

Tuberculosis - An increasing global health problem, presenting Russia as an example.

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1 Summary

Background

Tuberculosis (TB) is an important global public health problem. Although increasing, the prevalence of TB in Norway is low, however the situation changes completely crossing the border to our neighbor country Russia. We wanted to learn more about management of TB, the global TB situation and the situation in Russia.

Materials and methods

We made a study tour to Arkhangelsk and visited the Arkhangelsk Antituberculosis Dispensary to learn some of the basics about TB care in high prevalence settings. Back in Norway we used WHO reports, searched in the PubMed database and other written sources to gather the appropriate information.

Results and interpretations

According to the WHO, TB caused 1,7 million deaths in 2009. For the last decades considerable resources have been mobilized in the fight against TB. The WHO indicators tell that the situation is improving at a global level, but there are still challenges to overcome. One of them is the high incidence of multi-drug resistant TB, as in Arkhangelsk Oblast in the Russian Federation. TB still requires the world's attention as a global health problem.

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2 Introduction

Although Norway is a country with low prevalence of tuberculosis, the disease is a threat to global health. Considering as well, the high prevalence in the northwestern parts of Russia, we thought it could be useful to learn more about TB management in general and to give an overview of the current TB situation, both globally and in Russia. Spending time at the Antituberculosis Dispensary in Arkhangelsk in November 2009, provided us an inside view on the actual situation, and encouraged us to further investigate this health topic.

We have tried to give an overview of the TB situation today, and want to include an understanding of why resistance has become such a considerable problem.

We think that understanding the basic clinical aspects regarding TB is important for the overall understanding of the changes in the situation both in a global and local perspective. An overview of different clinical aspects therefore constitutes a considerable part of our paper. There are important topics regarding TB only mentioned briefly in this text. We chose to focus more on multi-drug resistant tuberculosis than comorbidity with HIV and TB, although the latter is a huge challenge globally. The reason for this was that multi-drug resistance is a problem in Arkhangelsk oblast and other regions in the northwestern part of Russia, whereas HIV/TB comorbidity is not, or at least to a much lesser extent than in a global perspective. We have also not chosen to focus on the controversy of BCG vaccine, or the difficulties of introducing new drug in treatment of TB, although both are highly interesting subject at the present. Also we have concentrated mainly on TB in adults, it must be mentioned that the disease presents differently in children.

During the work on the thesis it has been necessary to make some changes from the original plan for the project. This plan included collecting statistics

from the Arkhangelsk region during our stay at the Antituberculosis Dispensary in Arkhangelsk city. Because of linguistic difficulties among other reasons, we had to change our plans in regard to this. Anyhow our stay in Arkhangelsk was most valuable to us, considering the opportunity we had to experience the different apartments of the dispensary, like the laboratory department, the different inn-patients departments, epidemiology department and so on. All this was only possible by the welcoming and helpful staff at the dispensary.

3 Materials and methods

The basis for our thesis is a literature study. When finding information, facts from the World Health Organization are essential. We have used WHO publications and guidelines in our work. We have also searched the PubMed database for articles related to TB, information available from web sites of organizations working in the TB field, and textbooks. In addition, we did a study tour to Arkhangelsk and spent time at the Antituberculosis Dispensary.

4 Basic science of tuberculosis

4.1 Characteristics of *Mycobacterium tuberculosis*

M. tuberculosis is a fairly large non-motile aerobic bacterium. It is obligate aerobic, thus it can only survive in an oxygen-containing environment. The rods are 2-4 micrometers in length and 0.2-0.5 μm in width. [1] The cell envelope is composed by 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. [2]

The bacterium divides slowly, with 16-20 hours between each cell division. Other bacteria usually divide in less than an hour, and the fastest-growing strain of *E. coli* divide roughly every 20 minutes. [3]

4.1.1 Exposure and primary infection

Practically, the only reservoir of *M. tuberculosis* that contributes to spreading TB-infection is the patient with pulmonary TB, with their chronic respiratory symptoms such as cough and sputum production. When they cough, speak or sneeze they produce aerosol droplets from the bronchi. [4] Aerosols are solid or liquid particles in a gas, with a size from 0.001 to over 100 μm . A single sneeze can release 40 000 droplets, and a cough about 3000 droplet nuclei, the same number as talking for 5 minutes. [5] When they come in contact with air they dry rapidly and become very light particles that still contain live bacilli, and remain suspended for a long time. [4]

When the bacteria penetrate the pulmonary alveoli of a healthy person, they are phagocytized by macrophages, in which they multiply. This creates a response where other macrophages and monocytes are attracted and participate in defense against the infection. This creates a primary focus; an

infectious focus made up of inflammatory cells. [4] This is also called the Ghon focus. [5]

The bacteria and its antigens are drained by the macrophages to the nearest lymph node through the lymphatic system. Inside the lymph node, the antigens are recognized by T-lymphocytes, leading to transformation into specific CD4 and CD8 lymphocytes and liberation of lymphokines such as interferon- γ . This activates macrophages to kill intracellular mycobacteria and/or inhibit the growth of the phagocytized bacilli.

The specific lymphocytes are central to TB immunity. Their fundamental role is demonstrated in studies of HIV-infected individuals. These have a reduced number of specific circulating lymphocytes, in particular CD4 lymphocytes, which diminish as their disease develops. This is why they are more likely to develop TB following infection. [4, 6]

In the primary focus, inflammatory tissue is formed and later replaced by scar tissue in which the immune cells containing *M. tuberculosis* are isolated and die. This is basis for the site of TB-specific necrosis. It contains 1000- 10 000 bacteria which gradually multiply more slowly. Some become latent bacilli that can survive for years. The same event occurs in the lymph node, and caseating lymph nodes are formed. These resolve toward fibrosis followed by calcification, in the majority of cases. [4]

Some infected individuals never develop active disease, but the reason is not fully understood. In 1926 newborn infants from Lübeck in Germany received live *M. tuberculosis* instead of the vaccine BCG. Some were unaffected, while others became gravely ill. This indicates that at least some individuals produce an effective immune response; in addition this episode in infants known to have immature adaptive immunity suggests that the innate host defense is an important anti-mycobacterial host defense. [6]

Immunity due to the formation of circulating antibodies plays a marginal role in TB, as the mycobacteria are resistant to the direct effect of antibodies and their products. [4]

4.1.2 Development of secondary foci

Bacteria from the primary infectious focus or nearest lymph node are transported throughout the body by the lymph system and bloodstream, constituting secondary foci of infection. These are in particularly in the liver, bones, kidneys and meninges. Due to immune response most of these foci resolve, but many bacteria may remain latent for months or even years. [4]

4.2 Pulmonary and Extrapulmonary Tuberculosis

Approximately 85% of reported TB cases were limited to the lungs, before the beginning of the HIV epidemic. The remaining 15% involved only non-pulmonary or both pulmonary and non-pulmonary sites. This has changed with the involvement of HIV, and although the distribution amongst the HIV positive population has not been described in any national data, studies describe a percentage of approximately 33% in each category (pulmonary, non-pulmonary, both). [7] A person with active but untreated TB can infect 10–15 other people per year. [8]

4.2.1 Pulmonary TB

Pulmonary TB occurs in a previously infected individual when there are major amounts of bacteria, and/or in the presence of immune deficiency, but seldom due to progression during primary infection. It is more commonly seen by endogenous reactivation of bacteria that have remained latent after primary infection, or as a new infection in a previously infected individual (exogenous re-infection). In absence of treatment and immune deficiency, the risk of endogenous reactivation is estimated at 10% in 10 years following infection, and later 5%.

