for Acid Fast Bacilli (AFB) after staining by Z-N method in the laboratory of Lumbini Zonal Hospital. TB was diagnosed by the microscopic examination of acid-fast bacilli.

Sample collection

The patients were asked to submit sputum samples of two consecutive days i.e. spot and morning samples. During the collection of sputum samples, patients were instructed to inhale deeply 2-3 times and coughed up deeply from the chest and spit closer to mouth. It was made sure that the collected sample is of good quality i.e. thick, purulent and avoid of saliva. About 5ml of sputum sample was collected in disposable container.

Laboratory Examination of Sputum

Decontamination of sputum sample

1. Sputum samples were transferred into a centrifuge tube and equal volume of NAOH was added.
2. Samples were centrifuged after tightening of cap.
3. Tube was filled to within 2 cm of the top with phosphate buffer and was again centrifuged for about 15 minutes.
4. Supernatant was poured off into a discard container containing 5% phenol.

Smear preparation and fixation

1. Disposable container was opened carefully.
2. A small portion of sputum was separated from the container with the help of bamboo stick and transferred to the slide where the sputum specimen number were written.
3. It was spread to a size of about 1×2cm.
4. Smear was dried at room temperature.
5. It was fixed by passing through the flame 2-3 times.

Staining of fixed smears by Ziehl-Neelsen (Z-N) method

1. The fixed slides were placed on the staining bridges.
2. The smear was flooded with Carbolfuchsin stain and heated from below with spirit cotton until the vapour just begins to rise. It was noted that, carbolfuchsin was not allowed to boil.
3. Heated Carbolfuchsin was allowed to remain on the slide for about 10 minutes.
4. The smear was covered with 20% sulphuric acid solutions for about 5 minutes or until the smear was sufficiently decolorized.
5. Smear was covered with 0.1% methylene blue solution for about 2 minutes.
6. The smear was washed off by tap water and tipped to drain off the water.
7. Backside of the slide was wiped out by cotton and placed at the draining rack.

Observation of stained smear

Immersion oil was put on the smear and examined by magnifying to thousand times. The interpretation of the AFB stain of microscopic examination was done according to WHO protocol.

3.3.3 Questionnaire survey to assess KAP towards TB

An structured questionnaire based on knowledge, Attitude and Preventive Practices (KAP) on tuberculosis were prepared and face to face interview was performed among 200 TB suspected patients whose sputum samples were taken for the screening. Details about knowledge on tuberculosis like parts of the body affected by TB bacilli, mode of transmission, clinical symptoms and nature of disease were included in the questionnaire. The questionnaire also contained knowledge of the participant on preventive method of tuberculosis transmission and also attitude of respondents on TB.

Photo Plates

Photo No 1. Sputum sample collection

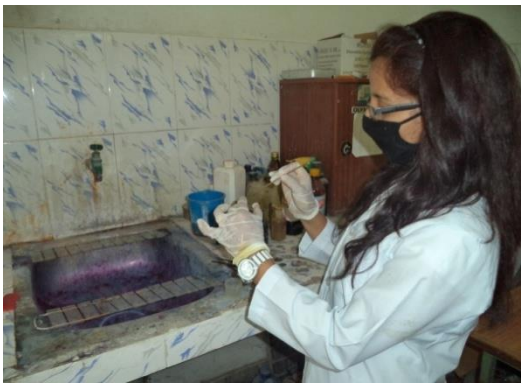

Photo No 2. Sputum smear preparation

Photo No 3. Staining and fixing smear

Photo No 4. Decolarization

Photo No 5. Restaining

Photo No 6. Drying of smear

Photo No 7. Microscopic observation

Photo No 8. Questionnaire with TB patient

Photo No 9. Questionnaire with TB suspected patient

4. RESULTS

4.1 Distribution of MDR-TB patients and associated risk factors

A total of 61 MDR-TB patients were recorded at DOTS Plus clinic of Lumbini Zonal Hospital. Among them, 50 patients were involved in the present study. Along with the designed case-control study to identify the possible risk factors of MDR-TB, information related to HIV co-infection, diabetic status and frequency of relapsed cases were collected.

4.1.1 Age and sex wise distribution of MDR-TB patients in Lumbini Zone

Out of 50 MDR-TB patients, highest percentage of MDR-TB (40%) were found within the age group 21-30 years followed by the age group 41-50 years (20%) and 31-40 years with 18% while rest of the age groups of PTB patients had developed comparatively less MDR-TB (6 to 8%) (fig.1). Among 50 MDR-TB patients, 41 (82%) were male and 9 (18%) were female (fig.2).

