Pathogenesis

General Overview 1, 2

- **TB** is caused by an *organism* called *Mycobacterium tuberculosis* that is spread from person to person through the air. *M. tuberculosis* organisms are sometimes called tubercle bacilli. When a person with infectious TB disease coughs or sneezes, droplet nuclei containing tubercle bacilli may be expelled into the air. Other people may inhale the air containing these droplet nuclei and become infected. Each infected non-treated TB patient infects on average 10 to 15 other healthy individuals per year.

- **TB infection** begins when the tubercle bacilli multiply in the small air sacs of the lungs. A small number enter the bloodstream and spread throughout the body, but the body's immune system usually keeps the bacilli under control. People who have latent TB infection (LTBI) but not TB disease do not have symptoms of TB, and they cannot spread TB to others.

- In a percentage of infected people like HIV positives or other immunosuppressed persons, the immune system loses its ability to keep the tubercle bacilli under control and the bacilli begin to multiply rapidly, causing TB disease. This can happen very soon after TB infection or many years after infection. Up to 10% of people who have LTBI will develop disease at some point.

- TB disease usually occurs in the lungs (*pulmonary TB*), but it can also occur in other places in the body (*extrapulmonary TB*). *Miliary TB* occurs when tubercle bacilli enter the bloodstream and are carried to all parts of the body, where they grow and cause disease in multiple sites.

- **Primary infection** occurs in people who have not had any previous exposure to tubercle bacilli. Droplets are inhaled into the lungs. Infection begins with multiplication of tubercle bacilli in the lungs. The immune response develops about 4–6 weeks after the primary infection. The size of the infecting dose and the strength of the immune response determine what happens next. In most cases, the immune response stops the multiplication of bacilli. However, a few dormant bacilli may persist, and this is referred to as "Latent TB Infection", a state of TB infection without overt clinical disease. Such individuals are not infectious.

- Until recently *a positive tuberculin skin test* was the only evidence of infection, and the lack of specificity of this test, and its character of remaining positive essentially for life, has hampered understanding of the true rates of progression from the Latent TB state. In a few cases the immune response is not strong enough to prevent multiplication of bacilli, and disease occurs within a few months.
Pathogenesis

- **Post-primary TB** occurs after a latent period of months or years following primary infection. It may occur by reactivation of the *dormant tubercle bacilli*. Dormant bacilli persisting in tissues for months or years after primary infection start to multiply as a result of e.g. weakening of the immune system by HIV infection.

- Post-primary TB (PTB) usually affects the lungs but can involve any part of the body. The characteristic features of post-primary TB are the following: extensive lung destruction with cavitation and positive sputum smear. Patients with these lesions are the main transmitters of infection in the community.

[References: 3, 4, 5, 6, 7, 8]

Consequence of HIV / M. Tuberculosis Co-Infection

- Compared with an individual who is not infected with HIV, a person infected with HIV has a 10 times increased risk of developing TB disease.

- In populations where HIV/TB is common, health services struggle to cope with the large and rising numbers of TB patients.

- The consequences include the following:
  - Under-diagnosis of sputum smear-positive PTB (due to excess laboratory workload);
  - inadequate determination of active drugs (via drug susceptibility testing) and supervision of anti-TB chemotherapy;
  - low cure rates;
  - high morbidity and mortality during treatment;
  - interaction of TB drugs with HIV antiviral therapies;
  - high rates of TB recurrence;
  - increased transmission of drug-resistant strains among HIV-infected patients.
Pathogenesis

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[References: 9, 10, 11, 12, 13]
Clinical Aspects of TB

- Tuberculosis is defined as the **clinically, bacteriologically, and/or radiographically manifest disease**. The tubercle bacillus can affect many organs but prefers the lung (lung is involved in 85% of all infections), and the corresponding lymph nodes (“Lymphadenitis”). The bacteria cause granulomatous knots (“Tubercle”), tissue destruction and necrosis (“Caverns”).