Untreated, 30% of patients will achieve cure by the body's defense mechanisms, 50% die within 5 years, and 20% continue to remain sources of infection by continuing to excrete bacteria. [4]

Symptoms usually develop over several weeks. Chest symptoms can mimic virtually any respiratory condition. Cough is almost always present, as inflammation and tissue necrosis ensue sputum is produced. Possibly the patient will experience chest pain and/or dyspnea as accompanying symptoms, usually due to spontaneous pneumothorax. Hemoptysis may occur, but does not necessarily indicate active TB; it may result from post-TB bronchiectasis, rupture of dilated blood vessels in the wall of old cavities or bacterial/fungal infection, etc. [4, 7]

Systemic symptoms (night sweat, fever in the evening, loss of appetite, fatigue) are nonspecific. [4]

Physical findings are generally not helpful in defining the disease. Rales may be heard over the area of involvement and amphoric breath sounds may indicate cavities. [7]

4.2.2 Extrapulmonary TB

Extrapulmonary TB is defined as TB that affects any organ outside pulmonary parenchyma. It presents more of a diagnostic and therapeutic challenge than pulmonary TB. This relates to it being more uncommon, also it involves relatively inaccessible sites. [4, 7]

Certain forms of TB occurring in sites that are fully or partially within the chest are also considered extrapulmonary:

- Pleural TB and TB of the hilar or mediastinal lymph nodes are classified as extrapulmonary.
- Disseminated TB is a form of the disease that affects many sites in the body simultaneously and is not limited to the lungs. [4]

Disseminated (miliary) TB and tuberculous meningitis are acute forms of TB infection caused by the haematogenous spread of the bacteria, often occurring soon after primary infection. They occur most often in children and young adults, with a peak incidence of meningitis in children > 4 years of age. These acute forms are highly fatal. [4, 7]

The diagnosis of disseminated TB is based on clinical signs (general deterioration, high fever and dyspnea). Signs of involvement of other organs include: pleural effusion, digestive problems, hepato-splenomegaly and some times meningeal symptoms. It results in a characteristic chest radiography: a "miliary" pattern may be seen; extensive, tiny (1-2 mm) nodules resembling millet seeds, all the same size and spread symmetrically over both lungs. [4]

Meningitis is the most frequent form of CNS TB. The process takes place primarily at the base of the brain; hence symptoms include affection of cranial nerves (such as paralysis of the oculomotor nerve, leading to strabismus and/or ptosis and sometimes convulsions) in addition to headache, stiff neck and loss of consciousness. The diagnosis of tuberculosis meningitis is based on clinical signs, and cerebrospinal fluid obtained by lumbar puncture should be examined even if there are no clear meningeal signs. [4, 7]

The other forms of extrapulmonary TB are not as life threatening as disseminated TB. They can however lead to complications and severe sequela: deficit of a vital function (respiratory, cardiac, hepatic or renal), important neurological deficits (due to compression of the spinal chord) or sterility (genital tuberculosis). [4]

4.3 Diagnostics of Active Tuberculosis Infection

According to the WHO standards for diagnosis, all persons with a productive cough lasting for two-three weeks or more, without any other

explanation should be evaluated for TB. After taking a medical history and a clinical examination, sputum specimens and chest-X-ray should be performed. If the patient is suspected of having extrapulmonary TB, the specimens should be taken from the site of infection. [9] Microscopy of the specimen, either sputum or from the site of involvement in extrapulmonary TB is done. When the appropriate equipment and resources are available, culture should be performed and in the case of extrapulmonary TB histopathological examination should be done as well. [9]

According to the guidelines from the Norwegian Institute of Public Health, all patients in Norway in whom pulmonary TB is suspected will be examined with a chest-X-ray. If this is without findings, normally no more examinations are done. With findings, three sputum specimens for culture, microscopy and PCR are obtained. Treatment is started if the PCR or microscopy is positive for *M. tuberculosis* or if TB is still strongly suspected because of clinical findings. [10]

4.3.1 Chest X-ray

An adult patient with TB can have a chest X-ray showing infiltrates or consolidations and cavities. These are most commonly found in the posterior apical parts of the upper lobes, the apical segment of the lower lobes and then anterior segments of the upper lobes. It is not possible to distinguish TB from an ordinary pneumonia on a chest X-ray. In immunosuppressed patients the lesions seen on the x-ray can be more diffuse, or there are no findings at all. [10]

4.3.2 Bacterial examination

Bacterial examination in the patient with lung TB relies highly on sputum samples. The sample should be made from sputum from the lower respiratory tract, most often obtained by asking the patient to take a few deep breaths and then to cough. If possible, the specimen should be obtained early in the morning before the patient has had his first meal. At least three samples containing 5-10 ml each should be collected. [10] Extrapulmonal

TB is diagnosed according to localization; for meningitis they use cerebrospinal fluid, aspiration of lymph nodes, samples from the pleural cavity, etc. In a child who has difficulties expectorating on effort, gastric aspiration is used to diagnose pulmonary TB. [4]

4.3.3 Direct microscopy on sputum samples

Direct microscopy is important because it reveals if the patient is contagious, and the result can be obtained quickly, as soon as 1 hour after receipt of the specimen in the laboratory. [11] The method in use is the Ziehl-Neelsen staining. Due to the waxy cell walls of the mycobacteria, Gram staining cannot be used to diagnose TB. In the Ziehl-Neelsen procedure, heat is used to drive fuchsin stain into the mycobacteria. Decolorizing agents such as acid and alcohol will not remove the staining, hence the term acid-fast bacillus. [12] Other staining techniques are also available, the fluorescent dye auramine being one of them.

The sensitivity of examining sputum with the Ziehl-Neelsen method is low. It requires 5 000-10 000 bacteria per ml sputum to see mycobacteria in direct microscopy. In this examination it is not possible to recognize *M. tuberculosis* from other mycobacteria. [10] With the Ziehl-Neelsen staining, acid-fast bacilli will appear as red rods against a blue background in the microscope. [13] This method is still the most used to diagnose TB in many countries, [14] although it has a low sensitivity (40-60%) and even lower when there is HIV/TB comorbidity (20%). The reason for this is the limited resources in many developing countries, where there is a large number of TB cases. [15]

4.3.4 Culture

When culture is to be performed, the specimen is first treated with certain bactericidal chemicals to avoid contamination by other bacteria. [16] Growth of *M. tuberculosis* in culture can take up to 8 weeks. [10] Both solid media and liquid media are used. Löwenstein-Jensen medium is the most common solid medium in use. It is an egg-based media made of mineral salt

solution, malachite green dye and homogenized eggs. Agar-based media are also in use. Some are selective agars containing antibiotics, in that way inhibiting contamination by non-mycobacterial agents that survived the initial decontamination procedure.

Liquid media, like the BACTEC-method described later, give a much more rapid result. Within 2-3 weeks the growth of *M. tuberculosis* can be detected. Antimicrobial agents are added to the media to avoid contamination. [16]

4.3.5 Differentiating Mycobacterium Tuberculosis

There are several methods to differentiate *M. tuberculosis* from non-tuberculous mycobacteria after culture. One method is high-pressure liquid chromatography (HPLC), which analyses the cell-wall lipids of the bacteria, comparing them to known patterns of mycobacterial species. Nucleic acid probes, and DNA sequencing are also in use. Among the conventional methods in use are the niacin test, nitrate reduction test, pyrazinamidase test and thiophene-2-carboxylic-acid hydrazide (TCH) susceptibility. These tests identify *M. tuberculosis* and differentiate it from *M. bovis*.

M. tuberculosis will give niacin production and reduction of nitrate because of production of nitrate reductase. Many *M. tuberculosis* strains are susceptible to pyrazinamide whereas *M. bovis* are resistant because of pyrazinamidase production. *M. bovis* is the only mycobacteria susceptible to TCH, and will not grow when TCH is added to the medium. [16]

4.3.6 Susceptibility Testing

The high rates of resistance among *M. tuberculosis*-strains makes susceptibility testing important to avoid further development of resistance among the *M. tuberculosis*-strains. In the last years new methods of susceptibility testing are developed. In general these methods are faster than the conventional methods but at the same time more expensive, making them less available for countries with low income, and lack of adequate human resources and equipment. [17]

The conventional methods are still the most common in many countries. Among them are the absolute concentration method, the resistance-ratio method and the proportion method. The low costs comparing to other newer methods, and the fact that they are highly standardized for testing susceptibility on many drugs make them preferable in many countries. Their disadvantages are, as stated above, the prolonged time before the results are available. In addition to the 8 weeks it can take before pulmonary TB is confirmed, another six weeks are required for the drug susceptibility test results. [13]

The proportion method is preferred among the three methods, and will therefore be described shortly. This method gives information on the proportion of resistant bacteria among the total number of bacteria in the strain. Two dilutions made from the standard suspension of tubercle bacilli from the primary culture and distilled water are inoculated on to sets of tubes with the Löwenstein-Jensen media, one containing the drug and another without drug. [18] After 28 days the number of colonies in the tubes containing drug and the number of colonies in the tube not containing drug are compared, and the proportion (%) is calculated. [19] The procedure described is the indirect proportion method. If the specimen is decided to contain enough bacilli after microscopy, it can also be used for a direct resistance test. The advantage of the direct test is that the result can be available after about three weeks when utilizing the direct agar proportion method. There are other modifications of the proportion test such as using agar plates instead of the egg-based Löwenstein-Jensen medium. [19]

4.3.7 Liquid Media for Culture and Drug-Susceptibility Testing

In many industrialized countries liquid media are used in laboratory diagnostics of TB. The WHO recommends a step-wise approach to the use of liquid medium for low- and middle-income countries, but only with a simultaneous strengthening of laboratory capacity in the countries. [20] The BACTEC method is based on the radiometric detection of growth.

