Tuberculosis

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The most important causative agent of tuberculosis is Mycobacterium tuberculosis.

M. tuberculosis, together with M. bovis, M. africanum and M. microti, form the ‘M. tuberculosis complex’, which is a group within the genus Mycobacterium.

This genus also includes many different nontuberculous mycobacteria of which M. leprae and M. avium are best known.

Tuberculosis – Case definition

Clinical Criteria

- Any person with the following two:
- — Signs, symptoms and/or radiological findings consistent with active tuberculosis in any site
- AND
- — A clinician's decision to treat the person with a full course of anti-tuberculosis therapy
- OR
- A case discovered post-mortem with pathological findings consistent with active tuberculosis that would have indicated anti-tuberculosis antibiotic treatment had the patient been diagnosed before dying

Laboratory Criteria

- — Laboratory criteria for case confirmation
- At least one of the following two:
- — Isolation of *Mycobacterium tuberculosis* complex (excluding *Mycobacterium bovis*-BCG) from a clinical specimen
- — Detection of *Mycobacterium tuberculosis* complex nucleic acid in a clinical specimen AND positive microscopy for acid-fast bacilli or equivalent fluorescent staining bacilli on light microscopy
- — Laboratory criteria for a probable case
- At least one of the following three:
- — Microscopy for acid-fast bacilli or equivalent fluorescent staining bacilli on light microscopy
- — Detection of *Mycobacterium tuberculosis* complex nucleic acid in a clinical specimen
- — Histological appearance of granulomata

Epidemiological Criteria NA

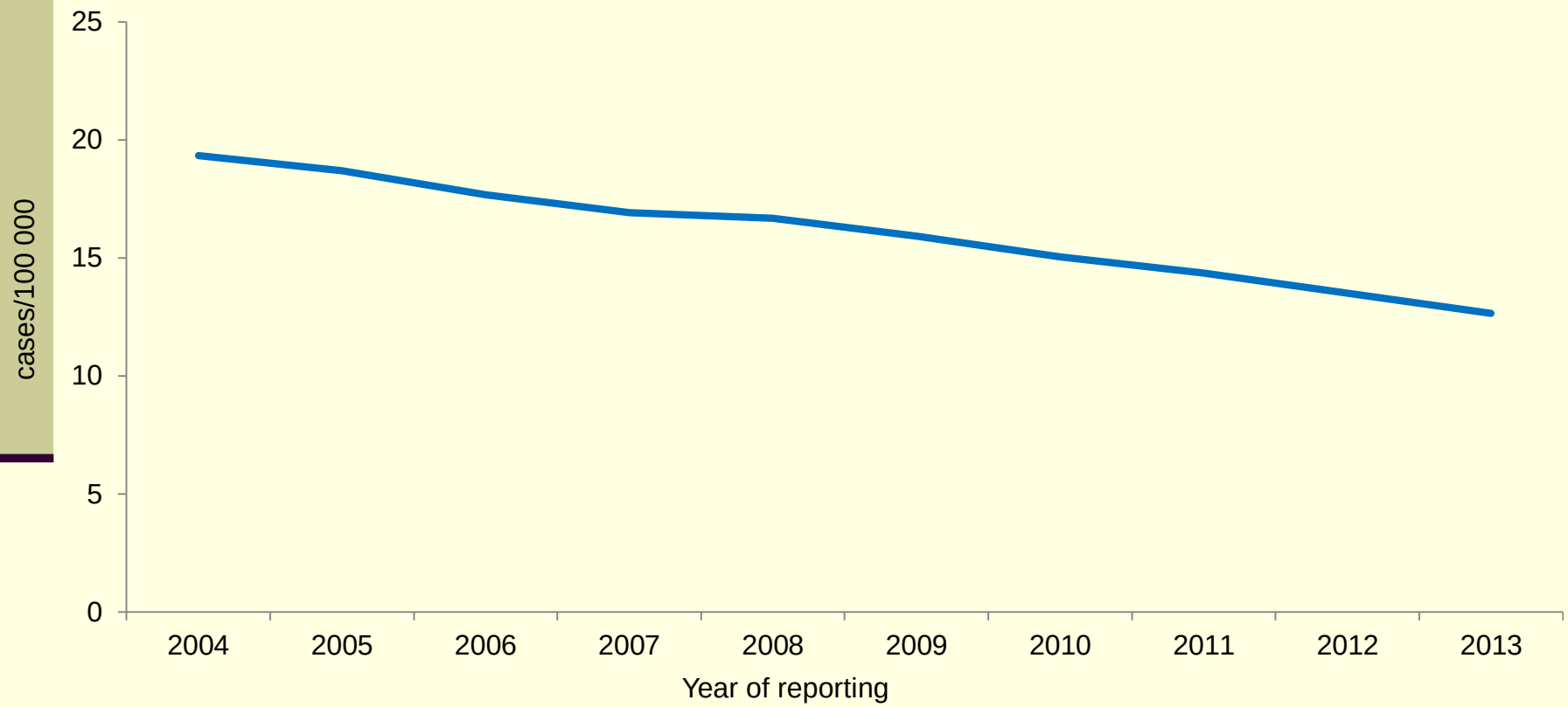
Case Classification

- A. **Possible case**
- Any person meeting the clinical criteria
- B. **Probable case**
- Any person meeting the clinical criteria and the laboratory criteria for a probable case
- C. **Confirmed case**
- Any person meeting the clinical and the laboratory criteria for case confirmation