- If *M. tuberculosis* is excreted with the sputum, urine or stool the TB is called **“overt TB”** which is **highly contagious**. In about 95% of all new cases *M. tuberculosis* was transmitted by aerosols.

- Where infection has occurred but the primary immune response has contained its extent, the subject has **“Latent TB Infection”** which is a subclinical infection with tubercle bacilli without clinical signs or symptoms of manifest disease. Although no symptoms are associated with LTBI, it is a precursor to the clinical disease. It is thought that about 10% of all infections, progress to the “Post-primary TB” or “Active TB” state. Clinical symptoms are chronic fever, loss of weight, night sweats and cough producing purulent or hemorrhagic sputum.

- **Progression to active disease** is enhanced by a weakened immune status. Malnutrition, stress, certain viral infections, diabetes mellitus, alcoholism, treatment with cortisone or radiation, drug abuse and other factors can weaken the immune system and force progression to active TB disease.

- **Active TB** is divided into **pulmonary** (80-90% of cases) and **extrapulmonary** (10-20% of cases) forms, and is further subdivided according to the presence (smear positive) or absence (smear negative) of stained *Mycobacterium tuberculosis* organisms in microscopically examined clinical specimens such as sputum. *M. tuberculosis* positive sputum smear is an indicator of high infectiousness.
Global epidemiology and measures to curb TB

- In 2004, 8.9 million new TB cases with active disease were estimated globally, thereof 3.9 million cases to be sputum positive. Fewer than half of the new cases were reported however.\textsuperscript{15}

- In addition to the millions living with active TB disease, one third of the world’s population, that is, two billion people, are suggested to be infected with \textit{M. tuberculosis}. This figure may be altered in the light of the more accurate tests for TB infection now available.\textsuperscript{14}

- \textit{Inadequate case detection} is a major constraint on TB control in high-incidence countries. Sputum microscopy is the most frequently used test for the diagnosis of pulmonary TB in low and middle-income countries, where 95% of TB cases and 98% of deaths occur. This test is simple to perform and cheap but the sensitivity of the test for identifying cases of pulmonary TB has been reported to be rather low. There are worldwide still 1.6 mil deaths a year and TB remains the world’s second most cause of death from an infectious agent, after HIV.\textsuperscript{15}

- The HIV epidemic has a huge impact driving up incidence rates dramatically. Globally, an estimated 13\% of new TB cases were infected with HIV in 2004.\textsuperscript{14} Smear microscopy is even less sensitive in HIV co-infected patients.

- New challenges are posed also by \textit{multi-drug resistant tuberculosis} (MDR-TB) which are resistant to 2 of the most widely used first line drugs, and now \textit{extensively drug resistant TB} (XDR-TB). The annual number of new cases of MDR-TB was about 423,000 in 2004 and more than 35 countries worldwide have seen cases of XDR-TB. Recently, as a result of an airline passenger infected with multi-drug resistant TB, the CDC (Centers for Disease Control and Prevention) started a search for other passengers and crew on 2 trans-Atlantic flights who most likely have been in contact with the infected person and might be cross-infected with this almost incurable form of TB. This indicates that in the current world of travel, it will be almost impossible to keep TB within country borders.

- In 1993, the WHO declared TB a global emergency and in 1995, the WHO recommended the \textit{DOTS} (directly observed treatment, short-course) strategy to curb global epidemiology with the “Framework for Effective Tuberculosis Control”. The DOTS strategy as originally formulated may not be sufficient on its own to bring TB under control in developing countries.

- The WHO launched in 2002 the \textit{Expanded Framework and DOTS}\textsuperscript{16} as a brand name to allow to control TB and to complete the basic strategy with additional diagnostic elements (e.g. culture, drug susceptibility testing, and screening in high-risk groups).
Epidemiology and trends in Europe

– In the last 50 years specific trends became overt in the low-incidence industrialized countries in central Europe:
  
  » Gradual increase of latent TB infection.
  
  » Emergence of groups at particularly high risk of TB (e.g. HIV infected patients, prisoners in certain settings, refugees, homeless and poor persons etc).
  