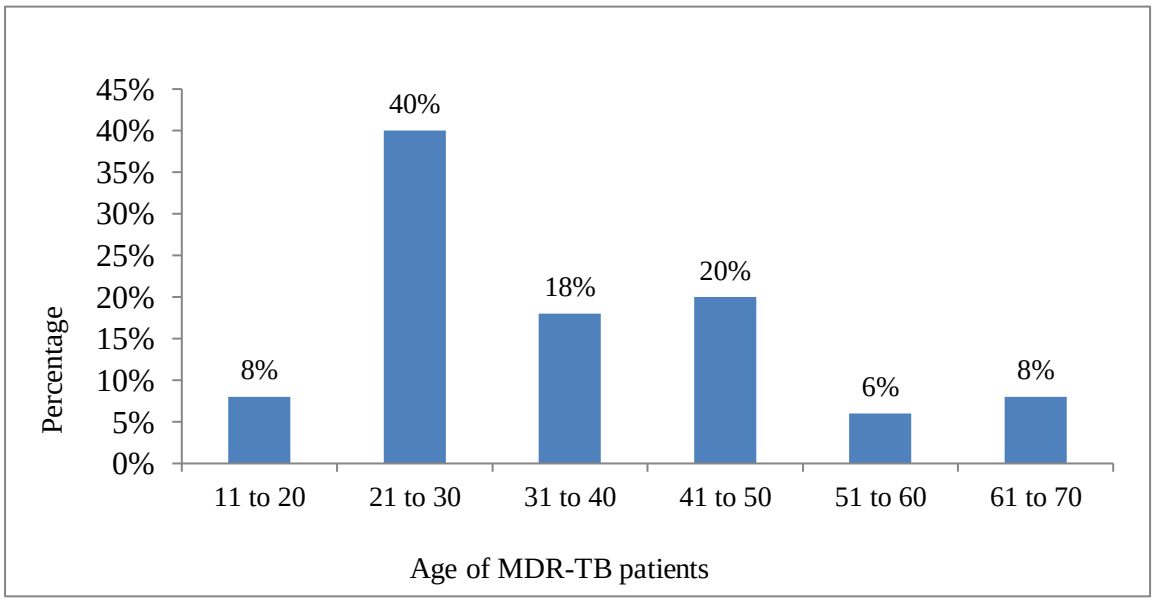

Fig 1: Age wise distribution of the MDR-TB patients

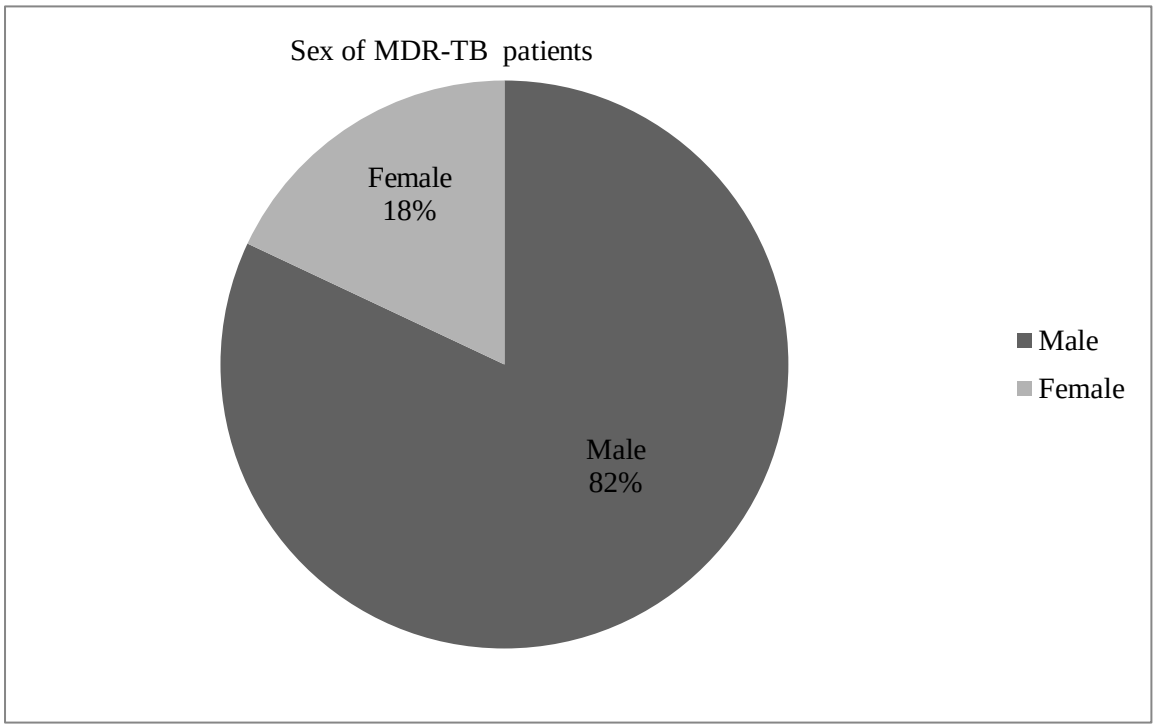

Fig 2: Sex wise distribution of the MDR-TB patients

4.1.2 Risk factors associated with the development of MDR-TB

A case-control study was designed to identify the risk factors for the development of MDR-TB among PTB patients. Fifty MDR-TB patients were considered as cases and 63 drug susceptible patients were considered as control. Twenty-three (46%) cases and 22 (34.92%) control had contact with TB patients either in their family or friends who had been diagnosed as TB. Habit of smoking and alcohol use was found in 23 (46%) cases. Among the control group, habit of smoking and alcohol use was found 44.44% and 60.31% respectively.

Irregularity in taking medicine was more common in cases (38%) than in controls (20.63%) which was significantly associated with the development of MDR-TB (P = 0.042). Odd ratio showed that patients with irregular intake of medicine were 2.36 times more likely to develop MDR-TB than the patients with regular intake of medicine. Fifteen (30%) of cases and 16 (25.40%) of controls had knowledge on DOTS. History of tuberculosis in the past was more common among cases (98%) than in controls (2%). History of tuberculosis was also significantly associated with the development of MDR-

TB (P < 0.001). Previously who had history of TB were more likely to develop MDR-TB than who had not history of tuberculosis in the past.

Greater differences were not observed in educational attainment among the cases and controls. Among the illiterate patient, 24% were cases and 19.04% were controls. Maximum cases (36%) and controls (28.57%) had primary education. Forty-two percent of cases and 63.49% of controls had five or less than five family members. Fifty-eight percent of cases and 36.51% of controls had more than five family members. Family size significantly contributed to the development of MDR-TB (P = 0.023). Large family size was 2.40 times more likely to develop MDR-TB than smaller one. Eighty-four percent of cases and 92.06% of controls had one to three rooms for whole family members.

Occupation was classified as farmer, service, business, students and housewife. Forty-four percent of cases and 34.92% of control group were service holder. Six percent of cases and 11.11% of control group had involved in business. Six percent of cases and 14.28% of controls were students. Four percent of cases and 20.63% of controls were housewife. Patients involved in farming were 40% of cases and 19.05% of control (P = 0.01). People involved in farming were 2.83 times more likely to develop MDR-TB than those involved in other occupation. Family income of both cases and controls ranges from 5,000 to above 15,000 per month. Development of MDR-TB was not found to be associated with their monthly family income.

Twenty-six (52%) of cases and 9 (14.29%) of controls had bovine at home. Presence of bovine at home showed significant association with MDR-TB (P < 0.01). Patients having bovine at home were 6.5 times more likely to develop MDR-TB than the patients with no bovine at home. About 42% of the cases and 44% of control had noticed that bovine at their home coughs (Table no.1).

Table 1: Risk factors associated with MDR-TB

Characteristics	**Cases n (%)**	**Control n (%)**	**Value of $\chi 2$**	**Value of P**	**Odd ratio**
Contact with TB patients	23 (46)	22 (34.92)	1.428	0.232	
Smoking	23 (46)	28 (44.44)	0.27	0.869	
Alcoholism	23 (46)	38 (60.31)	2.30	0.129	
Knowledge on DOTS	15 (30)	16 (25.40)	0.297	0.586	
Irregularity in taking medicine	19 (38)	13 (20.63)	4.141	0.042	2.36
Past history of TB	49 (98)	1 (2)	60.138	0.000	
Educational status			3.531	0.619	
Illiterate	12 (24)	12 (19.04)			
Primary level	18 (36)	18 (28.57)			
Lower secondary level	7 (14)	14 (22.22)			
Secondary level	7 (14)	11 (17.46)			
Higher secondary level	2 (4)	4 (6.35)			
Above higher secondary level	4 (8)	7 (11.11)			
Family size			5.183	0.023	
≤ 5	21 (42)	40 (63.49)			0.42
>5	29 (58)	23 (36.51)			2.40
Number of rooms			1.780	0.781	
1 to 3	42 (84)	58 (92.06)			
>3	8 (16)	5 (7.94)			
Occupation			13.348	0.01	
Farmer	20 (40)	12 (19.05)			2.83
Service	22 (44)	22 (34.92)			1.46
Bussiness	3 (6)	7 (11.11)			0.51
Students	3 (6)	9 (14.28)			0.38
Housewife	2 (4)	13 (20.63)			0.16
Family income			1.082	0.781	
< 5000	8 (16)	7 (11.11)			
5000 to 10000	25 (50)	32 (50.80)			
Between 10000 to 15000	11 (22)	13 (20.63)			
>15000	6 (12)	11(17.46%)			
Bovine at home	26 (52)	9 (14.29)	18.545	0.000	6.5
Do bovine cough			0.607	0.738	
Yes	11(42.3)	4 (44.44)			
No	9(34.61)	2 (22.22)			
Not noticed	6(23.07)	3 (33.33)			