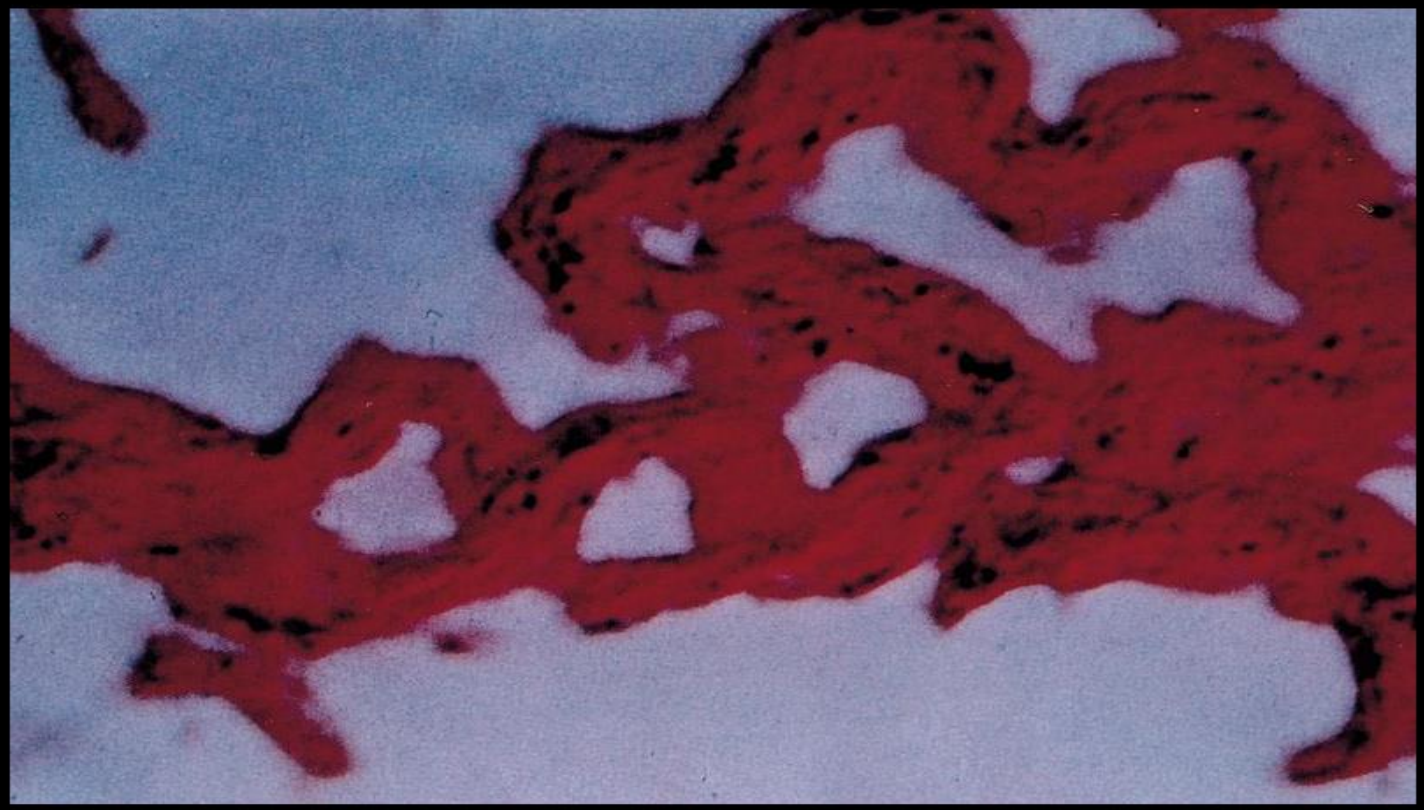
TB notification rate over time

- The TB notification rate has decreased from 19.3 per 100 000 population in 2004 to 12.7 in 2013.

Figure 2: TB notification rate per 100 000 population in EU/EEA 2004–2013



Ziehl-Neelsen stain of 'cords' of *Mycobacterium tuberculosis* isolated from a broth culture. Tubercle bacilli aggregate end to end and side to side to form serpentine cords, especially in broth cultures.



- **Clinical features and sequelae**

Infection with M. tuberculosis is asymptomatic. The symptoms that occur when TB disease develops are usually not very specific. Often there are complaints of tiredness, listlessness, loss of weight, sub-febrile body temperature and night sweating.

In the case of pulmonary TB, usually a cough has been present for weeks or even months, possibly accompanied by haemoptysis. Localisation in the vertebral column (spondylitis tuberculosa) can, apart from back pain, also present itself as an abscess with vertebral collapse. Lymphadenitis tuberculosa usually presents itself by painless lymph node enlargement in the neck. Blood in the urine (haematuria) can present as the only symptom of TB of the kidney.

In cases of co-infection with HIV, the clinical presentation can be less typical. This atypical presentation is usually seen in a more advanced stage of the HIV infection and is the result of impaired cellular immunity. HIV-infected patients show disseminated forms of TB relatively often.

In the pre-chemotherapy era, case-fatality from tuberculous meningitis approached 100 per cent. Pulmonary TB accounted for the majority of deaths. Sputum smear-positive TB has a much higher fatality than sputum smear-negative TB. Untreated sputum smear-positive TB leads to death in about 30–40 per cent of cases within one year and cumulatively kills about 50–70 per cent of cases within 5 to 7 years5.