  » Importation of TB including drug-resistant and multi drug resistant cases from Eastern European and other countries (like Africa). About 50% of TB cases in central Europe are foreign born (immigrants) and many are co-infected with HIV. This phenomenon is particularly highlighted by increased international migration from high- to low-incidence countries as a result of open borders within the EU. Of the almost 100,000 reported TB cases in Europe in 2005, 35% came from the new EU members Bulgaria and Romania. The overall notification rate in Europe was 18/100,000 with Romania, the Baltic States, Bulgaria and Portugal far above this average. Greece, Sweden and the UK experienced substantial increases between 2001 and 2005.
  
  » TB control measures became intermediately less strict, public health control measures were largely ignored even by TB specialists and specific knowledge was progressively lost. Inadequate treatment was not efficiently tracked any more and the result was a resurgence of micro-epidemics and resistance to anti-TB drugs.

Incidence de la tuberculose (Taux pour 100,000), Europe, 2004

Source: EuroTB
Epidemiology - Clinical Dimension

Epidemiology and trends in Europe

- **TB elimination strategy in low-incidence countries** aims at decrease of both TB incidence and prevalence. Elimination of TB means less than one infectious/sputum smear positive case per 1 mil inhabitants and declining.

- The basic **control strategy in low-incidence countries** aims at minimizing transmission of TB by maintaining high case-finding and cure rates especially among definite cases (bacteriologically confirmed):

  » **Risk group management**: As TB declines in a community, groups at particularly high risk become more visible, providing an opportunity for targeted intervention by ensuring early detection and treatment until cure. Risk groups for infection and active TB disease are **immunocompromised** individuals (HIV infection and patients with immunosuppressive therapy), intravenous drug users, healthcare workers, residents of jails and prisons, immigrants from countries with a high incidence, homeless people and elderly. Risk group management requires active case-finding and provision of effective treatment.

  » Prevention of transmission of infection in **institutional settings** such as jails, prisons, hospitals, nursing homes, shelters for the homeless and new immigrants by diagnostic services and isolation of suspects.

  » Reducing prevalence of TB through **outbreak management** and provision of preventive therapy for specified groups and individuals.

  » **Drug susceptibility testing**, surveillance and treatment outcome monitoring with special consideration of drug and multi-drug resistance.

- **Control and elimination strategy** in Europe requires national schemes and networks, legal framework with compulsory notifications of all TB cases. Access to accurate diagnostics is pivotal both for early and sensitive detection of infection, drug sensitivity testing of TB and TB monitoring.

- **A reasonable target for low-TB incidence countries is to screen 95% of high-risk groups, treat 95% of infected patients and reduce the proportion of patients with treatment failure/default/ to less than 10%**. 


Epidemiology – Economic Dimension

TB always is associated with considerable socioeconomic problems. A comprehensive survey entitled “The socioeconomic burden of TB” can be found in the 2006 WHO Study “Diagnostics for tuberculosis. Global demand and market potential”14.

Data from the US and Canada concerning direct and indirect costs of tuberculosis in industrial countries have estimated the cost at between $700 million (€560 million) and $1 billion (€800 million)19.

In 2004 a comprehensive study: “The cost structure of lung tuberculosis in Germany”20 was published, it delivers more actual data for a European country. These data can be considered to be more typical for the situation within the EU.

– Approximately 80 % of all cases in Germany are lung tuberculosis20.

– The study takes the point of view of the state health insurance system. The basic presumptions for the cost calculations are based on the official guidelines issued by the “Deutsches Zentralkomitee zur Bekämpfung der Tuberkulose” (DZK) for the therapy of lung tuberculosis20. The costs include diagnosis. The calculation of drug costs is conservative: It is based on the cheapest drugs available which fulfil the requirements of the guidelines21. However with the emergence of MDR and XDR-TB, these might be underestimated.