4.1.3 TB-HIV co-infection and status of diabetes among MDR-PTB and PTB patients

Among 50 MDR-PTB patients (cases) and 63 PTB patients (controls), TB-HIV co-infection was almost equal i.e. 2 (4%) and 4 (6.35%) respectively (fig.3). Similarly, diabetic status of both cases and controls were also similar (fig.4). Out of 50 MDR-PTB

patients, 27 (54%) had developed MDR-PTB in once relapse, 16 (32%) in second relapse and 3 (6%) in thrice and fourth relapse. One (2%) had developed MDR-PTB without any previous history of tuberculosis (fig.5).

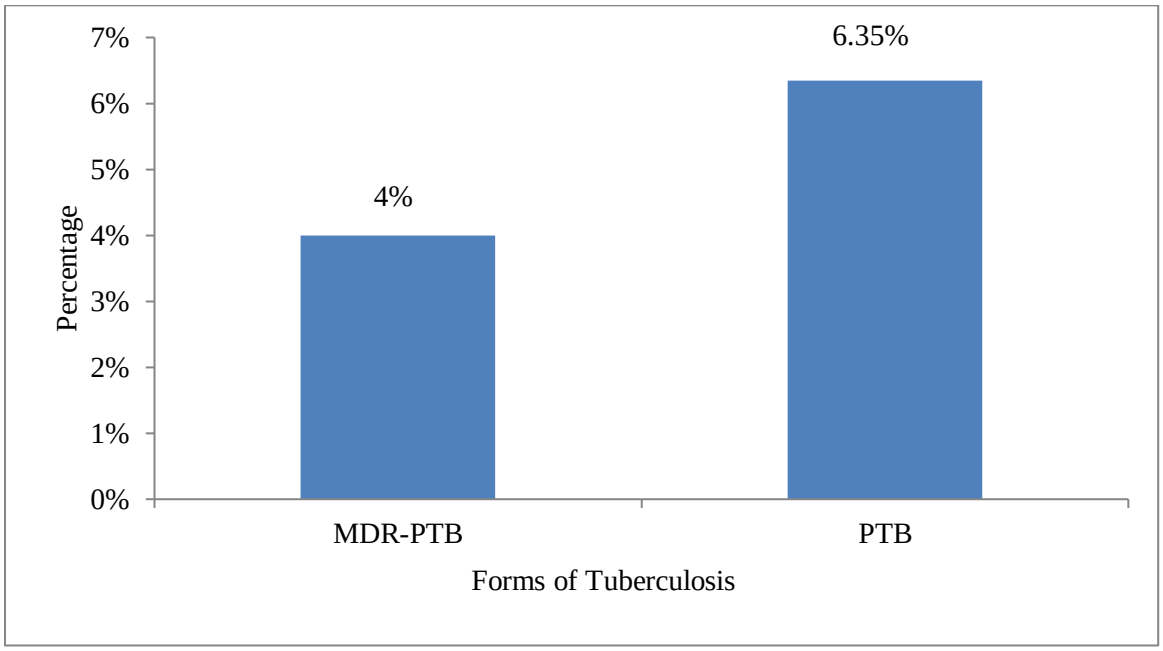

Fig 3: TB-HIV co-infection

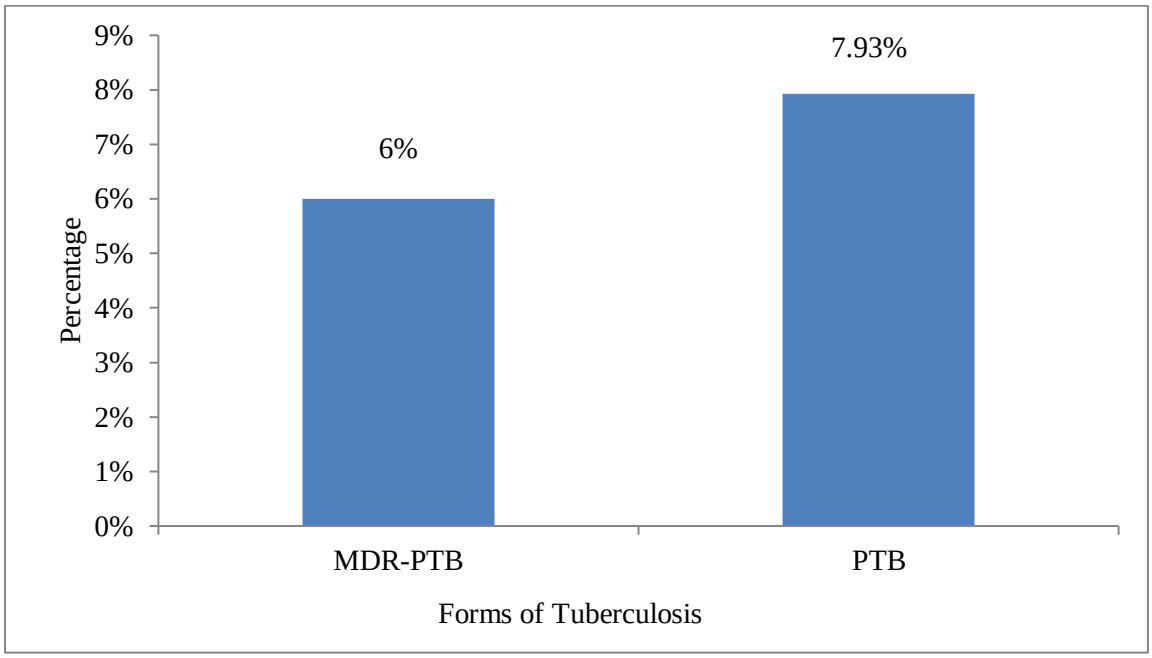

Fig 4: Status of the diabetes among the TB patients

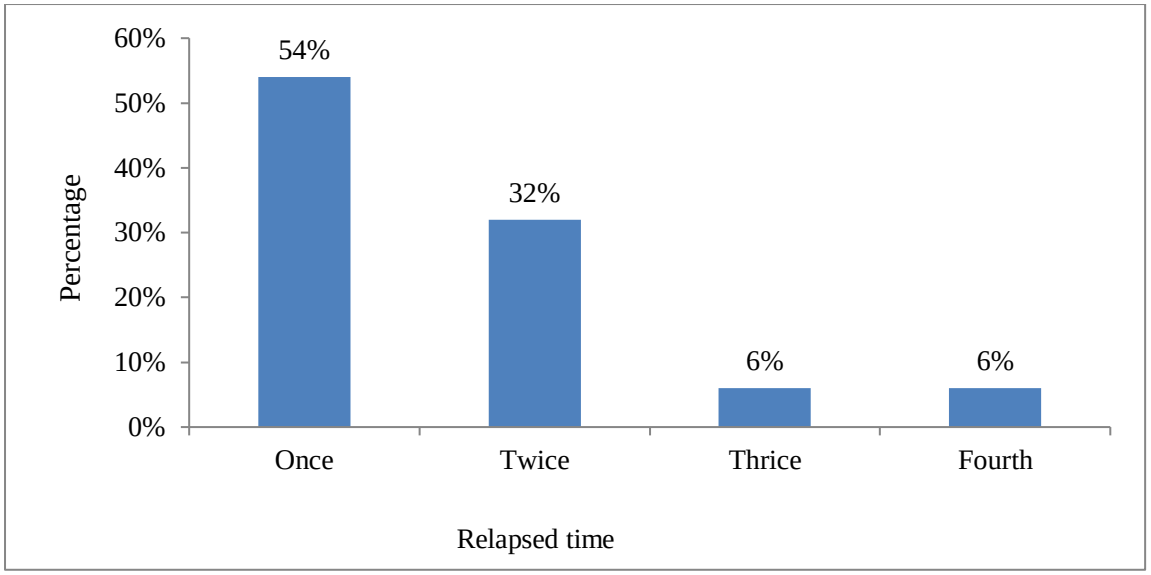

Fig 5: Development of MDR-TB in relapse

4.2 Prevalence of PTB among suspected patients visited at Lumbini Zonal Hospital

During the study period, sputum sample of 200 TB suspected patients were collected for the identification of *Mycobacterium tuberculosis* among which 24 (12%) patients were found to be AFB positive (fig.6).

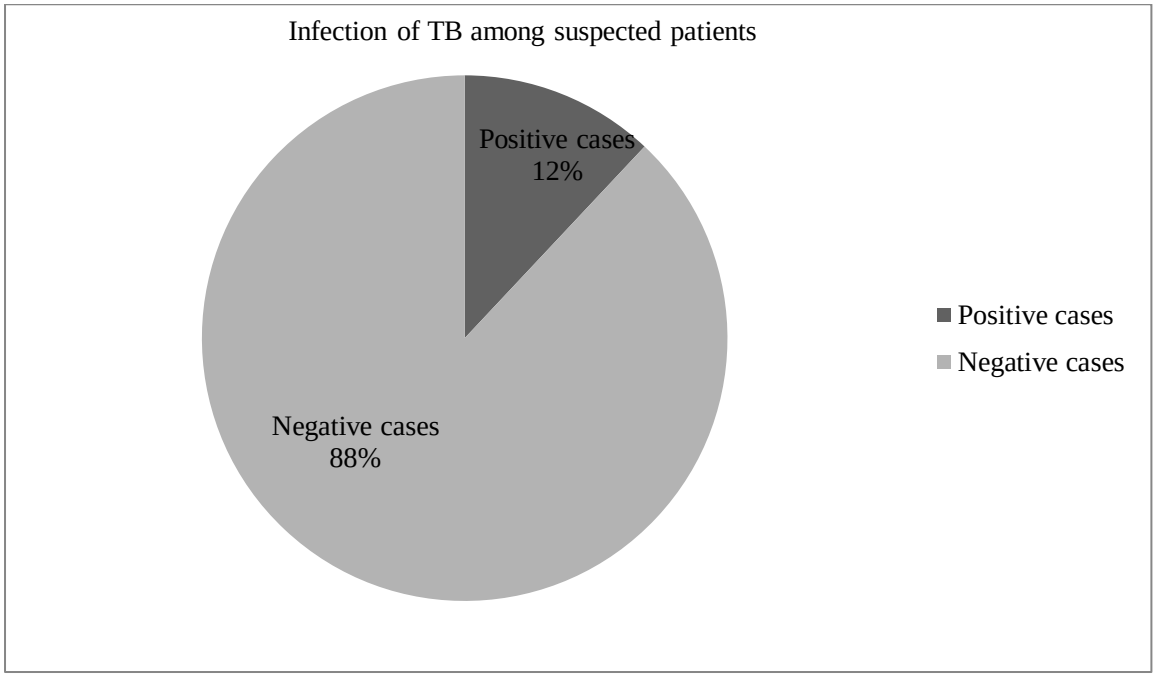

Fig 6: General prevalence of PTB among suspected patients

4.2.1 Age and Sex wise prevalence of PTB

