The World Health Organization's 13th annual report on tuberculosis was published on March 24, 2009 on the occasion of World TB Day. There were an estimated 9.27 million new cases of tuberculosis worldwide in 2007. This figure peaked in 2004 at 142 per 100,000 and fell to 139 per 100,000 in 2007. By 2015, WHO targets to reduce the burden of TB halving deaths due to the condition, through its 'Stop TB Strategy', completely eliminating it by 2050. Pakistan ranks eighth on the list of 22 high-burden tuberculosis countries with an estimated 291,743 new cases of TB annually (figure report of 2006).

Today, when swift advances in medical research are exploring the genome for all possibilities, tuberculosis has also been investigated for its potential connection with human genetic blueprint. Such studies are of interest to the clinicians and to the pharmaceutical industry since they have the prospects to open up new avenues of treatments.

A recent study showed genetic association of four polymorphisms of TLR8, a member of a well-known receptor family involved in pathogen recognition. This may explain the fact that despite approximately one-third of the world's population being infected with Mycobacterium tuberculosis, less than 10% of infected individuals are potentially threatened to develop pulmonary tuberculosis during their lifetime. Davila, et al. proposed that difference in polymorphisms within genes involved in host immune response, as a plausible reason to explain this phenomenon. The key component in determining the outcome of infection could be the initial phase of immunity, which involves a wide range of pathogen sensing mechanism. Toll-like receptors (TLRs) are homologous to a Drosophila protein called Toll 10 mammalian TLRs were identified in 2005. These TLRs are involved in specific recognition of pathogen associated molecules. So far, fifteen such functional TLRs have been identified in mammals. Upon ligand binding, these TLRs initiate a cascade of events leading to the transcription of mostly inflammatory genes. The four single nucleotide polymorphisms within the TLR8 gene (Gene ID:51311) on chromosome X that cause susceptibility to pulmonary TB. Taken together, these results provide strong evidence for the first time, of a role for TLR8 in adult pulmonary TB infection. The involvement of X chromosome also explains that any allele conferring susceptibility to disease may well have a higher impact among males who carry only one copy of the gene. Indeed, males have a higher risk of contracting pulmonary tuberculosis than females.

Another study by Stallings et al., identified CarD as an essential mycobacterial protein that controls rRNA transcription in the Mycobacterium. Loss of CarD was found lethal for mycobacteria in culture and during infection of mice. CarD depletion leads to sensitivity to killing by oxidative stress, starvation, and DNA damage, accompanied by failure to reduce rRNA transcription. CarD can functionally replace DksA for stringent control of rRNA transcription, even though CarD associates with a different site on RNA polymerase. These findings highlight a distinct molecular mechanism for regulating rRNA transcription in mycobacteria that is critical for M. tuberculosis pathogenesis.

The identification of a role of TLR8 and CarD as agents in TB development, has the potential to open up new avenues of exploration in TB host/pathogen interactions. This provide researchers and clinical scientists with novel targets for therapeutic intervention, especially when MDR-TB is posing a challenge to health professionals by its resistance to two of the first line drugs used to cure TB-rifampicin and isoniazid. Resistance to any agent emerges rapidly if there is overt or covert monotherapy or noncompliance. It is caused by either spontaneous mutation of the bacteria or patient’s default on treatment. More serious is the XDR-TB or eXtensively drug-resistant TB that is also resistant to fluoroquinolones and the injectables – Kanamycin, Capreomycin and Amikacin. MDR-TB and XDR-TB are the greatest health hazards for those infected with HIV/AIDS. According to WHO report, over 4,00,000 cases of Multi-Drug Resistant TB (MDR-TB) are reported across the world every year with more than 1,00,000 estimated deaths. Up to 80% of TB patients test positive for HIV/AIDS in countries with high AIDS incidence.

Directly Observed Treatment Short Course (DOTS) was introduced to combat TB by increasing compliance
through counselling. Dedicated DOTS providers regularly track TB patients and encourage them to continue with the treatment till they are completely cured. But in many parts of the globe, health systems are defective or simply overwhelmed and cannot cope with lack of funds and personnel or dysfunctional politics. This leads to sloppy implementation of DOTS programs, further aggravating the tuberculosis problem. According to the Weekly TB report issued on February 20, 2008, Pakistan's DOTS program has a treatment success rate of 85% and that more than 700,000 people have received DOTS treatment since the revival of the National TB Control Program in 2000.

It is time to work closely at the national vaccination program. The BCG shot at birth is not enough for lifelong protection against the infection.

Individuals with genetic tendencies towards acquisition of TB may need to be vaccinated with a new approach. Comprehensive strategies to control and eventually eliminate TB involve many interconnected components, including developing new TB vaccines and immune-boosting vaccine adjuvants to prevent infection or disease and evaluate the potential of synthetic vaccines to help shorten TB drug treatment regimens.

Knowledge of the genetic makeup of a person or a family member may present a significant information that may lead to a serious consideration of alternative life plans. A genetic test can alert people to advanced detection and management of some disorders, but currently, the ability to test for a genetic disorder often exceeds the ability of science to prevent or cure genetic disease. The interaction between genotype and environmental factors such as behaviours and exposures, also calls for extensive study to determine how such factors can be modified to improve health outcomes. The utility of certain genetic tests to prevent disease and promote health is yet to be evaluated, and standards for laboratory testing are only evolving. Policies are needed to ensure appropriate use of predictive genetic testing and counseling, and prevent inappropriate use of such testing. People must be assured that information about their genetic composition will remain confidential and that they will receive appropriate counseling about treatment compliance.

REFERENCES