– The hospitalisation rate for patients with lung tuberculosis is 80 %22.
Epidemiology – Economic Dimension

- The study discriminates:
  - direct outpatient costs,
  - direct hospital costs,
  - direct costs caused by sickness benefit, and
  - average treatment costs for lung tuberculosis in adults and children following primary hospitalisation.

- The conclusion of this study is: “The case costs calculated here for Germany referring to lung TB as an acute disease with average direct costs of €16,388.96 (€14,301.13 treatment costs plus €2,087.83 sickness benefit) and indirect costs of €2,460.83 for adults and €16,634 for children clearly indicate their economic significance.”

- These findings now can be linked with the official figures of the German “Robert Koch Institut” for 2004, which indicate 6,583 cases of clinically manifested tuberculosis.

- As a result the magnitude of direct economic impact of tuberculosis in Germany amounts to a minimum of €108 million. (This seems to be a conservative calculation, as in the 2004 report of the “Statistisches Bundesamt” the direct treatment costs alone are reported with €112 million.

- Transferred from Germany to the scale of the entire EU and considering the regional variation of incidence this would mean a magnitude of more than €1 billion. Thus a disease which has vanished from the awareness of many in Europe as a matter of fact still has a severe impact not only on public health, but also on economy.
Latent TB Infection

- The enormous pool of individuals with latent tuberculosis infection poses a major hurdle for (TB) elimination. The lifetime risk of developing disease is assumed to be 10% for those recently infected. In developed countries, the prevalence of latent infection in the general population is much lower, but can be high in certain populations such as immigrants, prisoners, homeless people, and contacts of new cases. Groups with low prevalence of TB infection but at high risk of progression if infected, such as HIV patients, other immunocompromised individuals, intravenous drug users, and health workers, are important foci of clinical investigation. However, HIV-coinfection may pose the highest risk towards active disease progression. It has been shown that a preventive therapy with Isoniazid (usually for 9 months) dramatically reduces this risk. In Western countries, TB develops typically from reactivation of a latent infection and rarely from a primary infection.

- Therefore, in low-prevalence countries like Germany (2003; TB incidence of 8.7/100,000), the focus is increasingly changing from diagnosis and therapy of active TB to identification of persons infected with M. tuberculosis. The two broad categories of persons who should be tested for latent TB infection are those who are likely to have been recently infected (such as contacts to infectious TB cases) and persons who are at increased risk of progression to TB disease following infection with M. tuberculosis (e.g. HIV infection and selected medical conditions; recent immigrants from high TB-burden countries). Full eradication of TB requires the reliable diagnosis of LTBI and its effective eradication by drug susceptibility testing to define adequate treatment.
Available Tests per Disease State

Latent TB Infection

– For nearly a century, the *tuberculin skin test* (TST) was the only tool available for the detection of LTBI. The diagnosis of LTBI can neither be made by clinical investigations nor by microbiological analysis, but so far only indirectly using the TST. Although the TST has proven to be useful in clinical practice, it has known limitations in accuracy and reliability.

– A major breakthrough in recent years has been the development of *in vitro assays* that measure T-cell release of interferon-γ (IFN-γ) in response to stimulation with highly TB-specific antigens. *Interferon gamma assays* (IGRAs) have higher specificity than TST and a better correlation with surrogate markers of exposure to *M. tuberculosis* in low incidence settings. Besides high specificity, other potential advantages of IGRAs include logistical convenience, need for fewer patient visits to complete testing, avoidance of somewhat subjective, measurements such as skin induration.

Despite a growing evidence base, several unresolved and unexplained issues remain. These include unexplained *discordance between the TST and IGRAs* results, like unknown predictive value of IGRAs for the development of active TB, insufficient data on test performance in high-risk populations such as children and individuals with HIV infection.

– *In summary, the emergence of novel tools, such as IGRAs has expanded the armamentarium of diagnostics available for LTBI. However, there is currently no accurate tool to predict which latently infected individuals are at greatest risk of disease progression*.27
Available Tests per Disease State

Active Pulmonary TB

- Disease of the lungs is the **most common form of active TB** and is the **infectious** form of the disease. A highly infectious person can transmit disease to 10–15 persons in a year, with household members being particularly at risk\(^{33}\).

