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RISK FACTORS FOR TUBERCULOSIS AND SPECIFIC MANIFESTATIONS OF DISEASE

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ABSTRACT

In countries with good epidemiological situation, incidence of tuberculosis (TB) is relatively high in immigrants, prisoners, the homeless and unemployed. In a number of regions, co-infection of *Mycobacterium tuberculosis* and HIV raises difficulties in controlling TB epidemic. A problematic issue is also drug resistance, especially in the countries of the former Union of Soviet Socialist Republics (USSR). Neither co-infection of *M.tuberculosis* and HIV nor drug resistance are of special concern in Poland. Incidence of extrapulmonary TB is very diverse (6-44%), however, in Poland such manifestation of tuberculosis is diagnosed rarely. There is a necessity of monitoring local epidemiological trends and developing appropriate diagnostic and therapeutic models for better control of infection.

Key words*: tuberculosis, epidemiology, immigrants, prisoners, homeless people, HIV, extrapulmonary tuberculosis, MDRTB*

Abbreviations: AFR – WHO African Region, AMR – WHO Region of the Americas, EMR – WHO Eastern Mediterranean Region, EUR – WHO European Region, SEAR – WHO South-East Asia Region, WPR – WHO Western Pacific Region

INTRODUCTION

Control of tuberculosis epidemic is hindered by the transmission of this disease in high-risk groups. Economic migrations resulted in an increase of TB incidence in immigrants in countries with good epidemiological situation. Since centuries, tuberculosis is associated with poverty and overcrowding. Conditions leading to a decrease of cell-mediated immunity, especially HIV infections, constitute a significant risk factor for tuberculosis. Nevertheless, an important issue is also infection with multi-drug and extensively-drug resistant strains of *Mycobacterium tuberculosis*. Extrapulmonary tuberculosis is not of epidemic potential, however, it causes diagnostic problems. Persons infected with *M.tuberculosis*, presenting with abundant expectoration of this pathogen, are especially dangerous source of infection.

GROUPS AT HIGH RISK OF DEVELOPING TUBERCULOSIS

In several environments, incidence of tuberculosis is considerably higher compared to the general population. Risk of contracting infections increases by 4-180 fold in some groups (1). It refers mainly to prisoners, homeless people and immigrants (2,3,4). High incidence rates were reported in a group of prisoners. Initially, such problem was noted in overcrowded, poorly ventilated Russian prisons, in which TB incidence rates amounted to 7,000/100,000 (5). A specific programme, that has been operating for many years in Russia, shows measurable effects. Since the last decade, incidence in prisons is decreasing at a faster pace compared to the general population (Fig. 1). Irrespective of significant improvement, incidence in prisons is still 11-fold higher compared to the general population (6). High incidence rates were also observed in the prisons of the former USSR countries – Azerbaijan – 2,500/100,000, Kirghizia – 3,000/100,000 and Georgia – 3,500/100,000

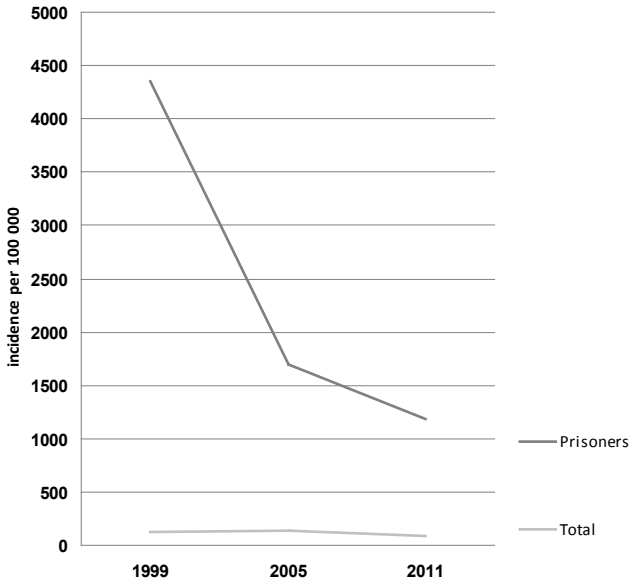

Fig. 1. Dynamics of TB epidemiological changes in Russia and Russian prisons in 1999-2011 - incidence rates per 100,000 population [based on WHO report 2013 (6)].

