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Tuberculosis as a public health problem in the World and in Slovakia

Gruźlica jako problem zdrowia publicznego całego świata, także Słowacji

Abstract:

Tuberculosis (TB) remains the most frequent and important infectious disease causing morbidity and death worldwide. An estimated one third of the world's population is infected with Mycobacterium tuberculosis. The World Health Organization estimates that about eight to ten million new TB cases occur annually around the globe. TB is in the top three, with malaria and HIV as being the leading causes of death from a single infectious agent, and approximately 1.7 to 2 million deaths are attributable to TB annually. Widespread global use/misuse of isoniazid and rifampicin over three decades has resulted in the emergence of the ominous spread of multi-drug-resistant TB (MDR-TB) and extensively drug-resistant TB (XDR-TB). MDR-TB is defined as TB that is resistant to the two most effective first-line therapeutic drugs available, isoniazid and rifampicin. In addition, virtually untreatable strains of M. tuberculosis are emerging globally. XDR-TB is defined as MDR-TB that also is resistant to the most effective second-line therapeutic drugs used commonly to treat MDR-TB: fluoroquinolones and to at least one of three injectable second-line drugs used to treat TB (amikacin, kanamycin, or capreomycin). Unfortunately, no new drugs besides rifabutin and rifapentine have been marketed for TB in the US and other countries in the 40 years since the release of rifampicin. There are a number of constraints that have deterred companies from investing in new anti-TB drugs. The research is expensive, slow and difficult, and requires specialized facilities. Development time of any anti-TB drug will be long (clinical trials will require a minimum six-month therapy, with a follow-up period of one year or more). It is hard to demonstrate the obvious benefits of new anti-TB agents over pre-existing drugs, since clinical trials involve multi-drug combination therapy using highly effective ordinary anti-TB drugs. XDR-TB has been identified in all regions of the world, including the United States. These difficult to treat resistant forms of TB are increasingly seen in Asia, Eastern Europe, South America and sub-Saharan Africa, disrupting TB and HIV control programmes. Because of the limited responsiveness of XDR-TB to available antibiotics, mortality rates among patients with XDR-TB are similar to those of TB patients in the pre-antibiotic era. To assess the frequency and distribution of XDR-TB cases, the CDC and WHO surveyed an international network of TB laboratories. Slovakia belongs to a group of countries with low incidence rates of TB. HIV-infected patients with MDR-TB have unacceptably high mortality; both antiretroviral and antimycobacterial treatment are necessary. Simultaneous treatment requires 6-10 different drugs. Given the increasing current global trends in MDR-TB, aggressive preventive and management strategies are urgently required to avoid disruption of global TB control efforts. Available data suggest that existing interventions, public health systems and anti-TB and anti-HIV programmes must be strengthened significantly.

Streszczenie:

Na całym świecie gruźlica (TB) nadal pozostaje najczęstszą i najbardziej znaczącą chorobą zakaźną, powodującą zachorowania i zgony. Ocenia się, że jedna trzecia światowej populacji jest zarażona prątkiem gruźlicy. Według światowej Organizacji Zdrowia pojawia się co roku na całym świecie osiem do dziesięciu milionów nowych zachorowań na gruźlicę.

Gruźlica obok malarii i HIV znajduje się w pierwszej trójce najczęstszych przyczyn zgonów spowodowanych pojedynczym czynnikiem zakaźnym. Przypisuje się jej około 1,7 do 2 milionów zgonów rocznie. Powszechne stosowanie i nadużywanie izoniazydu i rifampicyny przez trzy dekady doprowadziły do powstania i rozprzestrzenienia się wielolekowo opornej odmiany gruźlicy (MDR-TB) i szerokoopornej gruźlicy (XDR-TB) na całym świecie.