- Pulmonary TB can be diagnosed by chest radiography, sputum smear microscopy and by cultivation of *M. tuberculosis*, which is considered as the gold standard. However, clinical appearances of TB are multiple with non-specific symptoms\(^{34}\). Therefore, since the discovery of TB, the basis for its definite diagnosis has been the *detection of the bacillus in clinical specimens* via culture or other diagnostic methods\(^{14}\).

- **Radiographic methods for detection of active disease**
  It is still widely believed that tuberculosis of the lung can be diagnosed by chest X-ray alone. Practical experience and numerous studies have shown that no radiographic pattern is diagnostic of tuberculosis\(^{35}\). Many diseases of the lung have a similar radiographic appearance that can easily mimic *tuberculosis*\(^{36}\). Similarly, the lesions of pulmonary tuberculosis can take almost any form on a radiographic picture\(^{37}\). To establish the tubercular aetiology of an abnormality, further examination is necessary and only **bacteriology** can provide the necessary proof\(^{14}\).

- **Smear microscopy**
  Worldwide, the most common diagnostic test used to detect TB is microscopic examination of stained sputum or other clinical material smeared on a glass slide. When present in sufficiently high concentrations, the bacteria can be readily identified by a trained technician using this technique, which has changed little since it was invented over 100 years ago. Microscopy however requires a large number of bacilli to be present in order for the result to be positive (5000–10,000 per ml of sputum), and identifies only the most infectious subset of patients. It has a **limited sensitivity** (35 to 70%), especially for less advanced disease. Certain groups of patients, such as those with advanced HIV coinfection, people with TB outside the lungs, and children can not be diagnosed with this technique. Duplicate or triplicate sputum examinations are used but do not overcome this problem. This need for multiple tests, each of which requires sputum collection, drying, staining and meticulous examination, results in delays in reporting.
Available Tests per Disease State

Active Pulmonary TB

- **Culture**
  Bacteriological culture, considered the diagnostic gold standard, can identify the *M. tuberculosis* organism in over 80 to 90% of TB cases with a specificity of over 98%. As few as 10–100 viable bacilli per ml of sputum may be detected, with automated liquid culture methods being the most sensitive ones. Compared to smear microscopy, culture is more expensive but allows *detection of more forms of disease, including less advanced cases*. As *M. tuberculosis* grows slowly, conventional culture with visual detection of bacterial colony formation usually requires 2–6 weeks. Automated liquid culture systems shorten the detection period to 1–2 weeks in most cases\(^{14,38}\).

- **Nucleic acid amplification tests (NATs)**
  Nucleic acid amplification constitutes an improvement in the rapid detection and identification of *M. tuberculosis*. *Bacterial DNA* (or ribosomal RNA transcribed into DNA) is amplified and detected with an appropriate reading system via a signal-generating probe. The most widely used are *PCR* (polymerase chain reaction), *TMA* (transcription mediated amplification) and *SDA* (strand displacement amplification). Also upcoming is TRC (Transcription Reverse transcription Concerted reaction). Tests based on nucleic acid amplification are usually highly specific for *M. tuberculosis* (close to 100%). Positive results can be obtained with less than 10 bacteria/ml; therefore sensitivity is much better than smear microscopy, but slightly less than culture. Currently, nucleic acid tests are used primarily for confirmation of smear-positive results or for primary case finding using specific algorithms in risk groups in combination with other methods. The most outstanding feature of nucleic acid amplification methods is the short time-to-result (between a half and one working day, including sample preparation)\(^{14}\).
Available Tests per Disease State

Active Pulmonary TB

- For example, the German National Reference Center (NRC) for Mycobacteria performs 50-80 NAT tests on pulmonary and extrapulmonary specimens weekly. Investigated specimens are only from **patients with a strong suspicion of TB**. This includes patients with:
  » immunosuppression;
  » history of chronic pulmonary disease with cough, weight loss, and night sweats;
  » positive tuberculin skin test;
  » known risk factors for TB, such as homelessness or drug abuse;
  » history of TB with or without appropriate treatment;
  » history of contact with smear-positive patients;
  » children with suspicion of lymph node TB because of the high incidence of M. avium complex infections; and
  » specimens obtained by biopsies, surgery or other invasive procedures in patients with suspicions of TB. It is important to inform the clinicians about the criteria and limitations for requesting NATs (Ruesch-Gerdes 2002).