Age-specific prevalence was highest among suspected patients of age group 41-50 years accounting for 16% and least of age group 31-40 accounting for 7.89%. Statistically, age-specific prevalence was found to be insignificant ($\chi 2 = 2.833$, $P > 0.05$) (Table no.2). Similarly, sex wise prevalence of PTB among suspected patients showed maximum (14.50%) in males as compared to females (7.25%) which showed insignificant association ($\chi 2 = 2.25$, $P > 0.05$) of PTB with sex group (Table no.3).

Table 2: Age wise prevalence of PTB

Age	**Total cases examined**	**Positive cases (%)**
11-20	32	3 (9.37)
21-30	39	6 (15.38)
31-40	38	3 (7.89)
41-50	25	4 (16.0)
51-60	24	2 (8.33)
61-70	21	3 (14.28)
70 +	21	3 (14.28)
Total	200	24

Table 3: Sex wise prevalence of PTB

Sex	**Total cases examined**	**Positive cases (%)**
Male	131	19 (14.50)
Female	69	5 (7.25)
Total	200	24

4.2.2 Educational and Occupational status of PTB patients

Maximum TB infected patients (19.05%) had attained education upto lower secondary level. But statistically, educational level was found to be insignificant ($\chi 2 = 2.733$, $P > 0.05$) (Table no.4). Maximum number of PTB infected patients were service holder (18.37%) and farmer (14.29%). But, none of the housewifes were reported for the PTB infection (Table no.5).