MDR-TB jest definiowana jako ta odmiana gruźlicy, która jest odporna na dwa najbardziej efektywne leki pierwszorzutowe, tj. izoniazyd i rifampicynę. Dodatkowo, niemal nieuleczalne odmiany MDR-TB tworzą się na całym świecie. XDR-TB jest definiowana jako ta odmiana MDR-TB, która dodatkowo jest odporna na najbardziej efektywny lek drugiego rzutu w terapii MDR-TB, tj. fluorochinolony i przynajmniej na jeden z trzech leków podawanych pozajelitowo, tj. amikacynę, kanamycynę lub kapreomycynę. Niestety żadne nowe lekarstwa oprócz rifabutinu i rifapentinu nie zostały

wprowadzone na rynek w Stanach Zjednoczonych i w innych krajach w czterdziestoletnim okresie po wprowadzeniu rifampicyny. Jest szereg ograniczeń, które odstraszały koncerny farmaceutyczne przed inwestowaniem w nowe leki przeciwko gruźlicy. Badania są drogie, długotrwałe i żmudne. Wymagają ponadto specjalistycznych ośrodków badawczych. Czas opracowania jakiegokolwiek leku przeciwko gruźlicy jest bardzo długi (badania kliniczne trwać muszą przynajmniej pół roku, z rocznym okresem następującym). Jest niezwykle trudno wykazać istotną przewagę nowych leków przeciwgruźliczych nad tymi już istniejącymi, gdyż badania kliniczne opierają się na porównaniu do wcześniejszej terapii, często obejmującej wiele tradycyjnych środków przeciwko gruźlicy, których skuteczność była duża. XDR-TB rozpozna-wano we wszystkich regionach świata, w tym w Stanach Zjednoczonych.

Te trudne do wyleczenia odporne formy gruźlicy są coraz częściej odnotowywane w Azji, Europie Wschodniej, Ameryce Południowej i na terenach Afryki Subsaharyjskie, zakłócając działalność programów kontroli gruźlicy i HIV.

Z powodu ograniczonej reakcji XDR-TB na dostępne antybiotyki, śmiertelność pacjentów z XDR-TB porównywalna jest do tej, którą pacjenci z gruźlicą wykazywali w erze przedantybiotykowej. Aby ocenić rozmieszczenie i częstotliwość przypadków XDR-TB, Centrum Zapobiegania i Zwalczania Chorób (CDC) oraz Światowa Organizacja Zdrowia (WHO) powołały międzynarodową sieć laboratoriów gruźliczych.

Słowacja należy do krajów z niską zachorowalnością na gruźlicę.

Pacjenci zarażeni wirusem HIV cierpiący na MDR-TB wykazują nieakceptowalną śmiertelność: obie terapie są konieczne: antyretrowirusowa i antyprątkowa. Symultaniczne leczenie wymaga zastosowania 6-10 różnych lekarstw. Biorąc pod uwagę wzrastającą liczbę zachorowań na MDR-TB, zdecydowane strategie prewencyjne i zarządzające są niezwłocznie konieczne, aby nie doszło do zaburzenia działań na rzecz kontroli gruźlicy na całym świecie.

Dostępne źródła sugerują, że istniejące działania, systemy zdrowia publicznego i programy przeciwdziałania HIV i gruźlicy muszą zostać znacząco wzmocnione.

Introduction

Tuberculosis (TB) is still a major health problem worldwide. TB is one of the world's most devastating diseases primarily due to several decades of neglect and thus it presents a global health threat of escalating proportions. With an estimated one-third of the world´s population infected with *Mycobacterium tuberculosis* (MTB) and approximately 1.6 million deaths in 2006 attributed to tuberculosis (TB) world-wide, TB remains a major public health concern today [1]. TB is the second leading infectious cause of mortality today behind only HIV/AIDS [2]. The statistics on TB are horrifying, with a third of the world´s population infected with *Mycobacterium tuberculosis* and nearly 9 million people developing the disease each year and more than 2 million people dying from this infection each year [3].

The twentieth century was characterized by a decline in the incidence of TB in most developed countries. This was due largely to antibiotic drugs, active immunization, screening of people and livestock and better living conditions. More recently we have seen a disturbing rise in TB infections [4]. This appears to be due to immigration patterns, emergence of drug resistant strains of TB and a prevalence of conditions that impair immunity, e.g., HIV infection resulting in acquired immunodeficiency syndrome (AIDS) and organ transplant therapy.