- **Epidemiology**
- The average notification rate in the European Union (EU) and European Economic Area (EEA) region is 16.7 per 100 000 population (2008 data).
- In low-incidence countries (reporting a notification rate below 20 per 100 000), TB is predominant in vulnerable populations. Examples of vulnerable populations include individuals from high incidence countries, prisoners, contacts of contagious patients, persons who have previous had TB, drug addicts, alcoholics, illegal immigrants and the homeless. In some of these risk groups the incidence is increased due of ongoing transmission (e.g. prisoners, drug addicts and homeless people)7-10.

- **Transmission**
- Humans are the main reservoir for M. tuberculosis and M. africanum. For M. bovis, cattle are the most important host. Cases of TB can occur sporadically in monkeys and some other mammals.
- Transmission of TB is aerogenic. After coughing, sneezing, speaking or singing, infected sputum droplets can dry and form into droplet nuclei of approximately 6–18 μm. These droplet nuclei can float in the air for a longer period and penetrate into the alveoli of the host after inhalation. In moist warm air, the droplet nuclei can survive for hours.
- The lifetime risk of developing TB for people outside of the risk groups is approximately ten per cent11. For HIV-infected persons this risk is much higher, amounting to 8–10 per cent per year.
- Patients with a negative culture of sputum (‘closed’ TB) and cases of extrapulmonary TB are not considered to be contagious.
- In general, in patients with a positive Ziehl-Neelson slide and/or positive culture of their sputum, the start of coughing complaints is considered to be the start of the period of infectiousness.

Transmission II

The incubation period (between infection and the first signs of illness) varies between eight weeks to a lifetime. The greatest chance of progressing to disease is within the first two years after infection, with half of all cases of disease occurring within five years of the original infection. However, a lifelong risk of progression to disease remains for all those people with ‘dormant’ organisms.

People in whom infection progresses to disease are only a minority of all infected persons.

People with latent TB infection are never infectious.

The risk of transmission in cases of active TB is determined by patient factors and the type of contact made with their surroundings.

The level of contagiousness of TB patients depends on the concentration of bacteria in the sputum, the severity of the cough and the coughing hygiene practiced by the patient. In general, the closer and/or more frequent the contact, the higher the chance of transmission. Characteristics of the place of contact may also play an important role (e.g. size of the room, ventilation). Usually, intimate contacts (household) are at the highest risk of being infected14.

- **Prevention**
- The vaccine currently available is the BCG-vaccine (Bacille Calmette Guérin). This is a live, weakened strain of M. bovis. It mainly gives protection against severe forms of the disease, like meningitis TB and miliary TB, in children under five years of age.
- The World Health Organization (WHO) advises BCG-vaccination for all newborns in countries with a high incidence of TB within the framework of the Expanded Program of Immunization (EPI).
- Within the EU, the policy on BCG-vaccination varies between countries. Low incidence countries commonly vaccinate only persons with an increased risk of TB; for example, children whose parents come from high incidence countries and who travel regularly to their home country.
- BCG-vaccination should not be given to the immunosuppressed (e.g. HIV, leukaemia, chemotherapy) due to the increased risk for complications. Also, BCG-vaccination during pregnancy should be avoided, even though no harmful effects on the foetus have been observed.

- **Prevention II**
- Practising cough hygiene will decrease the spread of all types of infections that are spread through the air.
- Preventing the transmission of the disease is the foundation for effective TB control programmes. Preventive measures focusing on the early diagnosis and immediate effective treatment of people with contagious TB is therefore essential. Many factors have been shown to be associated with a delay in diagnosis including old age, low education/awareness, poverty, negative sputum smear, extrapulmonary TB, female sex and a history of immigration.
- Passive case finding is defined as the detection of TB cases among patients attending healthcare facilities because they have symptoms. Active case finding focuses on the screening of high-risk groups (immigrants, drug addicts, homeless people and prisoners) for TB. It aims to identify and treat TB cases at an early stage and to provide preventive treatment to those at the highest risk for developing active TB.

- **Management and treatment**
- Notification of TB cases is compulsory in most EU countries6.
- Cases of respiratory TB require infection control precautions until infectivity has been eliminated by effective chemotherapy; this often requires two weeks treatment with drugs to which the infecting strain is sensitive19,20.
- Contact investigation can be performed as soon as a contagious patient with TB has been diagnosed. The aim of this activity is to identify secondary cases of TB and/or newly infected persons. If a secondary case is identified through the contact investigation, this patient can be diagnosed early which then reduces the chance of further transmission21.
- Newly infected persons can be offered prophylactic treatment in order to reduce their chance of progression from latent to active disease1.
- The treatment of active TB has two phases: an initial intensive phase and a continuation phase. The recommended standard regimen by the WHO for all new cases is an intensive phase of two months with isoniazid, rifampicin, pyrazinamide and ethambutol and a continuation phase of four months with isoniazid and rifampicin.
- Drug resistance is increasing in many countries, and treatment failure and relapse are strongly associated with initial drug resistance23. Individual risk factors include history of previous treatment for TB, recent contact with drug-resistant case and HIV infection24.
- Persons at a high risk for developing TB (cases with recent M. tuberculosis infection and those with clinical conditions associated with progression to active TB like HIV, for example) will be given prophylactic treatment25,26.