Table 4: Education wise prevalence of PTB

Education	**Total cases examined**	**Positive cases (%)**
Illiterate	71	9 (12.68)
Primary level	51	6 (11.76)
Lower secondary level	21	4 (19.05)
Secondary level	25	3 (12)
Higher secondary level	20	2 (10)
Above Higher secondary level	12	0 (0)
Total	200	24

Table 5: Occupation wise prevalence of PTB

Occupation	**Total cases examined**	**Positive cases (%)**
Farmer	56	8 (14.29)
Service	49	9 (18.37)
Business	35	3 (8.57)
Student	37	4 (10.81)
Housewife	23	0 (0)
Total	200	24

Photo Plate

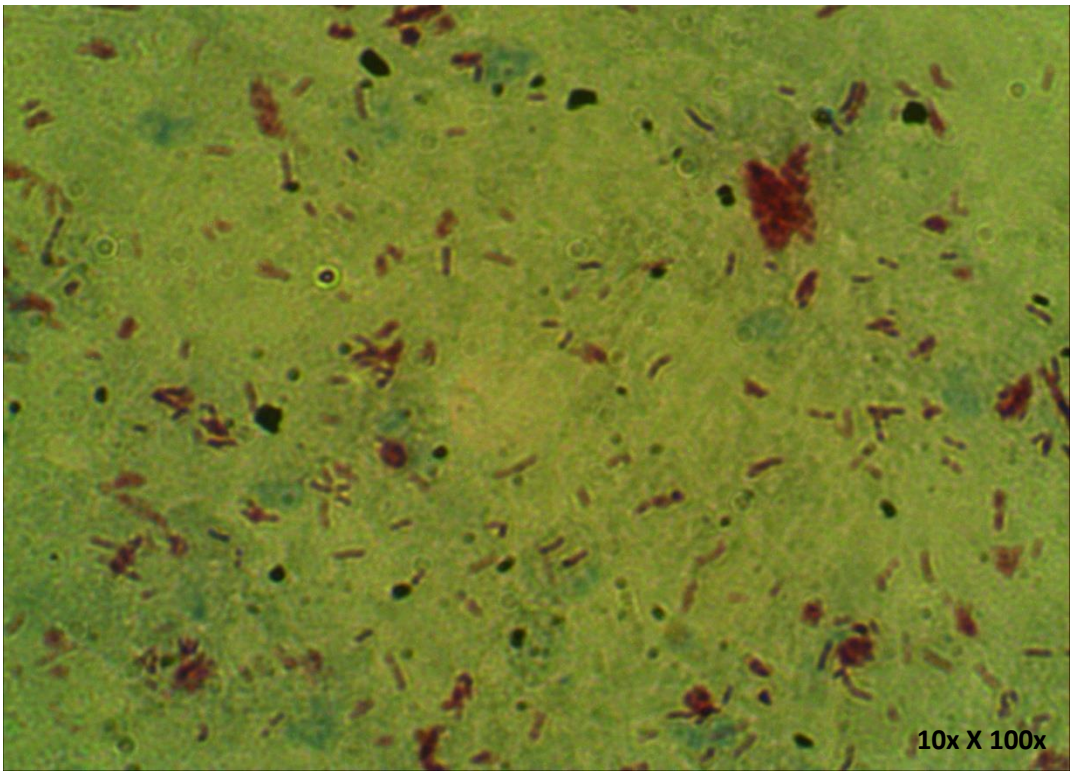

Photo No 10. ***Mycobacterium tuberculosis***

4.2.3 Tuberculosis trend recorded during 2009/2010 to 2013/2014 A.D. at Lumbini Zonal Hospital.

During the study period, secondary data of last five years was collected from the DOTS Clinic of Lumbini Zonal Hospital. Trend of new PTB (+ve) patients registered in DOTS clinic showed similar result during last five years. While new PTB (– ve) cases were found to be increasing during last two years as compared to previous three years. Highest EP cases were recorded in the year 2013/2014 and lowest in 2009/2010. Relapse rate and Return after Default (RAD) cases were found in the decreasing trend in last five years. Maximum failure cases (40%) were reported in the year 2009/2010 and 2013/2014. But, no failure cases were recorded in 2010/2011 and 2011/2012 (Table no.6).

Table 6: Treatment status of TB cases in Lumbini Zonal Hospital

Year	New PTB +ve (%)	New PTB – ve (%)	EP (%)	Relapse (%)	Failure (%)	RAD (%)	Total (%)
2009/2010	157 (22.16)	34 (15.96)	77 (16.92)	38 (24.84)	4 (40)	4 (23.53)	314 (20.18)
2010/2011	129 (18.22)	35 (16.43)	100 (21.98)	34 (22.22)	0 (0)	5 (29.41)	303 (19.47)
2011/2012	151 (21.33)	39 (18.31)	81 (17.80)	28 (18.30)	0 (0)	4 (23.53)	303 (19.47)
2012/2013	131 (18.50)	53 (24.88)	86 (18.90)	28 (18.30)	2 (20)	2 (11.77)	302 (19.41)
2013/2014	140 (19.77)	52 (24.41)	111 (24.40)	25 (16.34)	4 (40)	2 (11.77)	334 (21.47)
Total	708	213	455	153	10	17	1556

Source: Secondary data collected from Lumbini Zonal Hospital

4.3 Knowledge, Attitude and Practices (KAP) of TB suspected patients visited at Lumbini Zonal Hospital

Questionnaire survey was carried out among 200 TB suspected patients to understand their knowledge, attitude and preventive practices, using structured questionnaire.

4.3.1 Knowledge of suspected patients about tuberculosis

Maximum (47.5%) TB suspected patients had knowledge on pulmonary tuberculosis (PTB) while 31% of them had knowledge of extra-pulmonary tuberculosis (EP) with PTB. Among them, 64.5% gave correct answer regarding the communicability of pulmonary tuberculosis. But, still 9.5% of them believed that tuberculosis is uncurable

disease. Knowledge of suspected patients regarding route of transmission was good but not satisfactory. Most of the suspected patients were aware of clinical features of disease. Hence, knowledge regarding clinical features of disease was good (Table no.7).

Table 7: Knowledge of suspected patients about tuberculosis

Variable	**Frequency**	**Percentage (%)**
TB occurs in….		
Lungs	95	47.5
Skin	33	16.5
All the organs	62	31
PTB is a communicable disease.		
Yes	129	64.5
TB is a curable disease		
Yes	181	90.5
Route of transmission		
Respiratory route	125	62.5
Blood borne	30	15
Use of patients personal things	81	40.5
Physical contact with patients	49	24.5
Clinical features of disease		
Haemoptysis	95	47.5
Continue cough for more than 3 weeks	101	50.5
Chest pain	52	26
Loss of appetite	20	10
Evening rise in fever	49	24.5

4.3.2 Attitude of suspected patients about tuberculosis

Most of the suspected patients (66.5%) disagreed for that TB is a disease of poor people. But, Still 15% of the suspected patients believed on superstition. Most of the respondents (58.5%) disagreed that probability of TB is equal to the smoker and non-smoker. Attitude of the suspected patients regarding the organ to be affected by TB was good but not

satisfactory. Almost 30% of the respondents still agreed on that Dhami / Jhakri can treat TB. Twenty-eight (14%) of the participants were unaware about the importance of regular taking of medicine for the complete treatment of TB (Table no.8).