History

TB describes an infectious disease that has plagued humans since Neolithic times. Two organisms cause tuberculosis – *Mycobacterium tuberculosis* and *Mycobacterium bovis*. M. tuberculosis is a rod-shaped, slow-growing bacterium, [*M. tuberculosis´*] whose cell wall has high acid content, which makes it hydrophobic (i.e., resistant to oral fluids). The cell wall absorbs a certain dye used in the preparation of slides for examination under the microscope and maintains this red color despite attempts at decolorization, hence the name acid-fast bacilli. Physicians in ancient Greece called the illness "phtisis" to reflect its wasting character. During the 17th and 18th centuries, TB caused up to 25% of all deaths in Europe. In more recent times, TB has been called "consumption". In the 19th century, patients were isolated in sanatoria and given treatments that involved injecting air into the chest cavity. Attempts were made to decrease lung size by means of a surgery called thoracoplasty. Robert Koch reported the discovery of tubercle bacilli on 24 March 1882. During the first half of the 20th century, no effective treatment was available. Streptomycin, the first antibiotic to fight TB was introduced in 1946, and Isoniazid (Laniazid, Nydrazid) became available in 1952. Mycobacterium tuberculosis continues to kill millions of people yearly worldwide. In 1995, 3 million people died from TB. More than 90% of TB

cases occur in developing countries that have few resources and a high number of people infected with HIV. In the United States, the incidence of TB began to decline around 1900 because of improving living conditions. TB cases have increased since 1985, most likely due to the increase of HIV.

Tuberculosis Cases

All cases of TB are passed from person to person via droplets. When someone with a TB infection coughs, sneezes, or talks, tiny droplets of saliva or mucus are expelled into the air, which can be inhaled by another person. Once infectious particles reach the alveoli (small sac like structures in the air spaces in the lungs), other cells, called macrophages, engulfs the TB bacteria. The bacteria are then transmitted to the lymphatic system and blood stream, where they spread to the other organs. The bacteria further multiply in organs that have high oxygen pressures, such as the upper lobes of the lungs, the kidneys, bone marrow, and meninges – the membrane-like coverings of the brain and spinal cord. When the bacteria cause a clinically detectable disease, the individual has TB. People who have inhaled the TB bacteria, but in whom the disease is controlled, are considered to be infected. Their immune system has walled off the organism in an inflammatory focus known as granuloma. They have no symptoms, but frequently have a positive skin test for TB, yet cannot transmit the disease to others. This is referred to as latent tuberculosis infection or LTBI.

Risk factors for TB include the following: HIV infection – people infected with human immunodeficiency virus (HIV), low socioeconomic status, crowded living conditions, homelessness (homeless people), alcoholism, and migration (immigrants) from a country with a higher number of cases. Groups who appear to be particulary at risk are elderly people, intravenous drug users, immuno-compromised people (those with diseases that weaken the immune system) and certain occupational groups such as health care workers (HCW).

Although most initial infections have no symptoms and people overcome them, they may develop fever, dry cough, and abnormalities that may be seen on a chest X-ray. This is called primary pulmonary tuberculosis. Pulmonary tuberculosis frequently goes away by itself, but in 50% – 80% of cases, the disease can return. About 15% of people may develop tuberculosis in an organ other than their lungs. About 25% of these people usually experienced inadequate treatment when infected with TB. The most common sites include the following: lymph nodes, genitourinary tracts, bone and joint sites, meninges and the lining covering the outside of the gastrointestinal tract.

Prevention

Treatment to prevent TB in a single person aims to kill walled-up germs that presently are not doing damage but could break out years from now and become active. Treatment also can stop the spread of TB in large populations. Many countries vaccinate children in early infancy (6 days after birth) and between 10-12 years of age, according to the Tuberculin Skin Test (TST). Vaccination is cheap and effective. The tuberculosis vaccine known as bacilli Calmette-Guérin (BCG) may prevent the spread of tuber-culosis and tuberculous meningitis in children, but the vaccine does not necessarily protect against pulmonary tuberculosis. It can, however, result in a false-positive tuberculin skin test that in many cases can be differentiated by the use of the QuantiFERON-TB Gold test. Another important aspect of tuberculosis treatment is public health. A doctor will likely seek and contact a patient's relatives and friends, who would then need to undergo appropriate skin tests and chest X-rays.