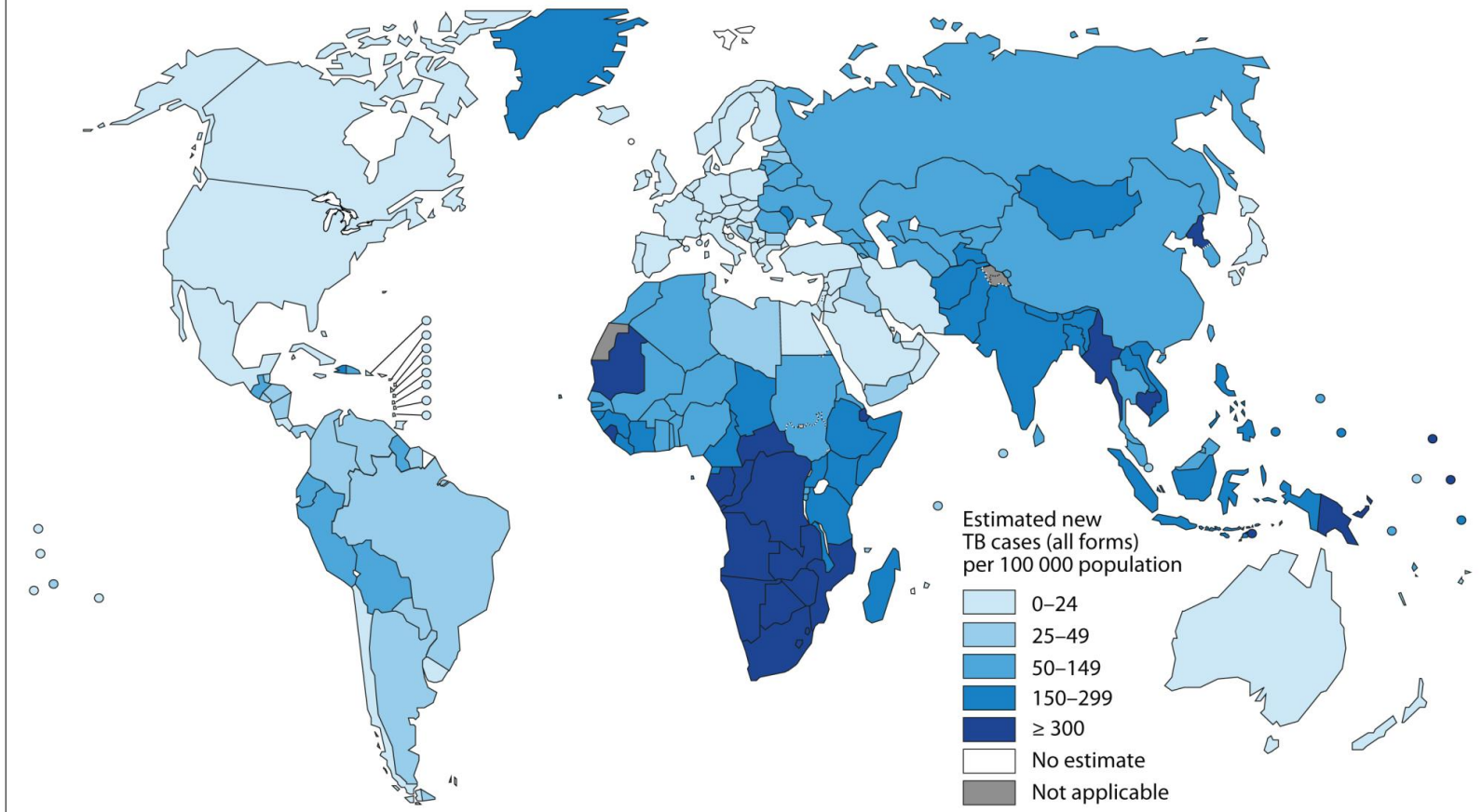
- **Areas of uncertainty**
- Use of interferon gamma-release assays (IGRA): IGRA, a new diagnostic tool, is gradually being introduced in circumstances in which the tuberculin skin test is currently used.
- Caution is necessary when testing certain populations because of limited data in the use of IGRAs. More data are necessary on their use in younger age groups, among persons recently exposed to M. tuberculosis, and in immunocompromised persons (e.g. cases of HIV, users of immunosuppressive drugs, selected haematological disorders, those with specific malignancies along with cases of diabetes, silicosis and chronic renal failure). Limited data are available on the use of IGRA to determine who is at risk for developing active TB.
- Treatment and prophylaxis of MDR TB and XDR TB cases: There is little evidence regarding the treatment of MDR TB and XDR TB. In the absence of controlled trials, expert opinions prevail and perspectives differ according to personal experience. As a result, significant discrepancies are found in the guidelines published by scientific societies29,30. Success rates for the treatment of MDR TB patients vary between 50–80 per cent, depending on the treatment setting.
- Also, evidence for the effects of latent TB infection treatment in people exposed to MDR TB is extremely limited both in quantity and quality. For the treatment of MDR TB at present, we see a great variety in recommended treatment.
- Further studies are required on the level of recurrence of TB following successful treatment from real-life directly observed treatment, short-course (DOTS) programmes.

Key conclusions for the European Region

In 2011, the countries of the WHO European Region reported 295 968 new episodes (new and relapses) of TB (33 per 100 000 population) out of an estimated 380 000 (range 321–437 000), which would correspond to 42 cases per 100 000 population (range 36–49). More than 85% of them were in the 18 high priority countries (HPC) of the WHO European Region.

- The Region maintained a relatively high case detection rate for all cases: 78% (range 67–92%).

Estimated tuberculosis (TB) incidence rates, 2011



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 and dashed lines on maps represent approximate border lines for which there may not yet be full agreement.