Table 8: Attitude of suspected patients about tuberculosis

S.N	Attitude of the TB suspected patients	Agree	Percent	Disagree	Percent
1	TB is a disease of poor people	67	33.5	133	66.5
2	TB is due to past life's bad action	30	15	170	85
3	Probability of TB is equal to the smoker and non-smoker	83	41.5	117	58.5
4	Lungs is the only organ to be affected by TB	63	31.5	137	68.5
5	DOTS is very effective for TB patients	90	45	110	55
6	Dhami / Jhakri can treat TB	59	29.5	141	70.5
7	Regular taking of medicine is most important for the complete treatment of TB	172	86	28	14

4.3.3 Preventive practices of suspected patients about tuberculosis

Preventive practices that can be adopted to prevent PTB transmission as expressed by PTB suspected patients includes: by using masks during visiting the public area (52.5%), but only 25% of them believed that PTB can be prevented by avoiding personal contact with known TB patients. Similarly, to prevent PTB they believed that changing the smoking (17.5%) as well as alcoholic (12.5%) behaviour can prevent PTB transmission (Table no.9).

Table 9: Preventive practices of suspected patients about tuberculosis

Variable	Frequency	Percentage (%)
TB transmission can be prevented		
Yes	139	69.5
Preventive measures of TB		
Personal protection using masks	105	52.5
Avoiding personal contact with TB patients	50	25
Avoiding alcohol	25	12.5
Avoiding smoking	35	17.5

5. DISCUSSION

Risk factors of MDR-TB

TB has returned in a deadly form called multidrug-resistant tuberculosis. MDR-TB is microbial, clinical and programmatic issue. From a microbiological perspective, resistance is caused by a genetic mutation that makes a drug ineffective (NTP 2009). MDR-TB cases are increasing in alarming rate and around 480,000 MDR-TB cases estimated to have occured in 2013 (WHO 2014). The risk of tuberculosis is greater in areas of residence characterized by crowding, poverty and lower education (Lifson et al. 1999). An inadequate or poorly administered treatment regimen allows drug-resistant mutant to become the dominant strain in a patients infected with TB (NTP 2009).

Case-control study was carried out with 50 cases and 63 controls for the identification of risk factors responsible for the development of MDR-TB. MDR-TB patients and drug susceptible PTB patients were considered as cases and control respectively. Our study showed irregularity in taking medicine, family size, occupation, past history of TB and bovine at home have a significant association with MDR-TB and regarded as the risk factors for the development of MDR-TB.

Most of the patients (98%) in our study had previous history of TB. Numerous studies had shown a very significant co-relation between past history of TB and MDR-TB (Marahatta et al. 2010, FMOH 2012, Hirpa et al. 2013, Biadlegene et al. 2014). If the patients does not complete his/her antibiotic dose in the previous treatment or if the physician does not prescribe the proper antibiotic regimen, resistance can develop. Also, drugs that are of poor quality or less in quantity, especially in developing countries contribute to MDR-TB (Sharma and Mohan 2004). Bacteria develops the resistance to the drugs, if taken for the longer duration which leads to the development of MDR-TB.

Another important risk factor identified in present study includes irregularity in taking medicine. If the treatment is irregular, the number of bacterial death and growth cycles will be greater giving more opportunities for individual mutation of different independent genes to accumulate. According to Pant et al. (2009), 67% of cases missed medicine at least a few weeks during their previous treatment. Irregularity in taking medicine was

shown statistically associated with MDR-TB in the study conducted by Barroso et al. (2003), Kritski (2003) and Flora et al. (2013).

Low socio-economic status leads to poor adherence to treatment thereby leading to the development of MDR-TB. In the study conducted by Casal et al. (2005), Akl and Mahalli (2012) and Rifat et al. (2014), occupation was found to be statistically associated MDR-TB which is similar to our study. From the occupational status of TB infected patients also, higher percentage of patients has been actively involving in jobs that need to get exposed to outer environment to greater extent and need to spend more time out of home. Amin et al. (2009) conducted a study in Bangladesh, which showed that the highest proportion of MDR-TB cases (61.2%) were involved in occupations like agriculture, production and transport but no significant difference was obtained in income level between cases and controls. In other study done by Baghaei et al. (2009) and Barman et al. (2014) family size showed significant association with MDR-TB as in our study. Individual staying in a crowded living condition are more vulnerable to develop MDR-TB.

Family income, number of rooms, education, smoking, alcoholism, knowledge on DOTS and contact with TB patients showed no statistical association with MDR-TB while the study conducted by Antunes et al. (2003), HERD (2012) and Chen et al. (2013) had showed the co-relation between low family income and development of MDR-TB. Although family income was not statistically associated with the development of MDR-TB, most of the cases had low family income. Patients with a low family income might have more limited access to medical treatment and healthcare services. Also, their crowded and poor living conditions may facilitate the spread of infectious diseases.

Since, TB is a air-borne disease, bacteria spread through air when people who have an active TB infection expel infectious aerosol droplets. Personal contact with TB patients and use of patients personal things play a vital role in the MDR-TB development and transmission. Several studies have shown that TB contact as strongest determinants of MDR-TB (Kliiman and Attraja 2009, Balabanova et al. 2012, Lange et al. 2014) but no statistical association was observed between TB contacts and MDR-TB in the present study. The study conducted by Kritski (2003) and Skrahina et al. (2013) demonstrated that the smoking habit and alcoholism are strongly associated with MDR-TB. But our

finding infers that the smoking habit and alcoholism have no any co-relation with the development of MDR-TB.

Educational status was found to be statistically associated with MDR-TB in a study conducted by Li et al. (2015). No significant association between MDR-TB and education was observed in the study conducted by Rahman et al. (2005) and Amin et al. (2009) as in our study but most of patients were illiterate and had primary education. Poor knowledge leads to the poor adherence to the treatment which finally leads to the development of MDR-TB.

A similar study conducted by Pant et al. (2009) reported that 70.97% MDR-TB patients were male. Faustini et al. (2006) and Ahmad et al. (2012) found that there was statistical association between male gender and MDR-TB. But, in present study although the majority of MDR-TB patients were male, statistical association was not significant. Males get exposed to the external environment than females and are supposed to do their job outside the home while females are more restricted at home due to which mostly male gender might be infected with MDR-TB. But, Taulox and Suarez (2000), Mdivani et al. (2008), Lomtadze et al. (2009) concluded that female gender was statistically associated with MDR-TB. In a study conducted by Ukanwa and Madiba (2013) also, more females (63.6%) than males (36.4%) were infected with MDR-TB. Male gender has quick access to health care services when they get ill but females generally depend on other members of family to have access to health centres as well as they can't freely express their health problems.

Age wise observation of the MDR-TB patients showed that the highest number of patients (40%) were found in the age group 21-30 years. In the study conducted by Vander-Werf et al. (2012) and Lange et al. (2014) younger age was found to be statistically associated with MDR-TB. The highest number of MDR-TB patients of the productive age group might be due to the exposure of these age group people to different environment during their work and activities that would make their health more prone to infection by TB organisms.

Among 50 MDR-TB patients, 4% had TB-HIV co-infection and 6% had been suffered from diabetes. Similar study conducted by Yimer et al. (2011) and Abebe et al. (2012) showed that HIV was considered as risk factor for the development of MDR-TB. Patients with HIV/AIDS lack the immunity to fight against TB infection and are at great risk of

developing drug resistance. Torres et al. (2000) and Baghaei et al. (2013) concluded that diabetes is statistically associated with MDR-TB.

