Tuberculosis – return of a forgotten disease?

E. Richter

{**National Reference Center (NRC) for Mycobacteria, Borstel, Germany**}

Correspondence to: E. Richter (erichter@fz-borstel.de)

1 Extended abstract

In 2009 more than 9 million people were estimated to be diseased from active tuberculosis (TB), an infection caused by the tubercle bacterium *Mycobacterium* (*M.*) *tuberculosis* (World health organization (WHO), 2010a). The absolute number of cases is still increasing slightly, since slow decreases in incidence rates are outweighed by the increase of the world's population. The W H O has identified 22 high-burden TB countries that combined contribute 80 percent of the global burden of TB. These include (ordered by burden of TB beginning with highest): India, China, South Africa, Nigeria, Indonesia, Pakistan, Bangladesh, Ethiopia, Philippines, DR Congo, Myanmar, Vietnam, Russian Federation, Kenya, Uganda, Mozambique, Zimbabwe, Thailand, Brazil, Tanzania, Cambodia, and Afghanistan. Countries with the highest incidence rates are located in Africa, whereas countries with the highest total number of cases are India and China (WHO, 2010a). In most Western European countries, tuberculosis notification rates decline since years. This also applies for Germany, although this levelled off to a modest decline since the early 1990s (WHO, 2010a; Brodhun, 2010). Mainly, immigration from high incidence countries is held responsible for the delayed decline or temporary increase of TB in the Western European countries.

Among several aspects, the most profound causes for the worldwide resurgence of tuberculosis are the human immunodeficiency virus (HIV) pandemia and the neglect of TB control programs leading to rise of resistant TB strains. HIV is a high risk factor for developing TB. Approximately 10 % of all TB patients worldwide were HIV-positive (WHO, 2010a). 80 % of these cases were in Africa, being the driving force for the rise in TB incidence in the African countries. Furthermore, TB is responsible for more than a quarter of deaths in people living with HIV. Resistant strains are the

result of improper use of antibiotics in chemotherapy of drug-susceptible TB patients due to different reasons (inadequate treatment regimen, failures in national health programs, poor treatment compliance and case management, poor quality or wrong/insufficient supply of drugs) (http://www.who.int/tb/en/). Strains, which are resistant to the most important drugs for TB treatment, Isoniazid and Rifampicin, are called multi drug resistant (MDR). This form of TB does not respond to the standard treatment with first-line anti-TB drugs. In contrast, treatment has to be performed with drugs that are less potent, more toxic and much more expensive and may be taken for up to two years or more. The presence of MDR strains among new cases was estimated to range from 0 to 28.3 % in different countries (WHO, 2010b). The highest proportions of resistant strains occur in countries of Eastern Europe and Central Asia. To worsen the situation, extensively drug-resistant strains (XDR), which are resistant, besides to Isoniazid and Rifampicin, to the most important drugs used for treatment of MDR-TB, namely fluorochinolones and the injectable drugs (Amikacin, Capreomycin, Kanamycin), have recently been reported in many countries.

Transmission and Prevention

TB transmission normally occurs via airborne spread of droplet nuclei contaminated with TB bacteria. These are produced by coughing, but also sneezing and speaking of diseased patients. Thus, isolation of contagious patients is an effective means to interrupt transmission. To substantiate transmission of TB, molecular based fingerprint technologies are available. Not only individual cases of transmission can be proven by these techniques but also larger outbreaks which even may last several years (Murray and Nardell, 2002).

For preventive vaccination with an attenuated *M. bovis* strain, the bacillus Calmette and Guérin (BCG) is available. The vaccination is administered to children throughout the world. However, efficient protection is only proved for disseminated infection in children, but not for pulmonary disease in adults. In several countries (e. g. Germany) BCG vaccination is no longer recommended (STIKO, 2010).

Diagnostics

Rapid detection of tuberculosis infection is mandatory for optimal patient management and appropriate implementation of infection control measures.

The tuberculin skin test indicates previous contact with *M. tuberculosis* (Mack et al., 2009). However, cross-reactivity to the BCG vaccine strain and to some non-tuberculous mycobacteria can lead to false positive results. In contrast, the newly developed interferon-γ (IFN-γ) release assays (IGRAs) are not influenced by the BCG strain and most non-tuberculous mycobacteria (Mack et al., 2009). These assays measure the IFN-γ release of sensitized T-cells after stimulation with *M. tuberculosis*-specific antigens. National guidelines differ in recommendation for application of these tests, but for three main areas agreement for clinical practice of the tests is high. Assays can be used for contact tracing after identification of a TB patient, as well as for screening of health care workers. Furthermore, the tests are recommended before onset of tumor necrosis factor antagonist treatment (Zellweger, 2008).