- NATs can easily **discriminate between M. tuberculosis and non-M. tuberculosis** isolates, giving relevant information to the clinician with respect to diagnosis and optimal treatment of a particular patient. Currently, the U.S. Food and Drug Administration (FDA) requires that culture (still considered the “gold standard” for TB diagnosis) must be done in conjunction with each amplification-based test[^39].
Available Tests per Disease State

Extrapulmonary TB, Pediatric TB and TB in HIV-Seropositive Patients

- TB is not limited to the lungs but can affect virtually any organ of the body. Persons with extrapulmonary tuberculosis make up about 10–20% of all those with active TB.

- Diagnosis of TB in HIV-seropositive individuals, in children, and in persons with extrapulmonary forms of TB, remains an unmet challenge in both high-prevalence and low-prevalence settings. Persons with extrapulmonary TB do not transmit disease and those immunocompromised by HIV and/or of paediatric age generally transmit less owing to the lower frequency of cavitary disease and/or expectoration (children). While this makes them less of a public health threat, they remain a dilemma of nightmare proportions for physicians in clinical practice. Often lab diagnosis is the only tool as clinical symptoms are asymptomatic and radiography and TST are unreliable.

Multidrug Resistant TB

- Anti-tuberculosis drug resistance is a major public health problem. 4.3% of all new and previously treated cases are MDR\textsuperscript{25}. Strains that are resistant to a single drug have been documented in every country surveyed; what is more, strains of TB resistant to all major anti-TB drugs have emerged. Drug-resistant TB is caused by inconsistent or partial treatment, when patients do not take all their medicines regularly for the required period because they start to feel better or because doctors and health workers prescribe the wrong treatment regimens (not using culture to confirm drug efficiency). A particularly dangerous form of drug-resistant TB is multidrug-resistant TB, which is defined as the disease caused by TB bacilli resistant to at least isoniazid and rifampicin, the two most widely used primary drugs anti-TB drugs. Rates of MDR-TB are high in some countries, especially in the former Soviet Union and the Baltic States, which are now part of the EU with its open borders, and threaten TB control efforts. Drug-resistant TB requires extensive chemotherapy (up to two years of treatment) that is often prohibitively expensive (often more than 100 times more expensive than treatment of drug-susceptible TB), and is also more toxic to patients. More recently, extensively drug-resistant tuberculosis has emerged. XDR-TB is defined as MDR-TB plus resistance to any fluoroquinolone and at least 1 of 3 injectable second-line drugs like capreomycine, kanamycin, amikacin. XDR-TB has been found up to now in 4% of MDR-TB cases in the US and in 19% of MDR-TB cases in Latvia. However, XDR-TB strains have been found in all regions of the world. XDR-TB underlines the need for investment in the development of new TB diagnostics, treatments and vaccines, since the current tools are outdated and insufficient\textsuperscript{40}. 
Available Tests per Disease State

Multidrug Resistant TB

Worldwide 35 countries have confirmed presence of XDR TB up to March 19 2007. In the last 12 months before that day, 16 new countries have been added. Confirmed cases have so far been found in Europe in the Czech Republic, Germany, France, Ireland, Latvia, Lithuania, Norway, Poland, Portugal, Romania, Slovenia, Spain, Sweden, The Netherlands, UK, and now recently also in Italy where 2 cases of XDR-TB were found that were resistant to all available first and second line drugs, and as such virtually untreatable41.
Multidrug Resistant TB

- **Culture**
  
  *MDR-TB strains* have emerged within the last decade, and the rapid detection of these isolates is critical for the effective treatment of patients. As recommended by the MDR TB Task Force, to combat MDR-TB, culture **drug susceptibility testing** (DST) must be performed on all initial and follow-up *M. tuberculosis* isolates from each patient\(^4\). 