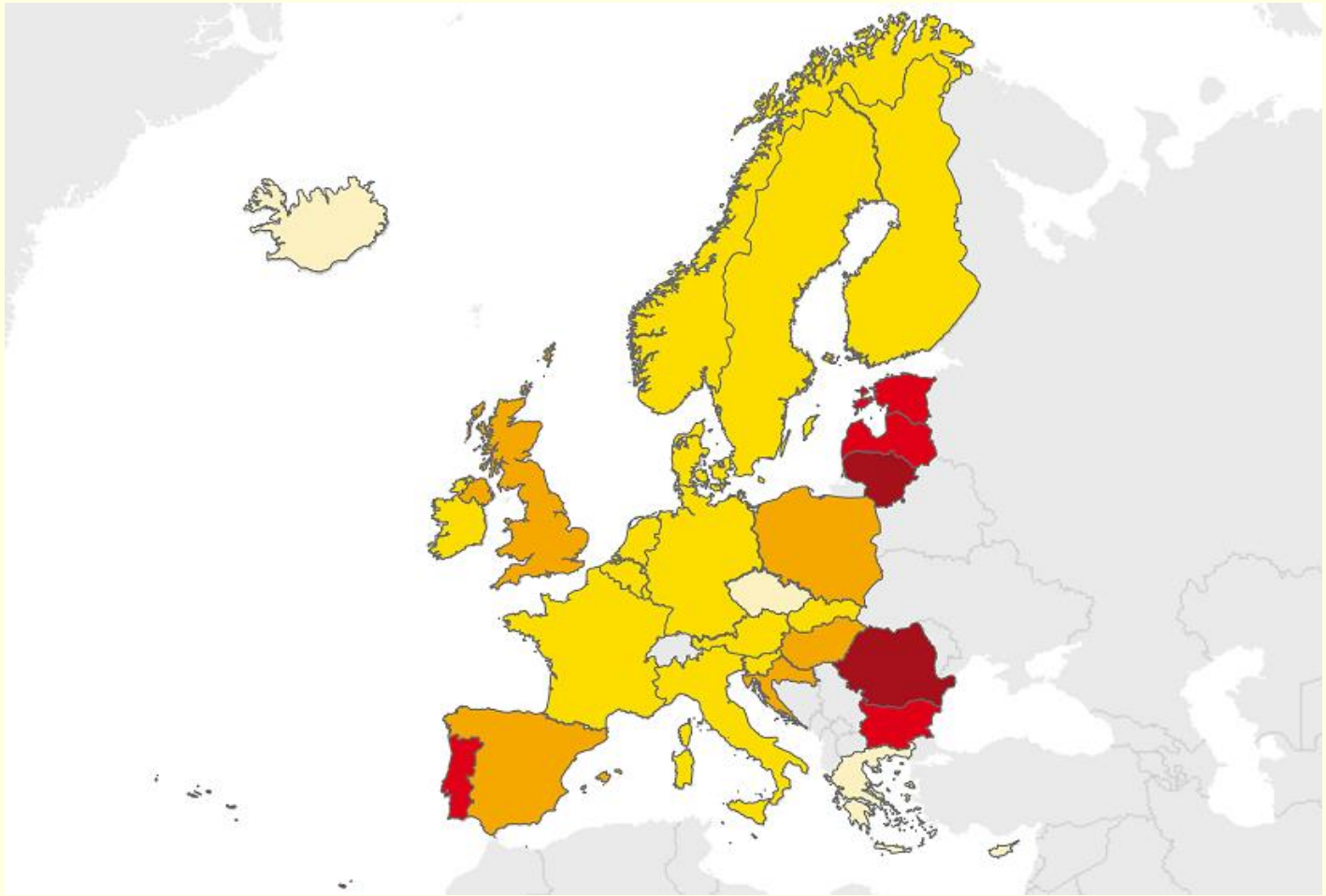
Source: *Global Tuberculosis Report 2012*. WHO, 2012.