Microbiological detection of *M. tuberculosis* still represents the final proof of TB infection (DIN 1996, CLSI 2008). Smear microscopy is the most rapid technique, however with a low sensitivity. It may help to recognize the highly infectious patients and to supervise treatment success. Comparably fast but with a higher sensitivity, nucleic acid amplification techniques (NAT) enable a rapid detection of TB bacteria from patient specimens. By NAT of smear positive specimens, TB can very quickly be proved or ruled out with a very high sensitivity and specificity in, . In smear negative specimens, sensitivity is generally lower (60-90 %). Thus, TB cannot be excluded by a negative NAT result from a smear negative specimen. Some new NA techniques enable not only the detection of TB bacteria but also the review of the presence of mutations, which are responsible for antibiotic drug resistance. By this, patients infected with an MDR strain can be identified immediately.

Reference standard for TB diagnostics still is the cultural investigation. Liquid culture media enable the growth of TB bacteria within one to two weeks, although solid media are still necessary due to a higher contamination rate of the liquid media. In case of mycobacterial growth, species identification has to be performed. More than 150 validly described species are currently summarized to the genus *Mycobacterium*. Sufficient discrimination of these species can only be obtained by the use of molecular techniques like line probe assays or sequence analysis. Beside the most important *M. tuberculosis*, several other, genetically highly related species are merged to a group named *M. tuberculosis* complex. This includes *M. bovis* ssp. *bovis* (syn. *M. bovis*), *M. bovis* ssp. *caprae* (syn. *M. caprae*), *M. bovis* BCG, the vaccine

strain, *M. africanum, M. microti, M. pinnipedii, and 'M. canetti'.* With the exception of *M. africanum* and *'M. canetti'*, the main hosts of the other species are animals, like cattle, voles, or pinnipeds. *'M. canetti'* is assumed to represent an ancestral lineage of the *M. tuberculosis* strains and has only been found in a restricted area of Africa (Fabre et al. 2010).

Current therapy of tuberculosis is a 6-month treatment composed of two phases (WHO 2009): within the first phase, which lasts two months, patients are treated with four antibiotics, isoniazid, rifampicin, pyrazinamide, and ethambutol. The duration of the second phase is 4 months and treatment is reduced to the two drugs isoniazid and rifampicin. It is essential to perform drug susceptibility testing on isolates of newly diagnosed patients to prove that the treatment regimen is adequate or to identify resistant strains. In case of drug resistances, treatment has to be adapted accordingly with regards to drugs and duration.

References

Brodhun, B., Altmann, D., and Haas, W.: Bericht zur Epidemiologie der Tuberkulose in Deutschland für 2008; Robert Koch-Institut, Berlin, 2010.

CLSI; Clinical and Laboratory Standards Institute: *Laboratory detection and Identification of Mycobacteria*; Approved Guideline M48-A. Clinical and Laboratory Standards, 2008.

DIN 58943-3: Medizinische Mikrobiologie – Tuberkulosediagnostik – Teil 3: Kulturelle Methoden zum Nachweis von Mykobakterien (DIN 58943-3:1996), 1996.

Fabre, M., Hauck, Y., Soler, C., Koeck, J.L., van Ingen, J., van Soolingen, D., Vergnaud, G., and Pourcel, C.: Molecular characteristics of "Mycobacterium canettii" the smooth Mycobacterium tuberculosis bacilli. Infect. Genet. Evol. 10:1165-1173, 2010.

Mack, U., Migliori, G.B., Sester, M., Rieder, H.L., Ehlers, S., Goletti, D., Bossink, A., Magdorf, K., Hölscher, C., Kampmann, B., Arend, S.M., Detjen, A., Bothamley, G., Zellweger, J.P., Milburn, H., Diel, R., Ravn, P., Cobelens, F., Cardona, P.J., Kan, B., Solovic, I., Duarte, R., Cirillo, D.M., and Lange, C.: LTBI: latent tuberculosis infection or lasting immune responses to M. tuberculosis? A TBNET consensus statement. Eur. Respir. J., 33(5), 956-973, 2009.

Murray, M. and Nardell, E.: Molecular epidemiology of tuberculosis: achievements and challenges to current knowledge. Bull. World Health Organ., 80, 477-482, 2002.

STIKO: Impfempfehlungen der Ständigen Impfkommission (STIKO) am Robert-Koch-Institut; Stand: Juli 2010; Epidemiologisches Bulletin, 02.08.2010, Nr. 30, 2010.

World Health Organization: Global tuberculosis report: WHO report 2010, WHO/HTM/TB/2010.37; ISBN 978 92 4 156406 9, Geneva, 2010a.

World Health Organization: Multidrug and extensively drug-resistant TB (M/XDR-TB): 2010 global report on surveillance and response, WHO/HTM/TB/2010.3; ISBN 978 92 4 159919 1, 2010b.

WHO: Treatment of tuberculosis: guidelines – 4th ed., WHO/HTM/TB/2009.420; ISBN 978 92 4 154783 3, 2009.

Zellweger, J.P.: Latent tuberculosis: which test in which situation? Swiss Med. Wkly. Jan. 26, 138(3-4), 31-37, 2008.