Antituberculotics

Drugs used in the treatment of TB are generally divided into two groups – first and second-line antituberculotics – on the basis of their efficacy, activity and adverse effects [5] (Tab. 1). A successful treatment requires administering multiple drugs and prolonged therapy. The initial phase involves providing at least three drugs and the continuation phase involves two drugs. Drug resistance is common in *Mycobacterium tuberculosis* [6].

Presently, drugs used to treat tuberculosis are termed first-line, second-line or third-line. The second-line drugs are used in cases where the first-line drugs are ineffective, the third-line ones are used in cases of multi-drug-resistant TB. In immunocompromised patients, multi-resistant organisms are common and stringent monitoring is needed after treatment is completed to ensure the infection has been eradicated. In HIV-positive patients, specialist advice is needed in order to avoid potential drug interaction. If the patient is unlikely to take their drugs without supervision, a different regimen, DOT (directly observed therapy), is implemented. To reduce the burden of TB in high prevalence countries, the so-called Directly Observed Treatment, Short-course strategy of TB control (DOTS) was introduced and has been applied in most developing countries, and thus the gap between high and low prevalence countries has been reduced in the past decade. The DOTS strategy of tuberculosis treatment reco-mmended by WHO was based on clinical trials done in the 1970s by the Tuberculosis Research Centre, Chennai, India. DOTS strategy combines an accurate diagnosis of TB and consequent registration of each patient detected, followed by a standardized multi-drug treatment with

a secure supply of high quality anti-TB drugs for every patient in treatment [1]. DOTS costs only three to seven USD for every healthy year gained. DOTS gets people back to school, work and their families. The decentralization of DOTS has increased the number of cured smear-positive TB patients. However, the rate of recurrence has increased mainly due to HIV infection. Recurrence rates could be considered as being an important measure of the long-term success of TB treatment.

The World Health Organization estimates that up to 50 million people worldwide may be infected with drug resistant strains of TB. During 1985-1992, the United States experienced an unprecedented TB resurgence marked by a substantial number of patients with TB who did not respond to treatment and who eventually died [7]. Physicians and epidemiologists quickly determined that these persons had multi-drug-resistant TB (MDR TB). Multi-drug-resistant tuberculosis (MDR-TB) is defined as being resistant to the two most effective first-line TB drugs: isoniazid and rifampicin [8]. The country in which a person with TB lives can determine which treatment they receive. Although people with MDR TB usually can be treated effectively by relying on second-line drugs (amikacin, kanamycin, or capreomycin), these have more side effects and are more expensive and less effective than first-line drugs and require regimens lasting 18-24 months. The fatality rate of MDR-TB is 20-80%. This is because multi-drug-resistant tuberculosis is resistant to most first-line medications, the use of second-line antituberculosis medications is necessary to cure the patient. However, the price of these medications is high; thus poor people in the developing world have limited or no access to these treatments.

Extensively drug resistant TB (XDR-TB)

Extensively drug-resistant TB (XDR-TB) is resistant to three or more of the six classes of second-line drugs and to at least isoniazid and rifampicin among the first-line drugs. In addition, it has a resistance to some fluoroquinolones (i.e., ofloxacin, ciprofloxacin and levofloxacin) and to at least one of three injectable second line antituberculosis drugs (i.e. amikacin, kanamycin and capreomycin) [9-11]. XDR-TB is a stark setback for global TB control. XDR-TB is rare but very problematic. This form of TB is very difficult to treat and often requires prolonged isolation of the individual to protect the community at large. If TB is treated properly and consistently, these resistant forms are much less likely to spread.