World Health Organization

TB notifications by country

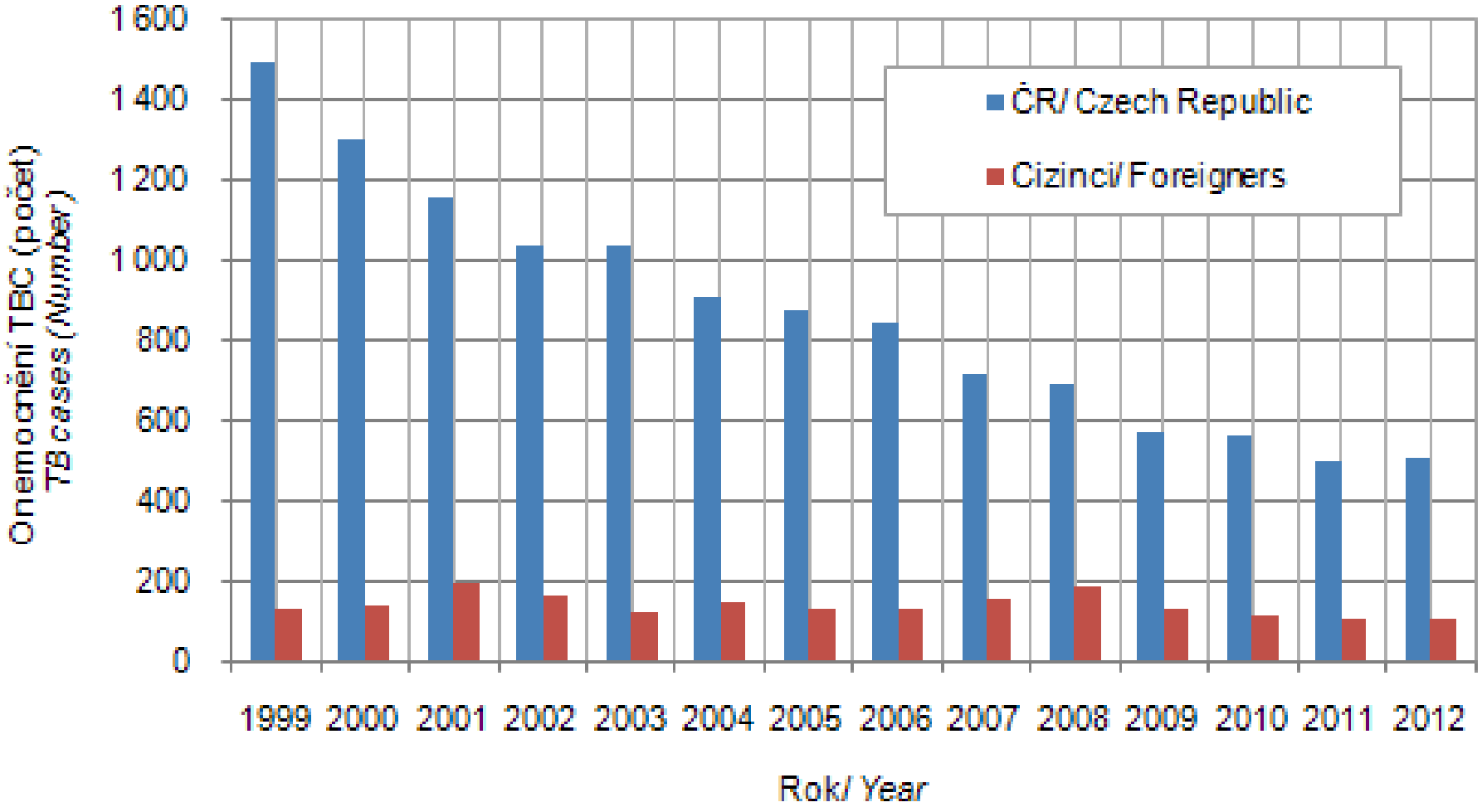
- In 2013, 64 844 TB cases were reported in the EU/EEA.
- The notification rate was 12.7 per 100 000 population (range 3.4–83.5).