Prevalence of PTB

Tuberculosis remains a major global public health problem particularly in developing and undeveloped countries (Lifson et al. 1999). Nepal is a high-burden country for TB. About 45% of the total population is infected with TB and an estimated 20,000 new infectious cases of TB are reported each year (NTC 2001). The total number of tuberculosis cases has been decreasing since 2006 and new cases have decreased since 2002 globally (WHO 2011). An estimated nine million new cases occurred in 2013 with associated deaths between 1.3 to 1.5 million globally (WHO 2014).

During the study period, a total of 400 sputum samples were collected from 200 TB suspected patients and examined in the Laboratory of Lumbini Zonal Hospital by using Z-N staining method. Twenty-four (12%) individuals were found to be positive for acid-fast bacilli (AFB). The higher prevalence of tuberculosis in the study area might be due to the lack of adequate knowledge and awareness on disease. Similar study carried out by Smith (1996) found that out of 1,630 samples, 78 (4.8%) were positive for AFB which was less than the present study. In a similar study conducted by Amgain et al. (2013), out of 200 TB suspected patients, 9% were found to be AFB positive. Amare et al. (2013) and Eliso et al. (2015) in Ethiopia demonstrated that the overall prevalence of smear positive pulmonary TB was 4.6% and 6.2% respectively.

Sex wise prevalence of PTB showed that males (14.50%) were infected more than females (7.25%) in Butwal. Smith (1996) also reported that as in most countries of the world, in Nepal also there was higher incidence of TB in men than in woman. A study done by Joshi et al. (2005) in far-western region also found the similar result (13% male and 5% female). Similar study done by Tamrakar (2002) in Ramechhap district Nepal, Sharma (2008) in Gorkha district Nepal and Amgain et al. (2013) in Chitwan district Nepal also found higher prevalence of pulmonary tuberculosis among male as compared to female. It was possibly because Nepali men are more frequently exposed to infection than woman as they stay out of house for longer time for the employment. Thapa et al. (2014) concluded that out of 123 participants, 78% male were AFB positive. A study conducted by Nakanishi and Shrestha (1990) in Sunsari and Morang district in 125 healthy subjects, in collaboration of Nepal National Planning Commission (NPC) and

UNICEF found that immunoglobulin M (IgM) and immunoglobulin G (IgM) concentration was higher in female than in male and these higher concentration of these antibodies in female has protective value against the infection which leads to the low prevalence of TB among female than in male.

Age-specific prevalence of pulmonary tuberculosis was highest among the age group 41-50 years (16%). Sudre et al. (1992) described that in developing countries about 70% of TB patients were under 50 years age group which was similar to the present study. But, in a similar study conducted by Joshi et al. (2005) highest prevalence was obtained in the age group 20-29 years (25%). Sharma (2008) revealed higher prevalence of TB among the economically productive age group of 20-49 years. A study conducted by Nayak et al. (2013) reported that the maximum number of TB patients (40.91%) were from age group 25-34 years followed by age group 35-49 years (36.36%). Maximum infection was found among age group 15-49 years i.e. 80.65% in productive age group than above 49 years (16.13%) in the survey conducted by Joshi (2004).

In the study conducted by Amgain et al. (2013) majorities of the respondents (49.1%) were employed in the agricultural sector as farmer and 16 (28.1%) of the respondents were illiterate. Similarly, in the present study prevalence of PTB was highest among service holder (18.37%) and individual with lower secondary level educational attainment (19.05%). Occupation of the individual also plays a major role in the prevalence of TB. Lack of the financial resources and proper knowledge on disease might be associated with TB occurance.

Knowledge, attitude and practices on TB

Despite various scientific studies carried out, there is still lack of research on the social science perspective especially on the spread of the disease. Social factors play an important role in managing the TB disease (Hoa et al. 2003). In addition, the low level of awareness among the public regarding TB has also become a leading to the increase of TB patients (Hashim et al. 2003, Khan et al. 2011). Knowledge on disease directly determines the preventive measures with suitable intervention. This study is an attempt to explore the understanding and attitude of the suspected patients on tuberculosis.

More than half of the respondents (64.5%) were well known about the communicability of disease. A similar study conducted by Sharma (2008) in Gorkha demonstrated that

88% of the respondents believed TB is an infectious disease. A study conducted by Joshi (2004) in Patan Hospital also found that 75.86% believed TB is an infectious disease. People visiting Lumbini Zonal Hospital, Rupandehi had poor knowledge about the infectious nature of TB in the present study.

In this study 90.5% of the respondents believed that TB is a curable disease. In a similar study conducted by Nikovaska et al. (2014), 89.3% knew that TB is a curable disease. Bhatt et al. (2010) carried out a similar study among the tuberculosis patients attending DOTS programme in Nepal and concluded that 83% of the respondents knew TB is a curable disease. Yadav et al. (2012) also reported that 93% of the respondents knew TB is a curable disease. This showed that in the present study people had good knowledge about curability of disease.

According to the present study, only 31% of the respondents believed that TB occurs in all the organs. Regarding the symptoms of TB, 50.5%, 47.5% and 26% believed that continue cough for more than 3 weeks, haemoptysis and chest pain are the major symptoms of disease respectively. Ten percent of the respondents believed that loss of appetite and 24.5% believed 'evening rise in fever' as the symptoms of disease. In the similar study conducted by Das et al. (2012) about 62.07% correctly answered that cough is the common symptom. Almost 82% of the respondents were aware of symptoms of disease in the study conducted by Khali et al. (2011). In a study conducted by Kenyi et al. (2014), 52% were knowledgeable of correct symptoms of TB. Majority of interviewers (74.3%) reported cough as the main symptoms of PTB in a survey conducted by Legesse et al. (2010). Variation in the understandings might be due to the eruption of different symptoms according to the geographical variations.

Among 200 TB suspected patients, majority of the respondents (62.5%) believed that TB is transmitted through respiratory route, through the use of patient's personal things (40.5%) and through physical contact with patients (24.5%). In a similar study conducted by Mokhtar et al. (2012), 77.8% of the respondents gave the correct answer about the mechanism of the spread of TB (i.e. cough). Ago et al. (2014) also reported that 63.1% of the respondents believed that TB spreads from person to person through air, coughing and sneezing. In a study conducted by HERD (2011) in five developments and three ecological regions, cough was considered as the major sign of TB transmission (60%). But, in a survey conducted by Tiwary (2008), only 37.51% of the respondents believed

that TB transmits through cough. According to PCI (2010), 87.8% of the respondents mentioned that a patient's coughs and sneezes can be an agent of TB transmission.