Consumption of ^{14}C -labeled carbon and production of radiolabeled CO_2 by growing bacteria is measured and recorded. The result can be available after about three weeks. During this time both isolation of mycobacteria and the susceptibility testing are done. The major disadvantages of this method are the production of radioactive material and the high costs. [19] Because of this, together with the complexity and demand of trained human resources, this method is difficult to implement in many countries where the need for such a rapid test is most present. [17]

Other systems for culture on liquid media, developed to avoid the problem with radioactive disposal, are MB/BacT, the EFP Myco System and Mycobacteria Growth Indicator Tube among others. [19]

4.4 Detection of Latent Tuberculosis Infection

4.4.1 *The Mantoux Test*

The Mantoux test is an unspecific test that reveals if the patient has been exposed to mycobacteria. It is the most used form of tuberculin skin test in the world. The tuberculin used in skin tests today is purified protein derivative or PPD. This form tuberculin was first made in the 1930s. Tuberculin consists of different proteins processed from a liquid culture of *M. tuberculosis*. The standard for tuberculin used in the Mantoux test is called PPD RT 23 and is kept in Statens Serum Institut in Copenhagen. [10] PPD RT 23 exists in two different compositions of tuberculin units (TU), 2 TU/0,1 mL and 10 TU/0,1 mL which contain 0,04 micrograms and 0,2 micrograms of Tuberculin PPD RT 23 respectively. 2 TU/0,1 mL is the recommended composition, unless low tuberculin sensitivity is expected. [21]

When performing the Mantoux test, the standard dosage of 0,1 mL tuberculin containing 2 TU is injected intradermal in the middle third of the forearm. After a successful injection, a papule of 8-10 mm in diameter will appear and then disappear in about ten minutes. [10] The result of the test is

seen after 48-72 hours, when the size of the induration is evaluated. The induration is often flat, uneven and surrounded by an area of redness. [21] It is measured transversely on the long axis of the forearm. An induration of 0-5 mm is considered negative, 6-14 mm is considered positive and 15 mm or more is considered strongly positive. A positive test can indicate either infection with the *M. tuberculosis* complex, infections with non-tuberculous mycobacteria or that the person has been immunized with the BCG vaccine. Individual risk factors, national guidelines and epidemiological factors must always be accounted for when interpreting the result. [10]

In some countries the Mantoux test is used not just for diagnostics, but also to verify immunization by BCG vaccine or to ensure that only persons who have not been exposed to *M. tuberculosis* are vaccinated. [21] When a person has symptoms of TB, further diagnostic procedures should be performed regardless of a Mantoux test results.

The major problems about the Mantoux test is the low sensitivity in immunosuppressed persons, and the influence on the test of the BCG vaccine and prior infections with non-tuberculous mycobacteria. [14] Old age and severe infection can also give a false negative test result. [10] Nevertheless the tuberculin skin test was the only method of identifying infection with *M. tuberculosis* in persons with latent TB infection just 10 years ago. [22] In settings where it is possible to treat persons with latent TB infection it is therefore important to detect these individuals.

4.4.2 Interferon Gamma Release Assays (IGRAs)

During the last ten years, two new blood tests for detecting latent TB infection have been developed. [23] In these tests interferon- γ secretion from T-cells is measured after exposure to the antigens ESAT-6 and CFP-10 that are specific for the *M. tuberculosis*-complex. Secretion of IF- γ indicates either latent or active infection, but is not suitable to distinguish the to states of infection. [24] Because the antigens used are not present in neither the

BCG vaccine or in most non-tuberculous mycobacteria, these tests are more specific than tuberculin skin tests. [23]

There are two different tests, the QuantiFERON TB-Gold (QFT) and the T-SPOT-TB. The QFT is an enzyme-linked immunosorbent assay (ELISA), where the IFN-gamma concentration is measured. The T-SPOT-TB is an enzyme-linked immunospot assay (ELISpot) counting the T-cells releasing IFN-gamma. In the ELISA there is an additional antigen to ESAT-6 and CFP-10, namely TB 7.7. [23] Both the T-SPOT-TB and the QFT have shown higher sensitivity and specificity than tuberculosis skin testing TST like the Mantoux test. In many countries they are already a part of the national guidelines for detecting latent TB.

One of the drawbacks with the interferon gamma release assays is that they appear more expensive than tuberculin skin tests, although analyses have shown that they are cost-effective because the numbers of persons treated unnecessary with chemoprophylaxis is reduced. [23] As already mentioned they cannot be used to differentiate between active and latent TB, neither for treatment nor for monitoring. The use of IGRAs in detecting latent TB is a method still in progress, and already an important diagnostic tool for latent TB in many countries.

4.5 Treatment of Tuberculosis

4.5.1 First-line anti-tuberculosis drugs

There are four key first-line anti-tuberculosis drugs:

- Isoniazid (H)
 - The major components of the envelope of *M. tuberculosis* are mycolic acids, significant evidence supports the theory that isoniazide blocks the syntheses of these acids, however its actions are complex. [25]
- Rifampicin (R)

- Inhibit bacterial DNA-dependent RNA polymerase, and appears to result from the drug binding in the polymerase subunit within the DNA/RNA channel and directly block elongating of RNA. [26]
- Pyrazinamide (Z)
 - A synthetic analogue of nicotinamide, but the mechanism is not fully understood. [27]
- Ethambutol (E)
 - The actions of ethambutol are not completely known. It targets the mycobacterial cell wall, which consists of an outer layer of mycolic acids bound covalently to peptidoglycan via the arabinogalactan. Ethambutol inhibits polymerization of cell wall arabinan, and this result in accumulation of a lipid carrier. Hence the drug interferes with transfer of arabinose to the cell wall acceptor. [28]

Streptomycin (S) acts by inhibiting bacterial protein synthesis. It is defined by WHO as a first-line anti-tuberculosis drug, [27] but the standard regimen for treating new TB patients presumed to have drug-susceptible TB does not include Streptomycin. It is however used in special cases; such as certain forms of extrapulmonary TB and in the treatment of multi drug resistant TB.

4.5.2 Combining First-Line Drugs for Effective Treatment

Several anti-tuberculosis drugs must be given together in order to cure a TB-patient, and the use of any of these as mono-therapy leads to selection of resistant strains.

A patient with TB is inhabited by different bacillary populations:

- Metabolically active bacilli inside lung cavities, which replicate constantly and rapidly.
- Bacilli situated inside macrophages. These replicate slowly due to lack of oxygen and the acidic pH in the cytoplasm they live in. Dormant bacilli are metabolically inactive; they replicate very

slowly, but can start to multiply as soon as the immune defense system weakens. [4]

Isoniazid (discovered 1952) and rifampicin (discovered 1957) are the most effective bactericidal drugs, and work both against rapidly multiplying bacteria, and also semi-dormant bacilli inside the macrophages. [4, 29, 30]

Pyrazinamide (discovered 1952) destroys intracellular bacteria that live in an acid environment. Streptomycin (discovered 1943, soon after penicillin) is active only against extracellular bacteria, as it cannot penetrate the cell membrane. These are of medium efficacy. [4, 31, 32]

To prevent emergence of resistant bacilli Ethambutol (discovered 1961) is used in conjunction with bactericidal drugs. Ethambutol is much less effective as it is bacteriostatic.

Rifampicin and pyrazinamide are the only medications that have a sterilizing action as it destroy persistent bacilli, and they are always used in short-course chemotherapy. [4]

4.5.3 Second line drugs

There are two major indications for the use of second-line therapy:

- Resistance to first line drugs.
- Patient intolerance to first-line drugs.

A parenteral aminoglycoside (streptomycin, kanamycin, amikacin, capreomycin) and a quinolone (levofloxacin, moxifloxacin) are recommended added when treating MDR-TB. These are usually given for 6 months and cure rates are high for regimens that include them. Treatment with at least four effective drugs should be continued for 18 to 24 months. [33]

4.5.4 Treatment Categories Recommended by the WHO

- New cases of smear positive TB – defined as a patient who has never previously been treated for TB or who has received treatment for less than one month.
- Cases who have already received treatment for at least one month in the past who need re-treatment:
 - ”Relapses” – Smear examinations are again positive after the patient having been treated and declared cured earlier.
 - ”Failures” – Smear examinations have remained positive or become positive once again five or more months after starting treatment.
 - ”Return after interruption” – Patients who return smear-positive after interrupting treatment for more than two consecutive months.
- Chronic cases defined as smear-positive cases of pulmonary TB who have already received a supervised re-treatment regimen. [4]

4.5.5 Monitoring the efficacy of treatment

Efficacy of treatment is measured by examination of sputum smears performed at following stages of treatment (in the case of pulmonary TB):

- Sputum conversion is observed at the end of the initial phase, and this phase should be prolonged by one month if the patient is still smear-positive.
- At the end of the 4th month for 6-month regimens, and at the end of the 5th month for 8-month regimens.
- During the last month.