Factors contributing to the development and spread of MDR and XDR-TB are:

- Poor quality treatment
- Inappropriate treatment regimens
- Erratic administering of drugs

- Poor quality drugs
- Weak TB programs (DOTS)
- Low completion/cure rates
- Lack of treatment follow up and patient support
- Unreliable drug supply
- Diagnostic delay
- Absent or inadequate infection control measures
- Uncontrolled use of 2nd line anti-TB drugs
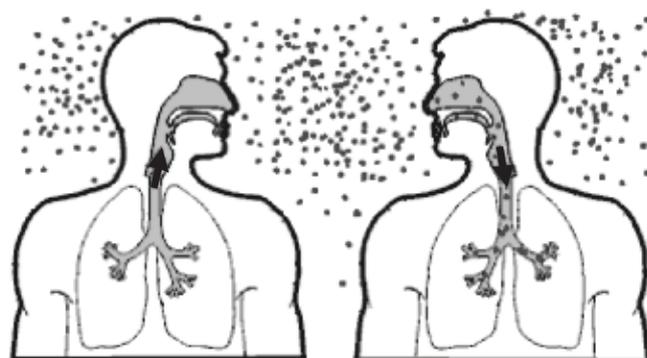
Key Concepts

- Primary (initial) resistance

Fig. 1. TB patient´s initial *Mycobacterium tuberculosis* population resistant to drug

- Secondary (acquired) resistance
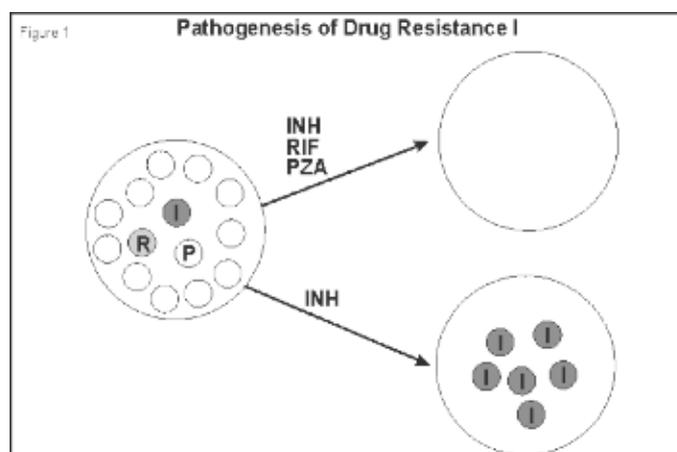

Fig. 2. Drug resistant M. tuberculosis in initial population selected by inappropriate drug use (inadequate treatment or non-adherence/non-compliance)

Unfortunately, there are no new drugs, with the exception of rifabutin and rifapentine, that have been marketed for TB in the US and other countries in the 40 years since the release of rifampicin. There are a number of constraints that have deterred companies from investing in new anti-TB drugs. The research is expensive, slow and difficult, and requires specialized facilities for handling *Mycobacterium tuberculosis*. There are few animal models that closely

mimic the human form of TB. The development time of any anti-TB drug will be long. In fact, clinical trials will require a minimum six-month therapy with a follow-up period of one year or more. In addition, it is hard to demonstrate the obvious benefit of a new anti-TB agents over pre-existing drugs, since clinical trials involve multi-drug combination therapy using highly effective ordinary anti-TB drugs. Finally, there is the perceived lack of commercial return to companies engaged in the development of new anti-TB drugs, because over 95% of TB cases worldwide are in developing countries [12]. The key challenges in the development of new treatments are the needs for novel drug combinations, new trial designs, studies in paediatric populations, increased clinical trial capacity, clear regulatory guidelines, and biomarkers for the prediction of long-term outcome.

XDR-TB has been identified in every region around the world, including the United States. These treatment-resistant forms of TB are seen increasingly disrupting TB and HIV control programmes in Asia, Eastern Europe, South America and sub-Saharan Africa.

Overburdened public-health systems with inadequate resources for case detection and management and high HIV co-infection rates in many regions have contributed to the emergence of XDR-TB. Patients with XDR-TB have poor outcomes, prolonged infectious periods and limited treatment options. In the United States, the cost of hospitalization for one XDR-TB patient is estimated to average $483,000, approximately twice the cost for MDR-TB patients. Because of the limited responsiveness of XDR-TB to available antibiotics, mortality rates among patients with XDR-TB are similar to those of TB patients in the pre-antibiotic era.