Regarding the attitude of the TB suspected patients, 133 (66.5%) of the patients disagreed that TB is a disease of poverty while 67 (33.5%) of the patients agreed that TB is a disease of poverty. But, Amgain et al. (2014) reported that 40.4% of the patients disagreed that TB is a disease of poverty. In our study, 170 (85%) of the patients disagreed that TB is due to past life's bad action. Out of 200 TB suspected patients, 41.5% agreed that probability of TB is equal to the smoker and non-smoker while 58.5% disagree that probability of TB is equal to the smoker and non-smoker. Sharma (2008) found that out of 155 smokers, 7 patients had PTB. According to the study conducted by Karki (1995), a positive co-relation between alcohol consumption, smoking, surti, etc and respiratory tract infection was found.

In our study only 90 (45%) of the respondents believed that DOTS is very effective for TB treatment. But, in the study conducted by Amgain et al. (2014), 68.4% strongly believed that DOTS is very effective for TB treatment. Majority of the respondents (70.5%) disagreed that 'Dhami/Jhakri can treat TB. One hundred and seventy two (86%) of the respondents in our study agreed that 'regular taking of medicine' is the most important for the treatment of TB. That means they were aware of its relapse.

Among 200 TB suspected patients interviewed, majority of them (52.5%) believed that TB transmission can be prevented through the personal protection like using masks and 50 (25%) believed that TB transmission can be prevented by avoiding the personal contact with TB patients. It showed that the knowledge about TB prevention was satisfactory among the TB suspected patients visiting Lumbini Zonal Hospital, Rupandehi. A similar study conducted in Sindhupalchok district by Ministry of Health and Population, National TB centre in collaboration with 'Britian Nepal Medical Trust' in 2009, found that about 40% of the respondents in the study area believed the infection could be prevented by 'covering mouth and nose while coughing and sneezing.' A study conducted by Kenyi et al. (2014) reported that 79.4% of the respondents in South Sudan believed personal protective measure like use of handkerchief while coughing serve as preventive measure for TB transmission.

6. CONCLUSION AND RECOMMENDATIONS

6.1 Conclusion

Tuberculosis is a chronic or acute bacterial infection, caused by *M. tuberculosis.* Most of the people in the world has been infected with TB causing bacteria. Pulmonary tuberculosis is the most common form of TB. Multidrug-resistance is a major public health problem that threatens progress made in TB care and control worldwide. Several risk factors play important role in the development of MDR-TB. Drug-resistance arises due to improper use of antibiotics in chemotherapy of drug-susceptible TB patients. Majority of people are unaware about the causative agent, TB transmission as well as regularity of treatment.

In order to assess the risk factors, TB burden and KAP assessment the present study was carried out. Case-control study was designed to determine the risk factors while detection of pulmonary tuberculosis among patients was done by screening. Out of 50 MDR-TB cases and 63 drug susceptible controls, the major risk factors identified includes: irregularity in taking medicine (OR = 2.36), large family size (OR = 2.40), farming as occupation (OR = 2.83), past history of TB and bovine at home (OR = 6.5) which were statistically significant while alcoholism, smoking, family income, education which had been identified as risk factors in previous studies were not associated with MDR-TB at Lumbini Zone. Male sex (82%) and individual of age group 21-30 years were found to be highly prone to MDR-TB infection.

Higher prevalence of pulmonary tuberculosis (12%) has been reported among 200 PTB suspected patients visiting DOTS Plus Clinic of Lumbini Zonal Hospital. Further maximum number of AFB positive were observed in male (14.50%) as compared to female (7.25%). Individuals of age group 41-50 years were found to be highly affected (16%). Higher prevalence of PTB was observed among service holder (18.37%) and individual with lower secondary level educational attainment (19.05%).

In a questionnaire survey of same 200 TB suspected patients done to assess their knowledge, attitude and practice for TB, majority of the patients had positive attitudes but knowledge regarding nature of disease, symptoms, route of transmission and prevention

of the TB was not adequate. So, there is a still need to strengthen the knowledge of TB through mass media to public level.

6.2 Recommendations

- Drug-resistant TB develops when patients with drug susceptible TB show carelessness at the time of taking medicine. Hence, all the drug susceptible TB patients should be made aware about the negative effect of irregularity in taking medicine.

- Since “bovine at home” is highly associated with MDR-TB, people should notice wheather their bovine cough or not. If any problem persist veterinarian should be consulted and habit of consuming raw milk/meat should be avoided.

- Public awareness programme related to causative agent, route of transmission, clinical features, DOTS programme, prevention and control measures should be expanded more through mass media like radio, television, as well as inclusion in school text books, etc.

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APPENDIX 1

Questionnaire Related to Risk Factors of MDR-TB

Name- Sex-

Age- Address-

1. Are/was there any TB patient in your home? _____

2. Do you smoke? _____

3. Do you drink alcohol? _____

4. How many persons are there in your home? _____

5. How many rooms are there in your home? _____

6. Are there bovine in your home? _____

7. If yes, do they cough? _____

8. How many times you have been treated for TB? _____

9. Had you regularly taken medicine during your previous treatment? (MDR) _____

10. If no, how many times you missed to take medicine? (MDR) _____

11. Have you ever suffered from diabetes , Psychiatric diseases? _____

12. Are you HIV-Positive ? _____

13. What is the mean income of your family? _____

14. a. Marital status _____ b. Educational status _____

c. Occupation _____

15. Do you take medicine regularly? (Suceptible TB &MDR) _____

16. If no, how many time you missed to take medicine? _____

17. At what interval of time sputum examination is done? _____

18. Have you got knowledge on DOTS? _____

Questionnaire Related to KAP

Name: Age/Sex:

Occupation: Educational Status:

Knowledge

1. Do you know about TB?

a. Yes b. No

2. If yes, what are the clinical features?

a. Cough b. Bloood in Sputum c. Headache d. Vomiting

3. What type of disease is TB?

a. Communicable b. Non-Communicable

4.How does TB spread?

a. Coughing b. Blood c. Droplet nuclei d.Contact

5.TB occurs in……

a.Lungs b.Skin c.All the organs

Prevention

6.Do you think TB transmission be prevented?

a. Yes b. No

7.If yes, what are the preventive measures?

a. Avoiding smoking b. Avoiding alcohol c. Personal protection

d. Avoiding personal contact to the TB patients

Attitude

8. Lungs is the only organ affecting TB?

a. Yes

9. DOTS is very effective for TB patients?

a. Agree b. Disagree

10. Dhami/Jhakri can treat TB?

a. Agree b. Disagree

11. Regular taking of medicine is most important for the complete treatment of TB.

a. Agree b. Disagree

12. We should not discontinue the medicine, even if the symptom is relived.

a. Agree b. Disagree

13. What is/ are the cause of TB?

a. Smoking b. Alcohol c. Polluted environment

d. Infection of *Mycobacterium tuberculosis*

14. Probability of TB is equal to smoker and non-smoker

a. Agree b. Disagree

15. TB is due to past lifes bad action(Purba Janam ko Paap)

a. Agree b.Disagree

16. TB is a disease of poor people

a.Agree b.Disagree