In the case of extrapulmonary TB, follow-up is essentially clinical. A specialized opinion is necessary. [4]

4.6 Drug resistance

The ability to survive the presence of a drug that normally kills or inhibits growth is known as resistance. Resistance is a phenotype. It is caused by mutation, and cannot be regarded the same as tolerance; a conditional phenotype mediated by the physiological state of the bacilli. [34] If a bacterium lacks a susceptibility target and is impermeable to an antibacterial agent, this is known as innate resistance. [27]

The MIC (minimal inhibitory concentration) of a drug is defined as the minimum concentration of the drug that kills 99% of cells. [34]

4.6.1 Drug resistance mechanisms

Drug-inactivating enzymes, drug extrusion mechanisms, target modification, target overexpression and barrier mechanisms are some of the resistance strategies bacteria develop. [34]

M. tuberculosis and other mycobacteria have several strategies of innate resistance, which make them a challenge to medicine and the pharmaceutical industry, amongst other reasons because:

- They are difficult to penetrate with antibiotics due to a waxy outer layer.
- Inhibition takes weeks or months to achieve as a result of extremely slow multiplication, and long-term therapy is therefore a challenge for drug delivery. Orally administrable drugs are desirable.
- Antibiotics have difficulties reaching the bacteria as they are localized intracellular, and the cells are surrounded by a caseous mass. [27]
- Recent reports have suggested that efflux pumps may also be involved. [29]

Spontaneous genetic mutations result in development of resistance in *M. tuberculosis*. This phenomenon is amplified due to use of drugs.

Spontaneous chromosomal mutations happens at a frequency of 10^{-6} to

10^8 . The probability of mutations against both isoniazide and rifampicin is 10^4 , and is not that uncommon in pulmonary TB, as there are huge amounts of bacteria involved. [27] If you treat an infected patient with mono-therapy, the majority of bacilli will die, but the resistant mutant will survive and multiply and cause a bacterial population dominated by the resistant strain. Acquired resistance to one or several drugs is caused when further mono-therapy by another drug is given and the mutant bacteria also resistant to the second drug are selected. [35]

Primary resistance is a term used regarding a patient whose disease is caused by a strain that is resistant to an antibiotic, and has been infected with it by another patient. This patient with primary resistance may have never received the drug in question. [4]

In other mycobacteria and bacteria you might find mutations caused by mobile genetic elements such as plasmids, but mutations in the genome of *M. tuberculosis* is always a result of mutations in the chromosomal DNA. [35] *M. tuberculosis* does not possess plasmids. [29]

Resistance to rifampicin and isoniazid is defined as multidrug resistant tuberculosis (MDR-TB). MDR in addition to a fluoroquinolon and resistance to at least one of three injectable second line-tubercular drug i.e. amikacin, kanamycin and/or capreomycin is known as extensively drug resistant tuberculosis (XDR-TB). [36] This requires the use of multiple second-line drugs and potentially surgery. [29]

4.6.2 Development of resistance

There are several factors contributing in the development of resistance.

- Genetic factors: Accumulation of changes in the genomic, content, spontaneous mutations, etc.
- Inadequate treatment is an important factor; use of a single drug to treat, the initiation of an inadequate regimen using first line anti-TB

drugs, addition of a single drug to a failing regimen and variations in bioavailability of any anti-TB drugs predispose for MDR.

- Inadequate treatment adherence: Non-adherence is related to psychiatric illness, drug abuse, homelessness and alcoholism.
- Also factors such as poor administrative control on purchase and no proper mechanism on quality and bioavailability tests. [36]

The specific molecular mechanisms for resistance to some of the anti-tuberculosis drugs are mentioned in figure 3 (*Antituberculosis drug and genes involved in their resistance*) in the appendix.

5 Tuberculosis as a global health problem

5.1 Changes in the Tuberculosis Situation During the 20th Century

Tuberculosis has existed for several thousand years. There was an increase of the disease in the 19th century lasting until the living conditions improved in the 20th century. The cause of the disease was discovered by Robert Koch in 1882 when he distinguished the *M. tuberculosis* from *M. bovis*. The tuberculin tests were available from 1890, and the Bacillus Calmette-Guérin (BCG) vaccine was used in humans for the first time in 1921 but became widely used in 1945. At the same time the first medications were used in treatment. [37] Despite the early known diagnostic tools and the existence of the vaccine, TB is still a global challenge.

After the global prevalence of TB had been falling for decades towards 1980, the situation changed. [38] An increase in incidence cases was notified both in Europe and the USA. The main explanation was the increased immigration to these regions. The decrease in TB prevalence in Europe and the USA during the 20th century had not been followed to the same extent in low-income countries. Two other factors were influencing the TB situation; the economical crisis in the former Soviet Union led to an increase in TB in this part of the World, and resistance became a bigger problem. Secondly, in the sub-Saharan African countries, the HIV epidemic was growing followed by an increase in TB. [38]

This quite sudden change in the global TB situation, also affecting Europe and the USA, led to a refocus of the international attention on TB. [38]

Between 1997-2000 there was an increase in global incidence rates by 0,4% per year. In 1997 the estimated global incidence rate for TB was 136/100 000. [39] The highest incidence was in WHO Region of Africa with 259/100 000 mostly due to high incidence rates in sub-Saharan African countries. In 2000 the incidence rate of TB in the same area was 293/100

000. The estimated TB burden measured by incidence for the Russian federation was 106/100 000 in 1997. [39] At this point, the growing TB-burden could be explained mainly by the simultaneously growing HIV epidemic, 8% of new cases were associated with HIV infection in 1997. [39] At the same time the problem with MDR in some countries was growing, among them Russia. [40]

5.2 The Current Tuberculosis situation

The situation today is described in the WHO report from 2010 Global Tuberculosis Control. [41]

Since 1997, the WHO has published an annual report on the global TB status. The latest report from 2010 contains numbers describing the TB epidemic up to 2009. According to this report the estimated global burden can be illustrated by the 14 million prevalent cases, 9,4 million incident cases, and 1,3 million deaths due to TB (excluding deaths among HIV positive cases). [41]

The global incidence rate of 2009 was 137/100 000, showing a slow decrease since the peak at 140 /100 000 in 2004. In 2000 the incidence rate was estimated 136/100 000. The highest incidence rate from 2009 was in the African region, estimated 345/100 000. For comparison the WHO numbers from 2000 show an incidence rate of 314/ 100 000 for this region, demonstrating an overall increase in this region the last ten years, again with a slow decrease after a peak in 2004. In Russia, the rate was 106/100 000 and has been quite stable the last ten years. Figure 1 illustrates the estimated TB incidence rates by country for 2009.

The treatment success rate of smear-positive cases has been increasing globally from 1995 (being 57%) to 86% in the cohort from 2008. Treatment success rates are however lower in the European Region, 66%. [41]

The highest numbers of MDR-TB in 2009 were notified by countries in the European region and in South Africa. The numbers are increasing and expected to increase even more towards 2015.

The Millennium Development Goal (MDG) regarding TB is to halt and reverse the incidence of TB by 2015. In addition, the Stop TB Partnership has set targets including halving the TB prevalence and death rates by 2015 compared to the levels in 1990. The MDG target can be reached if the current decrease of incidence rates of about 1% per year continues. The halving of mortality at a global level is still possible whereas halving the prevalence by 2015 seems to be out of reach. Some of the targets have already been reached in certain regions, like the prevalence in the Region of the Americas, which is already halved compared to 1990 levels. With the same progress as the last years, this target can be reached in the other regions as well, except the African region and the South-East Asian Region where it seems out of reach. Mortality rates are falling in all regions, and can be reached in all regions except the African region. Halving mortality before 2015 is still possible for some of the high burden countries, among them Russia. [41]

The trends in TB incidence, prevalence and mortality rates follow 15 years of international contribution in the fight against TB. This includes implementing the DOTS strategy from 1995 followed by the Stop TB Strategy from 2006. 41 million TB patients have been treated successfully by DOTS programs between 1995 and 2009. There are still some important challenges to overcome, including one-third of incident TB cases not being reported to be treated in DOTS programs, only 10% of patients with MDR-TB being diagnosed and treated according to international guidelines, missing TB status among HIV positive persons and HIV status among TB patients and funding gaps which are still large despite an increase in funding the last ten years. [41]

In 2009 an estimated 1,1 million of the incident TB cases were HIV-positive. This makes up 12% of all incident cases, illustrating the existing

challenge of HIV/TB co-disease. [41] 80% of these HIV positive cases were in the African Region [41] The risk of developing TB is 20 times higher in a HIV infected person than in a person not infected with HIV. [42] TB is an important cause of death amongst HIV infected people. The WHO recommends intensified TB case findings, isoniazid preventive therapy and infection control for TB to reduce the burden of TB among HIV positive persons. [43] Figure 2 illustrates the estimated HIV prevalence in new TB cases by country for 2009.