TB in the World and in Slovakia

There are areas in the world where TB is on the rise: Sub-Saharan Africa; Latin America from Mexico to Peru; in parts of Asia such as Iraq, Iran, Afghanistan, Pakistan, but mainly India and Bangladesh, which report 30-70 new cases per year per 1 000 inhabitants.

Slovakia belongs to those countries with a low incidence rate of TB. Incidence data in children and in adults are given in the table 3. In some countries with higher economic standards, national wide screening has been done (Czech Republic, Slovakia, Hungary) periodically in all working patient populations and children. National surveys have indicated that MDR-TB occurs at a higher rate in some countries such as Estonia and Latvia (14.1% and 9% respectively, in 1998) and Russia (although there are only limited validated data). In contrast, in Western Europe and in some countries of Eastern Europe, such as the Czech Republic, Slovenia, Slovakia and Poland with good tuberculosis (TB) prevention and treatment

programmes, the combined MDR-TB prevalence was 1% or less. Distribution of selected countries according to incidence of TB is given in the table 4. In state prisons in Slovakia, 18 people were documented as having TB in 2003, 22 people in 2004 and 23 people in 2005 without ATB resistance. On a positive note, only two cases of TB and HIV co-infection were reported in 2008. The task of providing public health services, i.e., preventive measures and increased supervision of compliance of therapeutic regimes among patients of Roma origin especially is of great importance. Figure 3 shows the comparison of incidences of TB with neighbouring countries. Only Czech republic has a lower incidence of TB than Slovak Republic.

MDR and XDR-TB and HIV/AIDS: The Perfect Storm

MDR-TB has emerged as a global epidemic, with ~425,000 new cases estimated to occur annually [13]. The global HIV infection epidemic has caused explosive increases in the incidences of TB and may be contributing to increases in the prevalence of MDR-TB.

- Immune compromised patients are more vulnerable to TB
- Diagnosis in TB is more difficult in HIV positive people
- Treatment is challenging
- Drug interactions
- Intolerance and adherence
- Protecting health care workers (HCWs) is important
- Special risk for HIV + HCWs
- Increased burden on health care system (Fig. 4)
- Need for hospitalization, heavier workload, stricter infection control
- Fear and stigma
- Alarmist messages → increase stigma
- Negative impact on health seeking behaviour.

Institutional outbreaks of MDR-TB have primarily affected HIV-infected people. Delayed diagnosis, inadequate initial treatment, and prolonged infectiousness lead to extraordinary attack rates and case-fatality rates among HIV-infected persons. Whether this sequence occurs in communities is less clear. MDR-TB does not appear to cause infection or disease more readily than drug-susceptible TB in HIV-infected persons. HIV infection may lead to malabsorption of anti-TB drugs and acquired rifamycin resistance. HIV-infected patients with MDR-TB have unacceptably high mortality; both antiretroviral and antimycobacterial treatment become necessary [12]. Simultaneous treatment requires 6-10 different drugs. In HIV-prevalent countries, TB programmes struggle with increased caseloads, which increase the risk of acquired MDR-TB. Surveillance data suggest that HIV infection and MDR-TB may converge in several countries [3b,12]. Estimates are summarized in the table 5.

Conclusion

It is unbelievable that TB which is a preventable disease by vaccination still represents a large problem on all continents. In addition resistance to anti-TB drugs (Multi-drug – MD, extensively drug – XD) among groups of patients with co-morbidity represents a significant threat. TB continues to be a major health problem worldwide. To assess the frequency and distribution of XDR-TB cases, the CDC and WHO surveyed an international network of TB laboratories. Given the currently increasing global trends in MDR-TB, aggressive preventive and management strategies are urgently required to avoid disruption of global TB control efforts. Available data suggest that existing interventions, public health systems and anti-TB and anti-HIV programs must be strengthened significantly. The main focus of the Stop TB Strategy is on making the best use of currently available tools for diagnosis, treatment and prevention of TB (i.e., programme-based operational research) and improved tools that are likely to become available in future (through research in developing new diagnostics, drugs and vaccines) [14]. The goal of eliminating TB by 2050 depends on the development of new diagnostics, drugs and vaccines. WHO is working in close collaboration with the Stop TB Partnership to enable and promote programme-based operational research and research in developing new diagnostics, drugs and vaccines.

