

## Letter to Editor

# The totally drug resistant tuberculosis (TDR-TB)

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In 2009, we proposed the term “Totally Drug-Resistant Tuberculosis (TDR-TB) “for TB strains that showed *in-vitro* resistance to all first and second line drugs tested (isoniazid, rifampicin, streptomycin, ethambutol, pyrazinamide, ethionamide, para-aminosalicylic acid, cycloserine, ofloxacin, amikacin, ciprofloxacin, capreomycin, kanamycin) [1]. Our detected TDR-TB patients remained smear and culture positive after 18 months median treatment despite second line drugs. Even changing the treatment to co-amoxiclav (625 mg per 8 h) or clarithromycin (1,000 mg/day<sup>-1</sup>) along with high dose of isoniazid (15 mg/kg<sup>-1</sup>) led to no improvement [1]. Majority of cases were expired or remained positive in the next 4 years of follow-up. These dangerous forms of TB bacilli were also found in other countries i.e., Italy and India [2, 3]. Just earlier this month “Centers for Diseases Control and Preventions” reported the first cases of TDR-TB in South Africa and they stated the disease is “virtually untreatable” [4]. National Reference TB laboratory (NRL) of Iran was among the first laboratories who could identify TDR-TB bacilli. Based on availability of TDR-culture isolates, investigation was started at cellular and molecular level. The primary results using transmission and atomic force microscopes, confirmed morphological variation in TDR-TB isolates [5, 6]. Considerable number of bacilli were round (35%), oval (15%) or even multiple branching forms. In addition, various type of cell division i.e., symmetrical, asymmetrical and budding were found in their exponential phase of growth (**Figure 1**) [5]. The cell wall was significantly thicker than MDR-TB isolates and recently, pilli like structure (10-15%) that protruded from the head, tail or side poles of

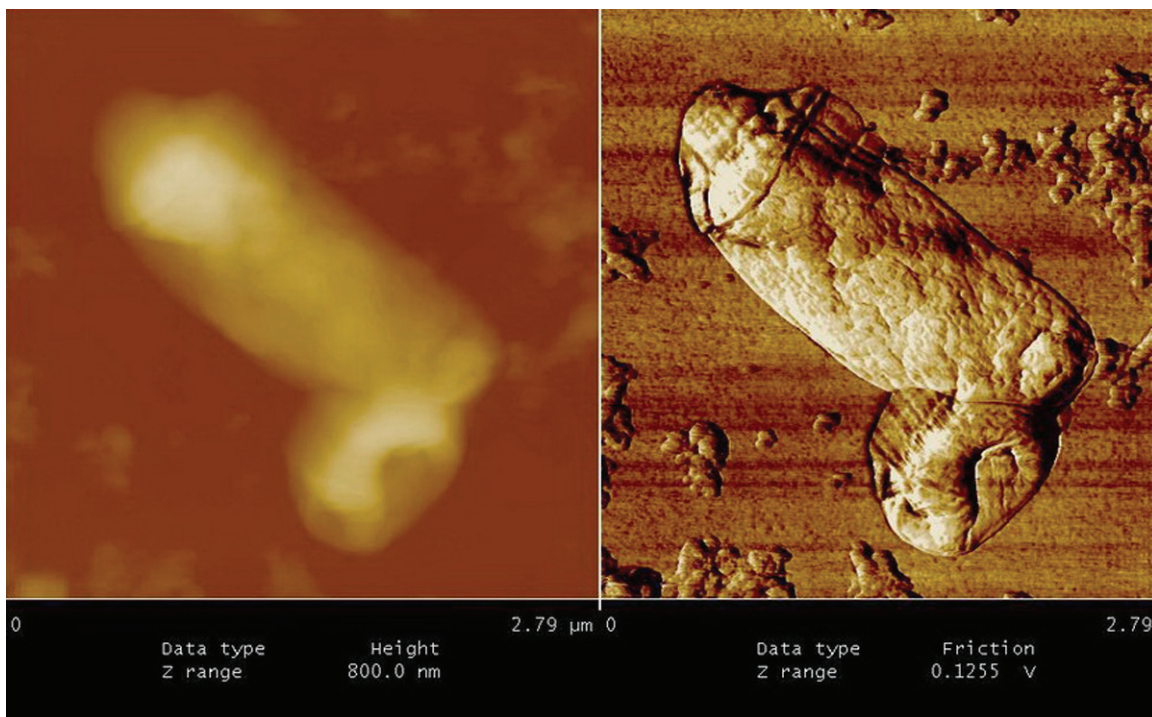
the bacilli were also detected [7-9]. Whether they use them for genetically or nutrients exchanges are still under investigations. These findings will rage a new debate on untreatable TB drug resistance phenomena, for example, whether variation in shape and size of bacilli could affect transmission rate? If so, then what will be the time that droplet nuclei (round or oval cells) can remain suspended in air?

Secondly, how to protect the health care workers when TDR-TB reported in the hospital? Do we need to keep the TDR-TB patients in “isolated ward” and if yes for how long? If size of bacilli reaches to minimum of 0.3  $\mu\text{m}$  [6] what will be the best protective cloth for laboratory personal?

Third concern is about host-microbe’s interaction? What is the fate of round or oval shape TB bacilli inside the host cells? Because, it is known that the shapes of microorganisms and not size considered as the dominant factor for being recognized or phagocytized by immune cells [10].

Finally, do we have to consider the thicker cell wall [7] in TDR-TB bacilli while designing new drugs and if it is so, whether the previously designed drugs could be effective?

Last but not the least; as far as, there is no cure for TDR-TB patient, hence it is not exaggeration to say that world is on danger of untreatable drug resistant tuberculosis strain. Therefore, if authorized health organization do not consider immediate action plan for such bacilli, then we may face a new outbreaks of untreatable TB.



**Figure 1.** Atomic Force Microscopy (AFM) shows budding type of cell-division in TDR-TB bacilli.

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