5.3 Strategies in Anti-Tuberculosis Work

From the 1990s the growing global challenge of TB led to the development of programs and other actions in TB control. A new system for global TB surveillance was implemented by the WHO, making the annual reports and strengthened control of the international TB situation possible. There was also an increased focus on resistance. Several foundations consisting of nations, non-governmental organizations, and private persons were, and still are, important in the process. The International Union Against Tuberculosis and Lung Disease, the Stop TB Partnership, The Global Fund to Fight AIDS, Tuberculosis and Malaria, A Global Drugs Facility and the Green Light Committee are examples of such foundations important in different areas of fighting the TB challenge. [38] Implementation of DOTS and later the Stop TB Strategy have, as already mentioned, been essential for the work against TB, [41] and will be shortly described.

5.3.1 DOTS

Directly observed treatment short course, DOTS, has been the core in controlling the global TB situation the last years. It was launched by the WHO in 1995 and 41 million patients have been treated according to this strategy. [8] DOTS has five main components:

- Political commitment with increased and sustained financing
- Diagnosis made from bacteriology.

- Standardized treatment with supervision and patient support. The treatment should be followed closely to avoid interruptions.
- An effective drug supply and management system. There should be national systems to assure a continuous drug supply to the institutions where treatment is given. Drugs should be free, both to decrease the expenses for each patient and because individual treatment has a preventive effect on TB in the society.
- Monitoring and evaluating system and impact measurement. The recommendations include establishing a reliable monitoring and evaluation system that facilitates communication between different levels of the health system. The system should be the same in all levels of the health system as well as in all parts of the country, and between countries, so that local and national conditions regarding TB can be identified. [44, 45]

5.3.2 The Stop TB Strategy

In 2006 the new Stop TB Strategy was introduced by the WHO. It is essential on the way of achieving a significant reduction in the global burden of TB according to the Millennium Development Goal and the targets of TB control set by the Stop TB Partnership. [45] The Stop TB Strategy is based on DOTS and has six components.

- Pursue high-quality DOTS expansion and enhancement.
- Address TB/HIV, MDR-TB and other challenges. Co-infection with HIV and TB has become a big challenge. The HIV epidemic gives good conditions for the TB epidemic, and collaboration in actions against HIV and TB is necessary in the approach to this problem. One of the other challenges to be addressed is the increasing MDR-TB incidence. Guidelines considering MDR-TB specifically are developed, the DOTS-plus.
- Contribute to health system strengthening. This is because strengthening of health systems is important for fighting any disease, TB makes no exception. A well functioning health system is especially important when it comes to diseases demanding a long-

term follow up and treatment such as TB. Therefore the Stop TB Strategy encourage TB programs and partners to participate in efforts to improve actions across all major areas of health systems, including policy, human resources, financing, management, service delivery, and information systems.

- Engage all care providers. This means involving health care-providers outside the public health care in standard case-finding procedures to avoid delayed diagnosis, wrong diagnosis and incomplete treatment.
- Empower people with TB, and communities. This includes involving the communities in the fight against TB by more information, better communication between the communities, current and former TB patients and the health care providers and financial and social support of TB patients.
- Enable and promote research. The last of the six components of the Stop TB Strategy is about the importance of research, both regarding effectiveness of different approaches to TB care to identify problems and find solutions, and regarding the development of new diagnostics and vaccines. The Stop TB Partnership's Working group should be supported in this work by countries.

6 The Case of Russia and the Growing Epidemic of Multi-Drug Resistant Tuberculosis

6.1 A Historical Perspective on Tuberculosis in Russia

6.1.1 *The Tsar Regime and The Russian Revolution*

From 1613 to 1917 Russia was ruled by the Romanov dynasty. [46] In the work "The House of the Dead" (1861) by author Fyodor Dostoyevsky (1821-1881) he described everyday life in a Tsarist prison confirming that TB in prisons is not a new phenomenon. [47] At the time TB outside the prisons also was a huge problem.

Following the revolution there were upheavals that led to increased risk of TB, and the early Soviet state established a nationwide network of anti-TB institutions. TB care was even organized in the prison camps of Stalin's gulag, where millions of people met their deaths. [47]

6.1.2 *The Soviet Union*

Mortality of TB before World War 1 was 400/100 000. While 1,7 million Russian soldiers were killed in war, 2 million civilians died from TB. [47] By the end of the 1950s, drug therapy had been introduced in most developed countries, and this reduced the need for sanatoria beds. All but the sickest patients could be treated at home, without the need for a hospital bed. [48] These changes were not introduced in the Soviet Union. The soviet states based the treatment on isolation, sanatoria, X-ray diagnosis and sometimes surgery. Medical personnel wanted it to continue this way, as they depended on it to keep their jobs, due to the existence of TB beds in hospitals and the carrying out of operations. A move to the DOTS system was considered a threat and a personal defeat; they had believed in their forms of treatment, and before the economic collapse they had good results. [47]

6.1.3 Dissolution of the Soviet Union

In 1989, at the end of the Soviet regime, the TB rate was 44.7/100 000. Nine years later (1998) the numbers in Russia had increased to approximately 100/100 000. The main cause of this increase was the sudden poverty that affected millions of people, and thus caused a dramatic reduction in living standards. [47]

Approximately 50 million people lived on less than 15 US\$ per day. As a consequence vegetables were unavailable, fruit and meat was used less and less as an element of the diet in the 1990s. Earlier, during Soviet regime, all land and buildings belonged to the state. By the early 1990s waiting lists prior to receiving own housing were not uncommonly more than 10 years. 20% of families in the urban areas lived in small apartments, or shared their space with one or several other families. This is an important factor in the spread of TB. [49] In addition, millions lost their jobs, and no longer had welfare and health services that had been provided by their work place, including TB screening. The work places also had contributed with sanatorias where people could stay in their jobs during treatment. This meant that TB rates were on the rise due to social problems, while the TB control systems no longer worked as they should. [47]

In the 1990s the health care system were massively criticized by the mass media, where they warned the population about the more adverse effects of the TB drugs and hazards of X-ray examinations. This led to the people being skeptical of using medicine, and regarding radiation safety. This was increased after the Chernobyl nuclear accident, and traditional screening based on fluorography declined. [49]

6.1.4 Tuberculosis in Prisons of Post-Soviet Russia

Prisons became the site of an epidemic. [47] Russia has an enormous prison system, including ~0.7% of the current population, which is nearly 1 million inmates. [50] As living standards were reduces outside prisons, they were

reduces parallel on the inside, in a population composed primarily by the homeless and poorest in society. [47]

As a heritage from the Tsar regime, the prisons system in both Russia and the Soviet Union were based on banishment and hard labor in prison camps. A prison would hold thousands of prisoners, which slept in huge dorms. Work was usually in mines or factories, and bad work conditions kept others than prisoners from taking such jobs. After the end of the Soviet Union, Russia had the second highest rate of imprisonment, holding 678 inmates per 100 000 population. [47]

In some regions the prevalence of resistance to at least one drug among new cases was 35-44%, and the mortality associated with TB in Russian prisons were 171 deaths per 100 000 prisoners. [50]

The prisons became so crowded that prisoners died from suffocation. They lacked beds and had to sleep in shifts. Kresty prison in St. Petersburg held 10 000 inmates in a prison constructed to keep 3000.