- **CDC guidelines** recommend that mycobacteriology laboratories work toward the goal of reporting first-line susceptibility results of *M. tuberculosis* within 15–30 days of receipt of the initial diagnostic specimen\(^4\). One of the major breakthroughs in culture-based testing was the introduction of radiometric liquid media on the semi-automated *BACTEC 460TB System* (BD Diagnostics – Diagnostic Systems, Sparks, MD) which led to a considerable shortening of the time required for the detection and DST of *M. tuberculosis*. DST for both primary and secondary antituberculosis drugs with the broth-based radiometric BACTEC 460 TB system and the **non-radiometric BACTEC MGIT 960** system are well established and are considered the "gold standard" (Ruesch-Gerdes et al. 2006). This new broth-based system was shown to report DST results on average in 6.5 days with similar accuracy compared to the radiometric Bactec 460 TB system while being fully-automated and using non-radiometric media\(^4\).\(^5\).

- **The rapid determination of drug resistance** via culture of Mycobacterium tuberculosis in clinical isolates is the prerequisite for the initiation of effective chemotherapy ensuring successful treatment of the patient and preventing further spread of drug-resistant isolates\(^6\).
Available Tests per Disease State

Multidrug Resistant TB

- **Nucleic acid amplification tests**
  The development of drug resistance in *M. tuberculosis* isolates is the result of random genetic mutations in particular genes conferring resistance. Based on this knowledge, molecular assays have been established that allow the prediction of drug resistance in clinical *M. tuberculosis* isolates within one working day and potentially are the most rapid methods for the detection of drug resistance. The utility of such assays depends on different aspects, such as the technical requirements of each method and the ability of different tests to detect the most common drug resistance mutations in a given area. However, one must be aware that the NATs for the detection of MDR-TB have the same limitations as other molecular tests for the detection of antibiotic resistance, and therefore, it cannot totally replace traditional culture-based methods for DST. This is basically due to the fact that none of the molecular tests established targets all possible genes or mechanisms (some are not identified yet) involved in resistance, and thus, a variable proportion of resistant strains will not be detected. The second inherent limitation is the detection limit of ca. 10% mutant DNA in a mixture of wild-type and mutant DNA. If the proportion of resistant cells in an isolate is less than that amount, it can hardly be detected by molecular methods, whereas classical susceptibility testing might give a more sensitive test result in these cases. Nevertheless, the NATs for the detection of MDR-TB appear to be a valuable tool that allows the detection of resistant *M. tuberculosis* isolates within one working day and can easily be included in routine workflow. Considering the high rates of resistant and MDR isolates in several parts of the world, especially in Eastern Europe, such a test has the potential to complement and accelerate the variety of different measures in laboratory diagnostics that are necessary for improved tuberculosis control in the future.

- **In summary, rapid detection of drug resistance is paramount, not only for effective treatment of TB patients but also for initiating adequate public health measures.**

- **Rapid and accurate diagnosis** is critical to the clinical care of tuberculosis patients and to the arrest of disease transmission.
Available Tests per Disease State

Multidrug Resistant TB

- Four issues are of paramount importance for control of TB:
  » the ability to make an early diagnosis;
  » the testing of drug susceptibility and the availability of effective anti-tuberculous treatment;
  » prevention of disease transmission to others; and
  » prevention of drug resistance.

- Early and accurate diagnosis of TB can be considered to be the most significant interventional step because this allows expedited treatment and limitation of spread, with inherent cost-saving implications. The diagnosis of TB is made based upon clinical and/or laboratory findings.