Tab. 1. Division of anti-TB drugs

Class	Active substances
First-line (basis)	Isoniazid, Rifampicin, Ethambutol, Streptomycin, Pyrazinamide
Second-line (reserve)	In cases of non-effectiveness (resistance to 1st line) or adverse effects Amikacin, Cycloserin, Ethionamide, Canamycin, Capreomycin Fluoroquinolones (e.g. Ciprofloxacin)
M-DR and X-DR tuberculosis	
Third-line	macrolides (Clarithromycin), Amoxycillin/clavulanate, Imipenem, Clofazimine + ? anti-TB agents presently in development

Tab. 2. Drug Sensitive versus Drug Resistant TB

Drug sensitive Tuberculosis	Drug Resistant Tuberculosis - Challenges
• Diagnosis - smear microscopy • Standardized treatment • 4 drugs, 6-9 months • Safe, effective, inexpensive • 95% cure rate, $20 (drug cost) • Based on evidence from ~ 30 years of drug discovery and clinical trials	• Diagnosis – smear, culture and drug-resistance testing • Treatment based on laboratory results and epidemiology information • 4-6 drugs, 2 years • Less effective, ↑ toxicity and side effects ($) • <80% cure rate • Higher relapse rates (30 – 40%) • Prolonged infectiousness • $3,500 - $5,000 (drug costs) • No clinical trials evidence to guide treatment or prevention

Tab. 3. TB Incidence in Slovakia per 100 000 Adults and Children in 1951-2005

Year	Children	Adults	Year	Children	Adults
1951	173	299.7	1996	4.2	28.0
1955	163.6	240	1997	2.3	24.1
1960	70.0	169.5	1998	3.2	23.9
1970	17.3	106.8	1999	1.88	22.5
1980	9.2	49.5	2000	1.42	20.6
1990	1.8	27.4	2001	1.99	20.1
1991	2.4	30.5	2002	1.97	19.6
1992	2.7	32.7	2003	1.73	18.4
1993	5.8	34.0	2004	1.95	13.6
1994	6.1	33.5	2005	2.25	13.8
1995	5.3	28.7	-	-	-

Tab. 4. Distribution of selected countries according to incidence of TB

Group 1 High incidence of TB	Group 2 Middle incidence of TB	Group 3 Low incidence of TB
5 countries with high priority: Russian Federation, Ukraine, Romania, Uzbekistan, Kazakhstan The remaining 11 countries: Tajikistan, Belarus, Kirgizstan, Azerbaijan, Moldavian Republic, Lithuania, Turkmenistan, Armenia, Estonia.	Turkey, Poland, Spain, Portugal, Yugoslavia, Hungary, Bulgaria, Bosna and Hercegovina, Creta, Macedonia, Albania	Germany, France, Great Britain, Italy, Greece, Czech republic, Belgium, Holland, Slovakia, Austria, Switzerland, Israel Finland, Íreland Slovenia Sweden, Norway Luxemburg, Malta, Andorra, Island, Monaco

Tab. 5. Global Estimates

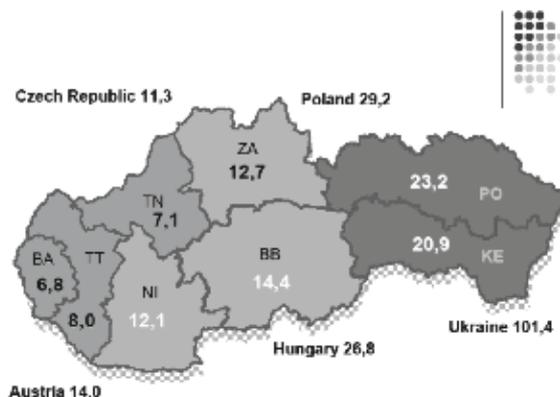| Classification	Estimated Number of Cases	Estimated Number of Deaths
All forms of TB MDR TB XDR TB	8.8 million 424 000 27 000	1.6 million 116 000 16 000