The prisons no longer had the state as an employer, and factories and mines closed. There were no longer work available in the prison camps, and therefore they had no income. Building deteriorated and food quality was reduced drastically. [47] Close to every prisoner was exposed to TB, and thousands of infected ex-convicts were released into the general population every year. In 1995 TB cases among prisoners were finally included in official statistics, and revealed a concentration in the penalty system. [51] A treatment program was established in the central prison in Baku, Azerbaijan, and the medical director of a Siberian prison asked Médecins Sans Frontières for help. The next year DOTS was introduced. In 2008 three non-governmental organizations stated that nearly 100 000 prisoners had active TB disease, and 20 000 of these were drug resistant. [47]

Late diagnostics, lack of isolation, inadequate treatment of those who are contagious, high turnover of prisoners, overcrowding and poor ventilation

are listed by the WHO among a number of reasons that contribute to the spread of TB. Poor nutrition, physical and emotional stress worsens the situation. It is also estimated that HIV is 75 times more common in prisons than in the outside community. [47]

6.2 Multi-Drug Resistant Tuberculosis in a Global Perspective

Resistance of *M. tuberculosis* to antibiotics appeared shortly after the introduction of the first anti-TB drugs in the 1940s and 1950s. To begin with, resistance in mycobacteria was mostly to isoniazid, streptomycin and p-aminosalicylic acid (PAS). Combination-therapy to prevent resistance was established, so was reliable techniques for testing mycobacteria for resistance to anti-TB drugs. MDR-TB was rare. [52] With the discovered outbreaks of MDR-TB in some European countries and the USA in the late 1980s, especially among HIV-positive persons, attention was again drawn to TB and resistance. [53]

An estimated 440 000 cases of MDR-TB emerged globally in 2008. [52] This constitutes 3,6% of the total amount of new TB cases that year. 27 countries are considered high MDR-TB burden countries, among them China and India, which together account for almost 50% of the estimated global number of incident MDR-TB cases, and Russia. In 2008, 150 000 deaths due to MDR-TB were estimated by the WHO report, including those with HIV infection. Resistance to second-line anti-TB drugs is also a growing problem. 963 cases of XDR-TB were reported to the WHO in 2008. The actual number is probably higher because of insufficient laboratory capacity of drug-susceptibility testing on second-line drugs. The proportion of XDR-TB among MDR-TB cases is thought to be 5,4%. [52]

As described in the WHO report, [52] the major challenges regarding MDR-TB are the lack of drug susceptibility testing to detect MDR-TB among previously treated cases where the probability of MDR-TB is greater, and in

the availability and costs of treatment of MDR-TB, which is 50 to 200 times higher than for a drug-susceptible TB patient. Different establishments have been important for treating MDR-TB, supporting treatment of patients directly. The EXPAND-TB Project was created because of the lack of resources in many countries to improve the laboratory capacity to diagnose MDR-TB. This is an initiative with several partners including the WHO, the Global Laboratory Initiative, the Foundation for Innovative New Diagnostics, the Stop TB Partnership through Global Drug Facility and UNITAID, working for access to MDR diagnostics in 27 countries. 60% of patients that received treatment from MDR starting in 2006 were cured overall. Even in well-resourced settings the overall treatment-success MDR-TB patients remains low. [52]

6.2.1 The Beijing Strain

One type of mycobacteria, the Beijing genotype family, has been coupled to a tendency of higher degree of virulence and resistance. The strain was first described in 1995, [54] when it was found to be the dominant strain of *M. tuberculosis* in China and some of the neighbor countries. It was characterized by the pattern of the repetitive DNA sequence IS6110, and further by IS6110-associated restriction fragment length polymorphism (RFLP). A high degree of similarity in the IS6110 RFLP patterns showed that the strains from China and neighboring countries were part of the same "family" or genotype.

Later, spacer oligotyping, or spoligotyping was described. This method makes use of polymorphism in the direct repeat region of the genome, with different number of short direct repeats separated by non-repetitive spacers. [55] Other methods for genetic differentiation are also used today.

Since 1995, strains from the Beijing family have been reported from several countries, not infrequently related to MDR-TB. [56] Because strains from the Beijing family show more homogeneity than strains from other genotype families, the hypothesis of selective advantages was formed. Several

subgroups of Beijing family strains exist, among them the W-strain. This strain first emerged in New York City mostly among HIV positive inmates and hospitalized patients and showed a high degree of multi-resistance. The Beijing family is dominating in East Asian countries, representing about 50% of the strains in this area and about 13% of the strains globally.

The causes of dissemination of strains from the Beijing family are not certain. Some studies on animal models have shown that BCG vaccination is less protective against infection with strains from this family, [57] while others have not. [58] Increased transmission of Beijing strains is another hypothesis of dissemination. In a study from Arkhangelsk oblast in the Russian Federation this was indicated by a high rate of clustering among strains belonging to the Beijing genotype. [59] An increased virulence among Beijing strains is also one of the hypotheses of this genotype becoming more frequent. [56]

Drug-resistance is shown to be associated with these strains in several studies. There are three main hypothesis of how to explain this; it can be due to a higher rate of mutations in these strains. Secondly the cell- wall structure of these bacteria, which can influence intracellular concentration of drug in the bacteria, can be an explanation. Lastly, an increased virulence demanding a prolonged time of treatment and sometimes use of several different drugs can make the development of resistance more probable. [56]

Finally, the various factors can have different roles in spread of strains of the Beijing genotype in different settings. [59]

6.3 Drug resistance in Russia

6.3.1 *The Present Situation in Arkhangelsk Oblast*

The Arkhangel oblast is situated in the northwestern part of Russia, a country with a population of 141 millions in 2009, and a high burden of TB with an incidence rate of 106/100 000 the same year. [60] In the

Arkhangelsk oblast there are 26 municipal districts and 26 TB coordinators. They all report to the central Antituberculosis Dispensary in Arkhangelsk city. TB-activities in the Arkhangelsk oblast have been according to WHO recommendations for more than 10 years. There is a well functioning system for monitoring the spread of drug resistance and drug susceptibility testing has been performed since 2004 in the central laboratory. [61]

Fresh numbers from the Arkhangelsk oblast show a decrease in TB-incidence (counting both new cases and relapses) over the last ten years, sinking from 118,7 per 100 000 population in 2001 to 64,7 per 100 000 in 2010. [61] Despite the decrease in incidence there are still many challenges considering the TB-situation in this area. The proportion of MDR among new cases is increasing. In 2001 the number of MDR-TB cases constituted 10 % of new cases, compared to 33,9 % in the first three quartiles of 2010. Among retreatment cases, the percentage was as high as 72,5 % in the first three quartiles of 2010. [61] The absolute numbers of new MDR-TB cases have actually been quite stable since 2005. The increasing proportion of MDR among new cases can partly be explained by the decrease in the total number of new TB cases.

XDR have also been detected in Arkhangelsk oblast, 9 cases were registered in 2010. [61] The treatment of this form of TB is difficult because the drugs in use are less potent, more toxic and a lot more expensive than the regular drugs. [62]

6.3.2 Resistance in Russia – The WHO Estimates from 2010

In Russia as a whole, the estimated proportion of MDR among new TB cases was 15,8% overall, in the WHO report from 2010. This estimate builds on subnational drug resistance data. On subnational level, as high proportion as 28,3% MDR-TB among new cases was reported from Murmansk Oblast to WHO in 2007-2008. Two other oblasts in the northwestern region of Russia also had proportions higher than 20% MDR TB, namely the Arkhangelsk Oblast and Pskov Oblast, with 23,8% and 27,

3% MDR-TB among new cases respectively. The proportions are of course even higher among previously treated cases: 35,7% in Murmansk Oblast, 58,8% in Arkhangelsk Oblast and 50,0 in Pskov Oblast. 5,4% was the lowest proportion of MDR-TB among new cases reported from a Russian oblast. [52] This demonstrates the importance of a continuous focus on MDR in this region.

There are already established well-organized systems for surveillance and reporting of MDR- and XDR-TB in parts of Russia. 12 oblasts are included in the group of countries and regions providing class A continuous drug resistance surveillance data according to the WHO report. This means that certain conditions are met, including a "detection rate of at least 50% for new cases, positive culture available in at least 50% of all notified cases, drug susceptibility testing (DST) results available in at least 75% of all culture positive cases, accuracy of at least 95% for isoniazid and rifampicin in the most recent DST proficiency testing exercise with a supranational reference laboratory". [52] In fact, all the 12 oblasts report a case detection rate of 85% and DST coverage of between 87-100%.

6.3.3 Special Features of the Tuberculosis Epidemic in the Northwestern Region

In a study from Murmansk of collected isolates from culture positive cases during 2003 and 2004, the prevalence of MDR-TB was 26% among new cases and 72,9% among previously treated cases. Spoligotyping of the isolates from new MDR-TB cases were performed, revealing that 79,8% belonged to the Beijing family, more specifically the SIT1 genotype. In total 44% of the samples, both susceptible and resistant, belonged to the Beijing family. [63] The study also indicates a considerable ongoing transmission of MDR-TB in the society. A study from Arkhangel Oblast on isolates from patients with pulmonary TB from 1998 and 1999, showed similar proportions of samples belonging to the Beijing strain family, 44,5%. This study also demonstrated that the proportion of multi-drug resistance is much

higher within strains from the Beijing family (43,4%) than other strains (10,6%). [59]

The high prevalence of the Beijing family in this part of Russia was again confirmed in a study published in 2009 of 176 isolates from Arkhangelsk Oblast, Murmansk Oblast, the Public of Karelia and the public of Komi. [64] The genetic diversity among the isolates and drug susceptibility were investigated. 47,1 % of the strains belonged to the Beijing family. However, there was a significant difference in prevalence of the strains between the oblasts, the Arkhangelsk and Murmansk oblast having the highest proportion of Beijing strains. The Beijing genotype was significantly associated with resistance to all first-line anti-tuberculosis-drugs, and also to the second-line anti-tuberculosis-drug ethionamide. The proportion of clustered isolates was higher among strains from the Beijing family, indicating more transmission of these strains.