Figure 1: TB notification rate per 100 000 population by country, EU/EEA, 2013

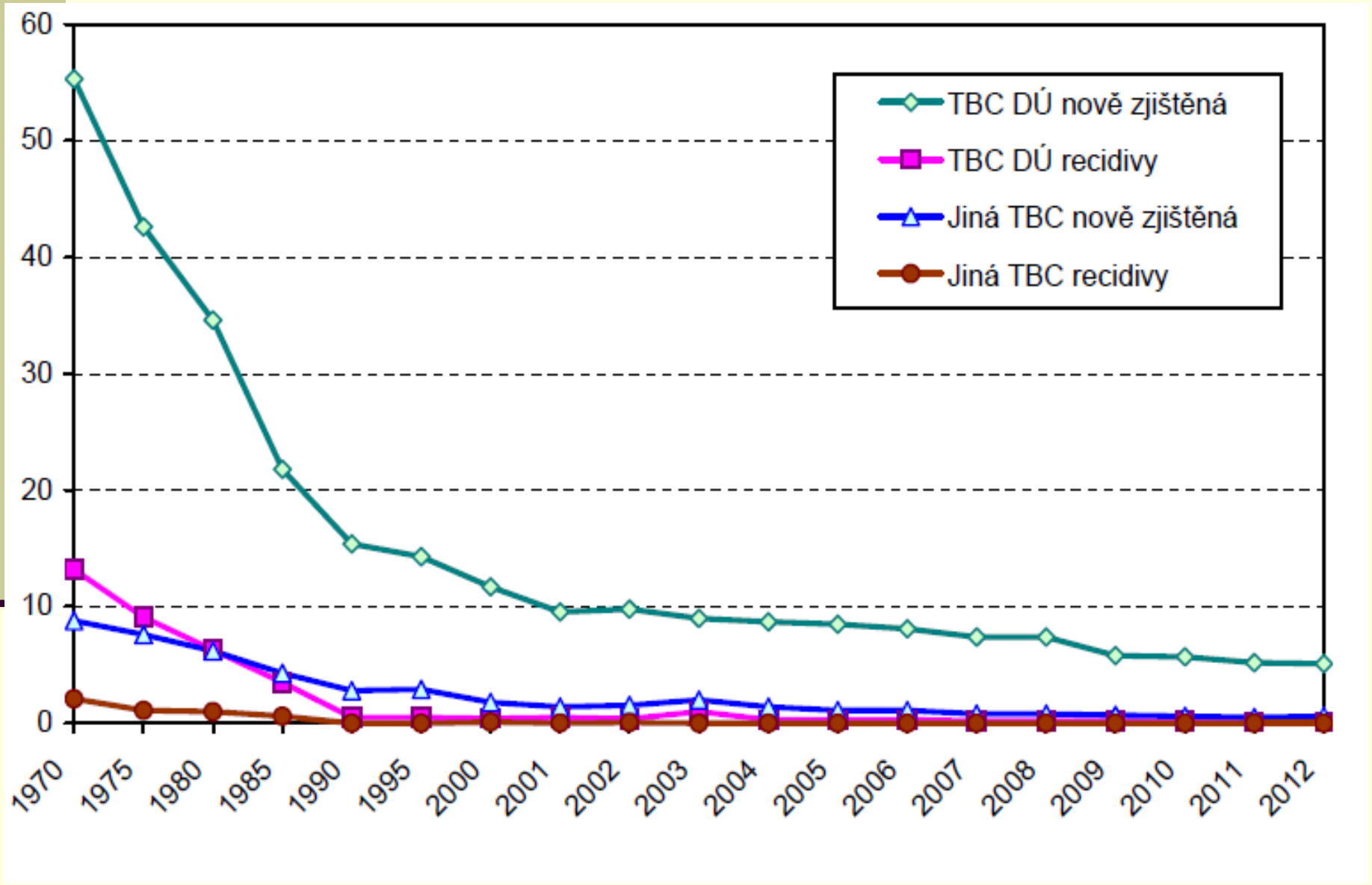


Nově hlášená onemocnění TBC v ČR, 1999-2012

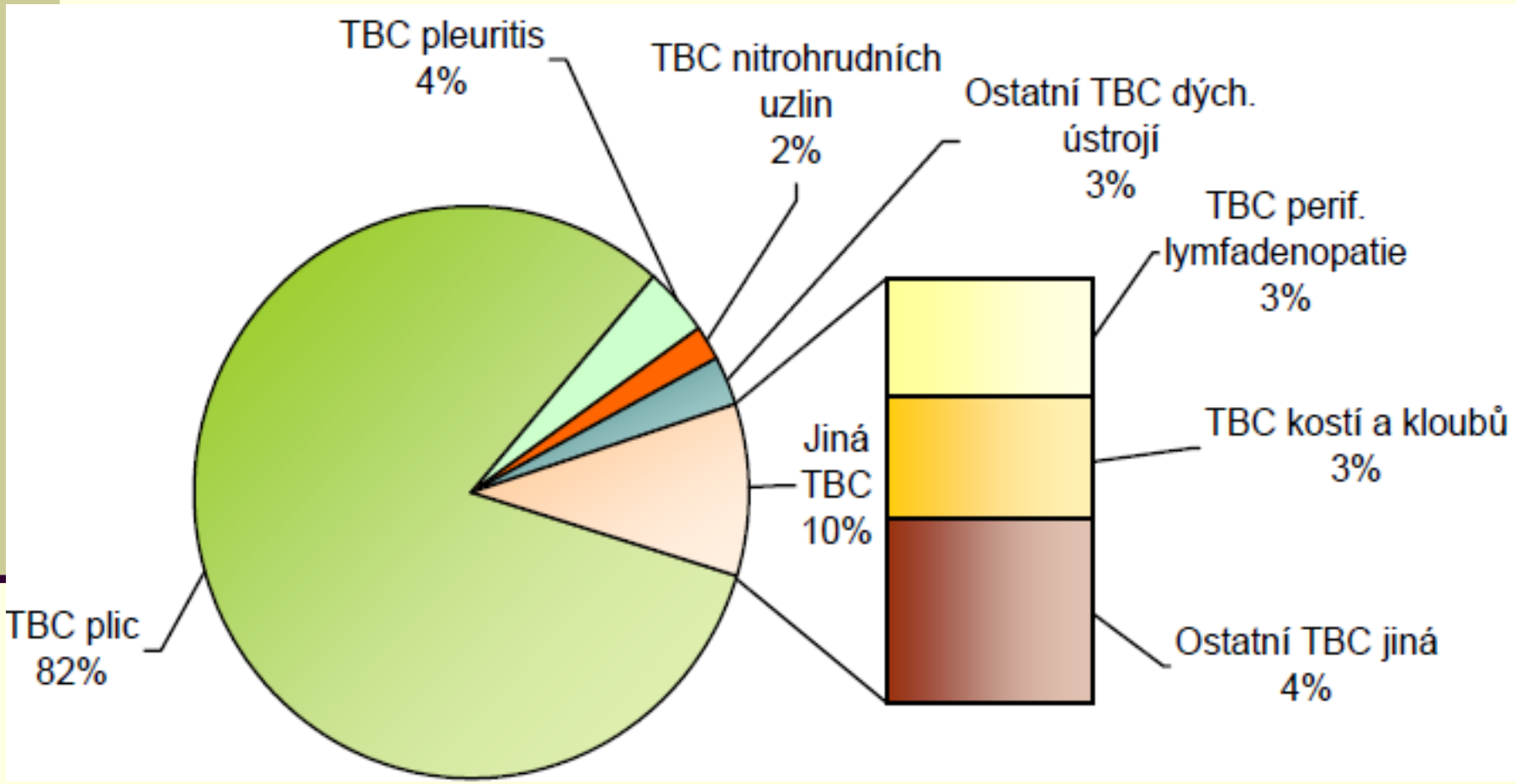
New notified TB cases in the CR; 1999-2012