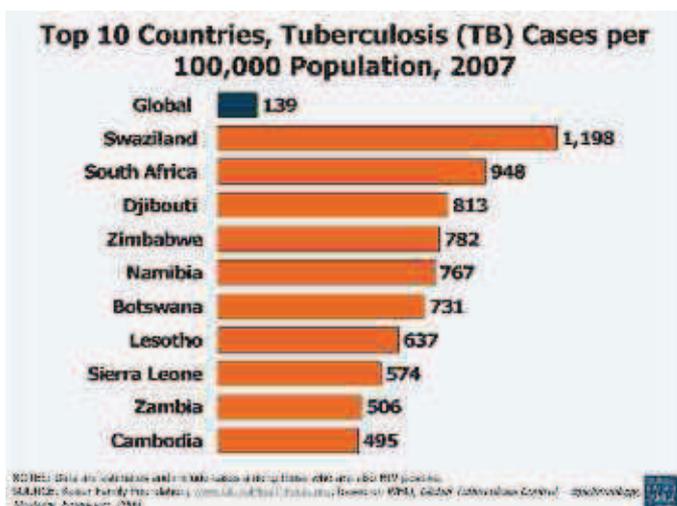Fig. 3. Comparison of incidence of TB in Slovakia and in neighbouring countries

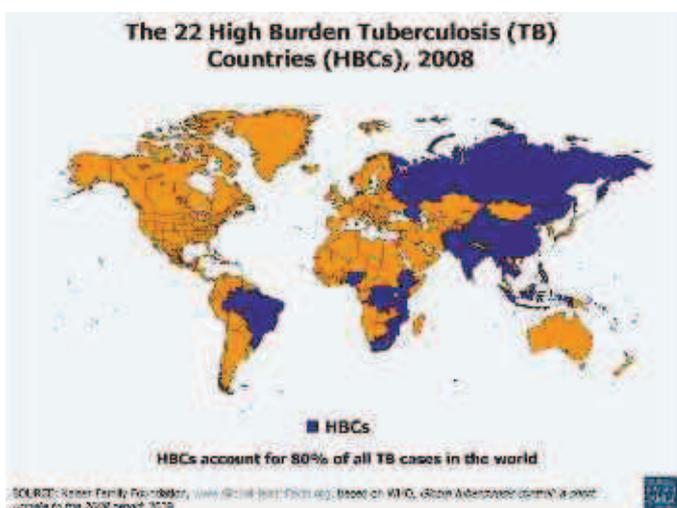Fig. 4. Top 10 Countries with very high incidence of TB in the world

Fig. 5. The 22 High Burden Countries accounts for 80% of all cases in the world

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Kalendarium Zdrowia

STYCZEŃ

26 stycznia — **Dzień Transplantologii**
24-30 stycznia — **Tydzień walki z Rakiem Szyjki Macicy**
31 stycznia — **Światowy Dzień Pomocy Chorym na Trąd**

LUTY

4 lutego — **Międzynarodowy Dzień Walki z Rakiem**
11 lutego — **Światowy Dzień Chorego**
14 lutego — **Światowy Dzień Chorych na Padaczkę**
23 lutego — **Ogólnopolski Dzień Walki z Depresją**

MARZEC

1 marca — **Światowy Dzień Walki z Otyłością**
11 marca — **Światowy Dzień Nerek**
17 marca — **Ogólnopolski Dzień Trzeźwości**
18 marca — **Europejski Dzień Mózgu**
15-21 marca — **Światowy Tydzień Mózgu**
21 marca — **Światowy Dzień Inwalidów i Ludzi Niepełnosprawnych**
21 marca — **Światowy Dzień Zespołu Downa**
24 marca — **Światowy Dzień Walki z Gruźlicą**