6.3.4 Risk Factors for Tuberculosis in the Northwestern Region

Several factors are pointed out as possible explanations on the MDR-status in the northwestern part of Russia, and Russia as a whole. The economic collapse following the dissolution of the Soviet Union had a great impact on the health of the Russian people in general. [65] There was a decrease in financial support to medical institutions, leading to deficient diagnosis and treatment of TB. The Soviet TB-control program relying on chest X-ray, vaccination and long-term hospitalization for treatment was partly continued after the dissolution. [65] Lack of capacity for sputum examination and drug susceptibility testing was one of the factors delaying an approach more similar to the recommendations from the WHO. [66] An inadequate drug supply led to treatment with separate drugs, [66] this again possibly contributing to development of resistance. [63] Then, when resistance developed, after a while representing a significant proportion of cases, and the capacity of diagnostics and treatment was insufficient, transmission of MDR-TB became a big problem. [66] Patients not completing treatment is another problem contributing to development of resistance, like in

Murmansk. [63] In some parts of Russia the HIV epidemic is also growing and has given rise to the problem of MDR-TB and HIV co-infection. [63]

Risk factors for infection with drug-resistant *M. tuberculosis* were investigated in another study from Arkhangelsk Oblast, revealing significant association between drug-resistance and female gender, previous TB treatment and interruption of ongoing treatment. [66] The same associations were significant for MDR specifically.

In many parts of the world, there is a high prevalence in prisons of both TB in general and drug-resistant TB. This is due to conditions that facilitate growth and transmission of the bacteria such as inadequate ventilation, overcrowded institutions and poor health of inmates. In Arkhangelsk, a study from 2001 revealed that MDR among new cases in prison were 2,5 times higher than in community settings. [50] Resistance among new cases, not being MDR, was also more common among prisoners than in the community. Strains belonging to the Beijing family occurred more often among isolates from prisoners than in the Arkhangelsk community, and there was a higher proportion (79,8%) than in the community (59,7%) of clustered isolates. [50, 66] The latter indicates a higher degree of transmission of the disease in the prison. In the isolates from prisoners clustered strains occurred more commonly among strains from the Beijing clone family (96,6%) than among other strains (25,9%). [50]

7 Conclusion

Through our studies we now have a better understanding of how complicated the matter of tuberculosis really is. According to the WHO the global prevalence in 2009 was at 14 million prevalent cases of active disease, and 1,3 million deaths due to TB (excluding deaths of the HIV positive). The Millennium Development Goal presented by the UN in 2000 involved halving the prevalence within 2015, a goal that is by the looks of it out of reach as of today. The reasons why the situation is so severe and why it is so difficult to reverse the occurrence of the disease are many and diverse.

The bacterium has a unique innate resistance to drug treatment and the human immune systems, with its structural characteristics, slow replication and being an intracellular organism. It has existed for thousands of years, and when effective drug treatment with antibiotics was discovered (and used in mono-therapy without adequate monitoring) it was the start of creating an epidemic of multi drug resistant disease. Later HIV has become a huge contributing factor to developing and dying from TB.

There is also evidence that certain strains (as the Beijing strain) may be more virulent than other, and have a higher tendency of mutating, and these strains have accumulated in particular areas.

It is both complicated regarding to logistics and expensive to diagnose TB in a proper way, and the huge amount of individuals with latent infection represent a practically endless amount of potential reservoirs of infection.

Tuberculosis thrives on the weak, ill and poor in society, and this has become clear as the sub-Saharan countries have the highest prevalence of the disease. This is also where you find the highest accumulation of HIV. The Russian federation and other countries that departed from the Soviet Union in the early 1990s are other examples of high prevalence areas. These

are regions that struggle with a still increasing problem of multi drug resistance.

Conditions during the soviet regime worsened a problem that was already considerable. Refusing to introduce modern treatment and harsh conditions in the many prisons are reasons that contributed to the high prevalence. As the soviet state resolved, economy in the new states collapsed, leaving people without housing, jobs and a proper health care systems. Again the prisons worsened the situation.

The WHO has fought for decades to improve treatment of the disease, and keep introducing updated guidelines to help countries battle it. DOTS was launched in the 90s, and have by today helped treat more than 41 million patients. Later, as it has become obvious that resistance is on the rise, the DOTS plus guidelines were introduced. The WHO also has an invaluable role in monitoring epidemiologic factors.

Between 1997-2000 there was an increase in global incidence rates by 0,4% per year. In the African region the incidence is as high as 345/100 000 (2009), and this is also where you find 80% of the worlds HIV positive cases. In 2008 there were registered 440 000 cases of MDR-TB, and yet many are undiagnosed. Also there were 963 cases of XDR-TB, which is virtually impossible to treat in certain countries due to high expenses. New cases of MDR-TB in Russia were 15,8% in 2010, while some areas present as high numbers as close to 30%.

Russia is an example of a country where they have gone to great measures to turn the negative trend. Well-organized systems for surveillance and reporting of MDR- and XDR-TB have been established in parts of Russia, following WHO guidelines.

In the Arkhangelsk oblast TB-activities have been according to WHO recommendations for more than 10 years. Drug susceptibility testing has been performed in the central laboratory since 2004. The efforts displayed have caused a decrease in incidence over the last decade, however there are

still many challenges as numbers of MDR-TB among new cases are still increasing.

8 Tables and Figures

Table 1: Treatment schedules recommended by case or treatment category

The medication is indicated by capital letters; numbers preceding the letters indicate the duration of treatment in months; numbers in subscript indicate the number of times per week the medications are given; when the letters are without subscript, the medications are given daily. E = Ethambutol, H = Isoniazid, R = Rifampicin, Z = Pyrazinamide, S = Streptomycine, T = thioacetazone,

Treatment category	Tuberculosis case	Recommended treatment schedule	
		Initial phase	Continuation phase
1	- New case of smear-positive PTB - Severe forms of smear-negative PTB - Severe extra-pulmonary tuberculosis	2 EHRZ (SHRZ) 2 EHRZ (SHRZ) 2 EHRZ (SHRZ)	6 HE or 6 TH 4 HR 4 H ₃ R ₃
2	- Smear-positive pulmonary tuberculosis: relapse failure return after interruption	2 SHRZE/1 HRZE 2 SHRZE/1 HRZE	5 H ₃ R ₃ E ₃ 5 HRE
3	- Smear-negative PTB - Less severe extrapulmonary tuberculosis	2 HRZ 2 HRZ 2 HRZ	6 HE or 6 TH 4 HR 4 H ₃ R ₃
4	Smear-positive pulmonary tuberculosis after re-treatment	Combinations of second-line drugs reserved for used by the reference centres	

From: Maher D et al. *Treatment of tuberculosis: guidelines for national programmes*, 2nd ed. Geneva, World Health Organization, 1997 (document WHO/TB/97.220).

Table 2: Side effects of anti-tuberculosis drugs

Side-effect	Drug responsible	Management
Minor: - Pain in the joints - Burning sensations in the feet - Anorexia, nausea, abdominal pain	Pyrazinamide Isoniazid Rifampicin	Aspirin Pyridoxine 100 mg/day Take with food
Major: - Itching, skin reaction - Deafness or dizziness - Jaundice - Visual impairment - Purpura, shock, acute kidney failure	- Thioacetazone or streptomycin - Rifampicin or isoniazid Streptomycin Isoniazid, rifampicin, pyrazinamide Ethambutol Rifampicin	Stop and do not give again (replace by ethambutol) Stop, then reintroduce with desensitization Stop and do not give again (replace by ethambutol) Stop until the jaundice disappears Stop and do not give again Stop and do not give again