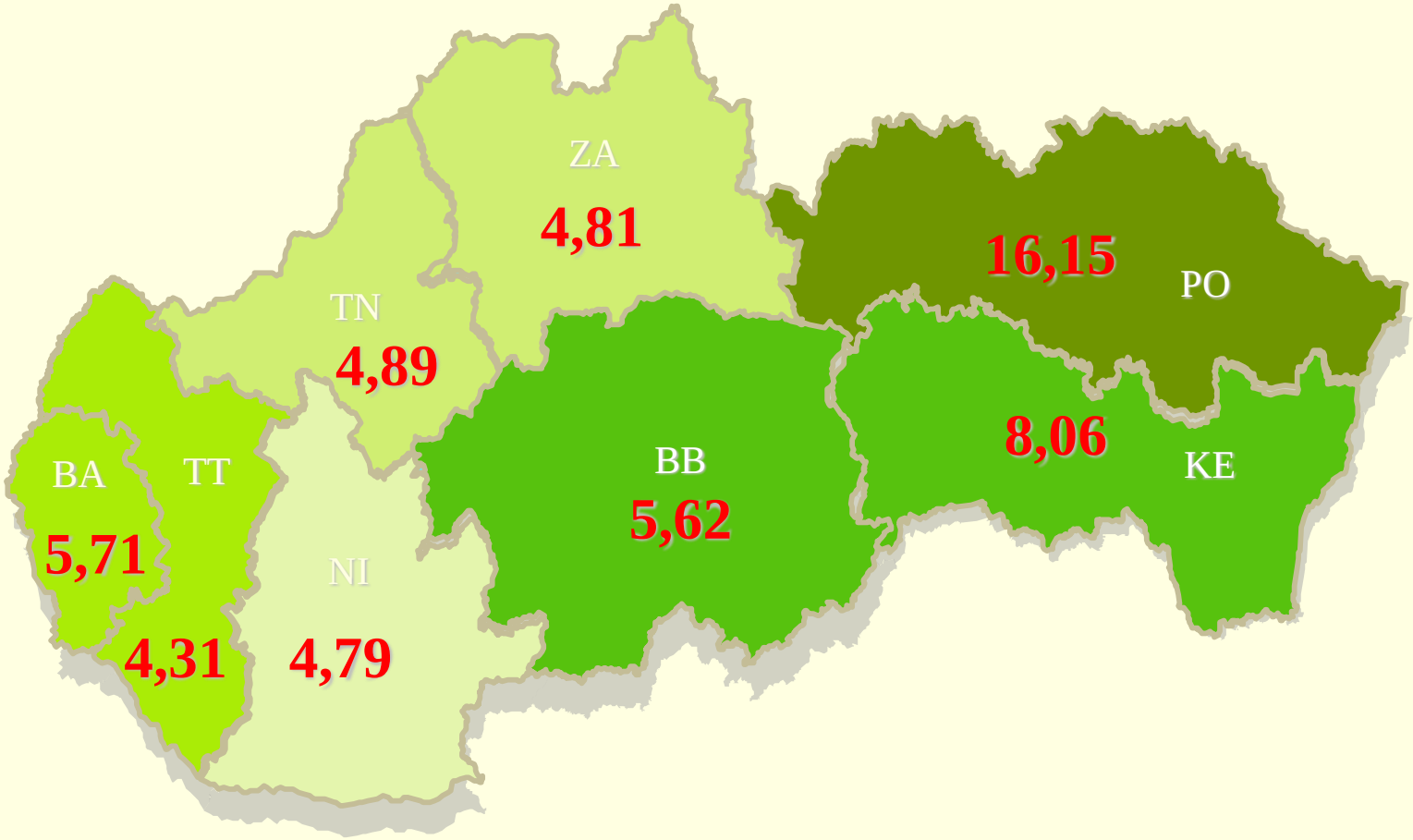
Vývoj počtu hlášených TBC/100 tis.obyvatel,ČR



Struktura hlášené TBC podle dg., rok 2012



TBC – in Slovakia - 2013
number of cases/100 000 residents



Source: Doc. MUDr. Ivan Solovič, CSc.

Key conclusions for the European Region

More than 44 000 (44–46 000) deaths were estimated to have been caused by TB in the Region (4.9 per 100 000 population) (range 4.7–5.3).
Overall, 92% of deaths occurred in the 18 HPC.
The notification shows a 24% decrease compared to 2005, however there is a significant difference in TB notification rates among the countries, from 2 to 119 per 100 000 population.

• In ten countries of the Region (all in EU/EEA), the under-fives accounted for more than half of the cases detected among children.

Key conclusions for the European Region

• In 2011, there were 12 751 (56.5%) TB cases with HIV co-infection detected from the 22 500 (range 18–27 000) estimated in the WHO European Region. Estimated prevalence of HIV infection among incident TB patients was 6% (range 5.6–6.2%), with 3.6% of these cases occurring in the EU/EEA countries and 6.5% in the non-EU/EEA countries.

Due to the low reporting coverage of HIV testing (60%), only 12 751 (6.2%) of the 205 578 new TB and previously treated cases were found to have HIV co-infections.

■ Three countries reported higher rates of HIV positivity among TB patients: Ukraine (18.5%), Malta (16.7%) and Estonia (15%).

Key conclusions for the European Region

- Of the 78 000 estimated MDR-TB cases in the Region, around 30 000 (38%) were detected in 2011.

In all, 98% of them were reported by 18 HPC. The prevalence of MDR among new TB cases in the Region amounted to 14% and 7.7% among previously treated cases.

Although testing coverage for XDR has almost doubled in the Region, it is still only at 9%, documenting that 11% of MDR-TB patients are XDR-TB.

In response to the alarming problem of MDR-TB, all 53 Member States have fully endorsed the Consolidated Action Plan to Prevent and Combat Multidrug- and Extensively Drug-Resistant Tuberculosis in the WHO European Region 2011–2015 and its accompanying Resolution EUR/RC61/R7 from the sixty-first session of the WHO Regional Committee for Europe in 2011. The Action Plan includes a set of activities for countries, WHO and partners in order to achieve universal access to prevention and treatment of M/XDR-TB. WHO is currently preparing a detailed report on progress with the implementation of the Consolidated Action Plan to Prevent and Combat Multidrug- and Extensively Drug-Resistant Tuberculosis in 2013.