- Unfortunately, there are no clinical findings which are exclusive for TB. The symptoms which suggest TB, such as a persistent, productive cough, fever, chills, night sweats and weight loss, are also suggestive of many other systemic diseases of infectious and noninfectious origin. Therefore, the diagnosis and clinical management of TB relies heavily upon laboratory testing\textsuperscript{47}.
Summary

- TB remains a serious public health problem among certain patient populations and is highly prevalent in many urban areas. The majority of *M. tuberculosis* infections are **latent infections** without any pathological findings. However, there has been renewed interest in the treatment of risk groups with latent TB infection as a TB-control strategy for eliminating the large reservoir of individuals at risk for progression to TB.

- The expansion of the EU and the looming threat of **MDR and XDR TB** make the reexamination of TB-infection control a matter of priority for many Public Health experts.

- The diagnosis of pulmonary and extrapulmonary TB cannot be made without **diagnostic tests** and more than one type of diagnostic test is needed to assist in TB care and control\(^1\). Modern IVD tests for tuberculosis are available throughout Europe.

- As discussed above, **IGRA tests** to detect TB infection, which causes TB disease, open new opportunities to Public Health officials in the fight against TB. Those tests, the introduction of which began in 2004, are currently offered by public and private laboratories in all countries of the EU.

- **Liquid-based automated growth indicator detection** methods, which shorten the time needed to provide proof that disease symptoms are due to *M. Tuberculosis*, and to define which drugs are active have been widely available since the 1990´s.

- **Molecular detection methods** (NATs), also introduced in the 1990´s, are offered by most laboratories providing classic culture growth detection methods.

- New, **strain-specific methods** are currently being introduced to examine in greater detail the genetic characteristics of isolated strains and furnish information to practitioners as to which therapies will be most appropriate to heal those diagnosed with TB.
Summary

- It is of tremendous value, both clinically and economically, to have access to rapid tests for TB. Not only does earlier detection lead to improved patient care for individuals suspected of having the disease, but there is also abundant data which shows that rapid diagnosis leads to overall savings within the hospital. Faster diagnosis means patients can be more appropriately managed at an earlier stage, resulting in better control of the spread of TB, avoidance of unnecessary suffering of patients, and more efficient utilization of hospital resources. There are also growing numbers of MDR cases in Western Europe in certain risk groups such as recent immigrants from high TB-burden countries, and many countries have seen the first cases of XDR TB. Active case finding and a good cooperation between public health institutions, clinicians and TB laboratories are essential in the prevention of TB.

- TB infection also has a huge burden on the patient and the community via potential cross-infection if it goes on undiagnosed and not treated efficiently.

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<th>Acronym</th>
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<td>CDC</td>
<td>Centers for Disease Control and Prevention</td>
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<td>DOTS</td>
<td>directly observed treatment, short-course</td>
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<td>DST</td>
<td>Drug susceptibility testing</td>
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<td>Extrapulmonary TB</td>
<td>TB occurring outside of lungs</td>
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<td>NRC</td>
<td>National Reference Center</td>
</tr>
<tr>
<td>LTBI</td>
<td>Latent tuberculosis infection (M. tuberculosis)</td>
</tr>
<tr>
<td>PCR</td>
<td>Polymerase chain reaction</td>
</tr>
<tr>
<td>PTB</td>
<td>Post-primary TB</td>
</tr>
<tr>
<td>Pulmonary TB</td>
<td>TB occurring in the lungs</td>
</tr>
<tr>
<td>SDA</td>
<td>Strand displacement amplification</td>
</tr>
<tr>
<td>TB</td>
<td>Tuberculosis</td>
</tr>
<tr>
<td>TMA</td>
<td>Transcription mediated amplification</td>
</tr>
<tr>
<td>TRC</td>
<td>Transcription Reverse transcription Concentrated reaction</td>
</tr>
<tr>
<td>TST</td>
<td>Tuberculin skin test</td>
</tr>
<tr>
<td>XDR-TB</td>
<td>Extremely drug resistant tuberculosis</td>
</tr>
</tbody>
</table>