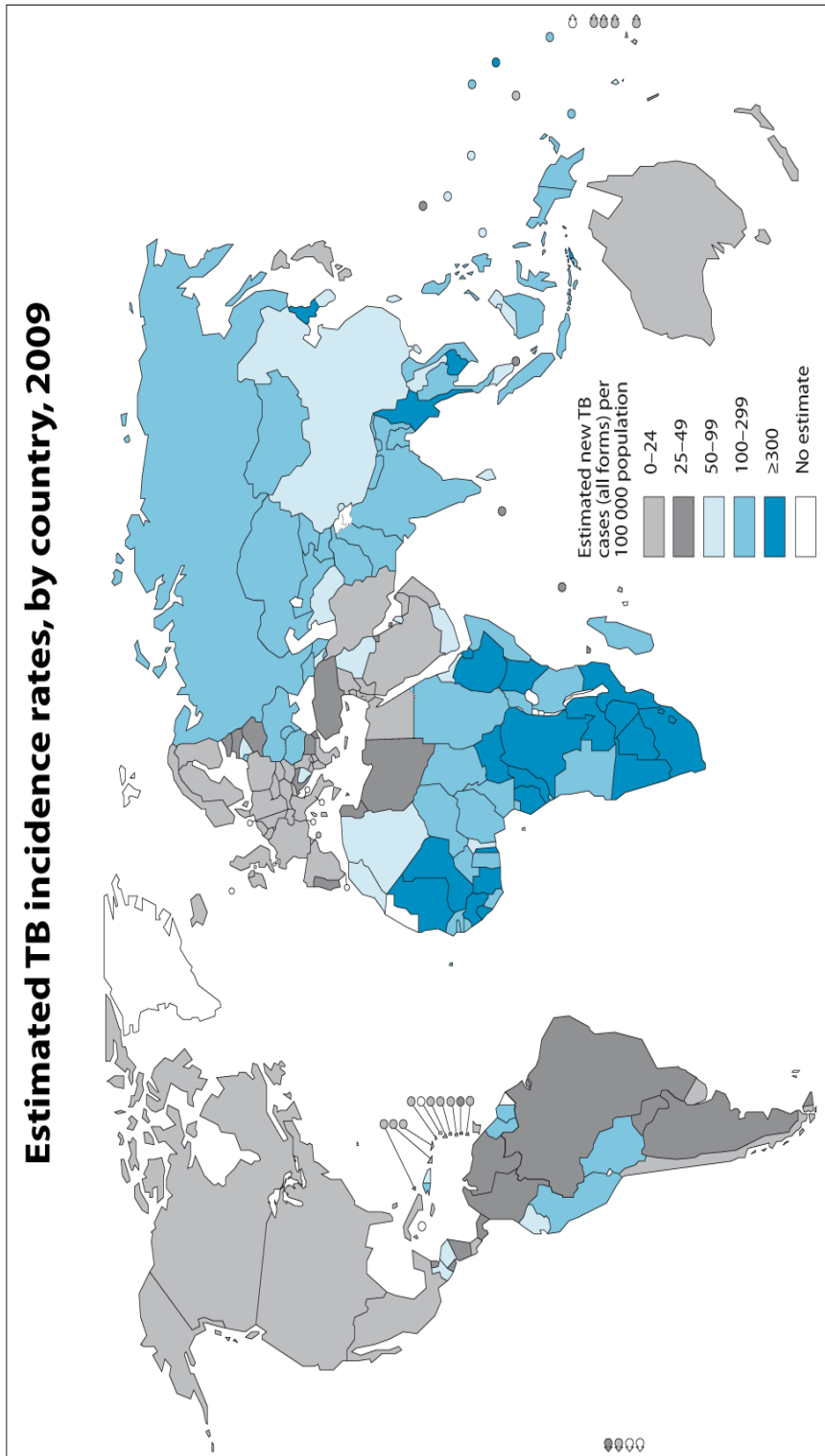
From: Maher D et al. *Treatment of tuberculosis: guidelines for national programmes*, 2nd ed. Geneva, World Health Organization, 1997 (document WHO/TB/97.220).

Table 3 Anti-tuberculosis drug and genes involved in resistance to the drug.

The table lists the drug target genes responsible for anti-TB drug resistance

Isoniazid	Enoyl acyl carrier protein (acp) reductase (inhA)
	Catalase-peroxidase (katG)
	Alkyl hydroperoxide reductase (ahpC)
	Oxidative stress regulator (oxyR)
	B-Ketocyl acyl carrier protein synthase (kasA)
Rifampicin	RNA polymerase subunit B (rpoB)
Pyrazinamide	Pyrazinamidase (pncA)
Streptomycin	Ribosomal protein subunit 12 (rpsL)
	16s ribosomal RNA (rrs)
	Aminoglycoside phosphotransferase gene (strA)
Capreomycin	Haemolysin (tlyA)
Ethambutol	Arabinosyl transferase (emb A, emb B and emb C)
Fluoroquinolones	DNA gyrase (gyr A and gyr B)

From S.K. Sharma, A. Mohan. "Multidrug-Resistant Tuberculosis: A Menace That Threatens To Destabilize Tuberculosis Control". Chest. 2006 Jul;130(1):261-72



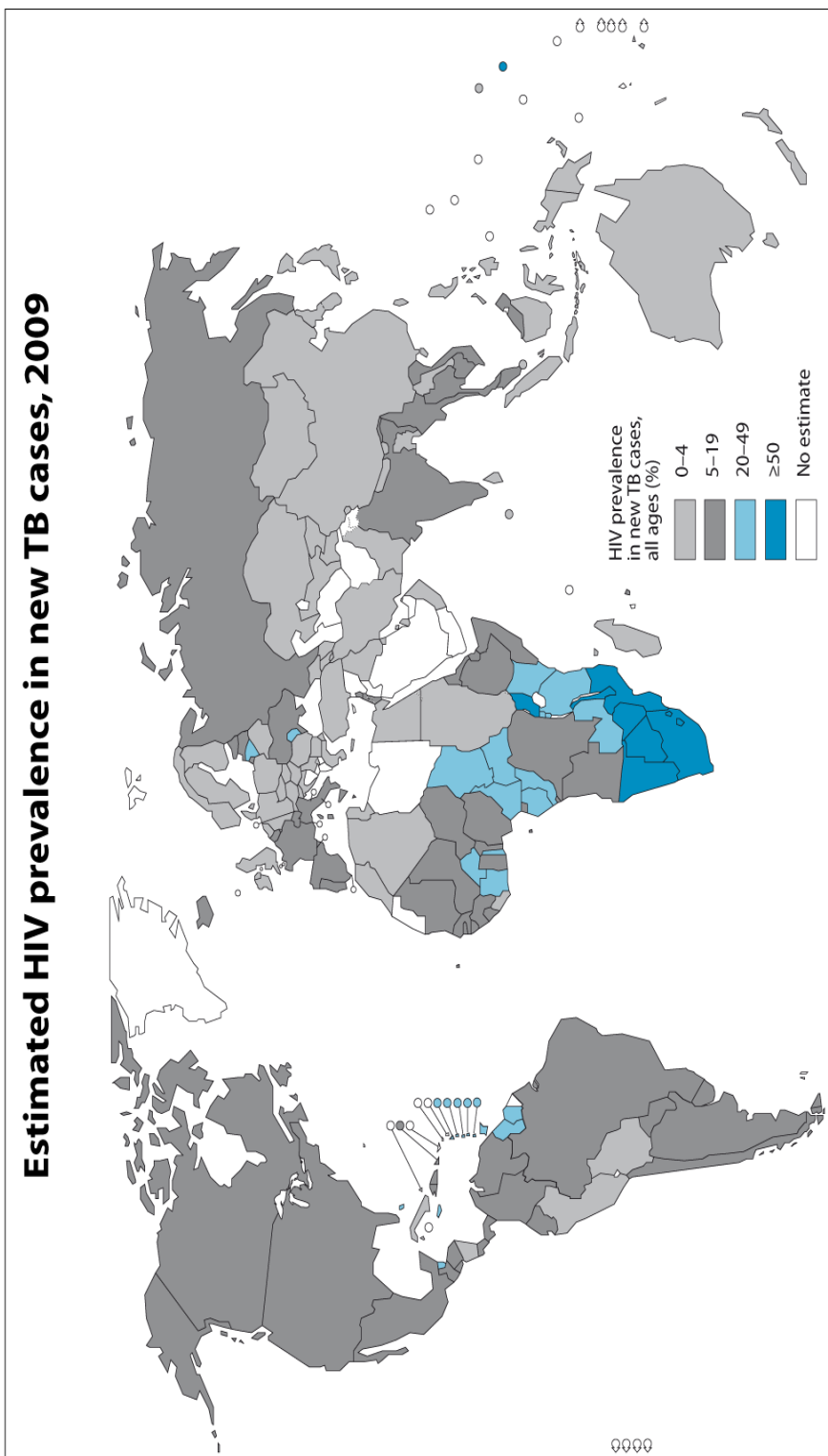
Source: *Global Tuberculosis Control 2010*. WHO, 2010.

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Figure 1. Estimated TB incidence rates, by country, 2009.

Source: Global Tuberculosis Control 2010. WHO, 2010.



Source: *Global Tuberculosis Control 2010*. WHO, 2010.

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The boundaries and names shown and the designations used on this map do not imply the expression of any opinion whatsoever on the part of the World Health Organization concerning the legal status of any country, territory, city or area or of its authorities, or concerning the delimitation of its frontiers or boundaries. Dotted lines on maps represent approximate border lines for which there may not yet be full agreement.

Figure 2. Estimated HIV prevalence in new TB cases, 2009.

Source: Global Tuberculosis Control 2010. WHO 2010.

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