(2,7,8). Even higher incidence rates were reported in prisons in African countries, i.e.: 7,200/100,000 in Ivory Coast and 5,200/100,000 in Malawi (9). Such problem is also present in the USA, where there is 50-fold difference between TB incidence in the general population and prisoners. Furthermore, these discrepancies are on the increase (2). In the WHO European Region (EUR), a correlation between TB incidence and the number of prisons was demonstrated (10). Therefore, WHO requires European countries to register all TB cases occurring in prisons. In Poland, TB incidence rate in prisoners is 15-fold higher compared to national average. It amounts to 288/100,000 (11). Compared to 2011, the number of infections in this group increased by 40% (12).

Another high risk group of developing TB is the homeless. It is a marginalized social group, however, incidence rates are considerably higher collated with the general population. Statistics relating to this groups are only available in highly developed countries in which there is a good epidemiological situation. Due to the attempts undertaken, the USA succeeded in reducing TB incidence rate in the homeless, i.e. from 270/100,000 in 1994 to 36/100,000 in 2010 (13). In the USA, homeless people account for 6% of all TB cases (14) while in Canada - 3%, but 39% of them are immigrants (15). In 1992-2006, the percentage of latent tuberculosis in this group decreased from 58% to 31% in New York (16). In London, TB incidence rate in the homeless was estimated at 788/100,000 while in drug users and prisoners - 354/100,000 and 208/100,000, respectively (17). In Poland, a significant increase in the percentage of homeless people in a group of TB cases is observed. However, no official data from the National Tuberculosis Register are available. Prior to 1989, they were not included in the statistics while only 20 years later they accounted for 10% of male (18) and 3% of female TB cases (19). From one article, where TB incidence rate in the homeless in Poland was calculated, transpires that it was 720/100,000 in 2008 (20).

In highly developed countries, tuberculosis occurs significantly more frequently in immigrants than autochthonous population. In several countries, persons of different ethnicity are predominant with examples being Turks in Germany, Indians in Great Britain, and refugees from Maghreb, Libya and Russia in France, Italy and Israel, respectively. A percentage of them stay in these countries illegally which hinders a precise estimation of TB incidence in these populations. In the following countries: Great Britain, Switzerland, Netherlands and Scandinavian countries, immigrants account for more than a half of all TB cases (21) while in the Czech Republic, Finland and other Baltic countries only a few percents of new TB infections are reported in immigrants (22). In Great Britain and France, TB incidence in immigrants is 10-fold higher compared to autochthonous population. Furthermore, it significantly affects the average incidence rate in these countries (23,24). TB incidence in the general population of Great Britain is 13/100,000 while in persons born there it does not exceed 5/100,000 (24). In Poland, it is a marginal problem as from the central register only 0.6% of all TB cases constitute immigrants. Since 2004, however, they are officially subject to registration (12). To the largest extent, they come from Ukraine, Vietnam, Russia and other former USSR countries (25).

A number of conditions favour the progress of tuberculosis with the most important ones being haematopoietic cancers, lung cancer, head and neck cancer, pneumoconiosis, chronic kidney disease and diabetes (26-29). Of importance are also organ transplantation, immunosuppression, glucocorticoid and tumour necrosis factor antagonist use, and history of gastrectomy (30-34).

CO-INFECTION OF *MYCOBACTERIUM TUBERCULOSIS* AND HIV

Co-infection with *M.tuberculosis* and HIV becomes one of the most important health-related problems. For the recent years, WHO runs a separate statistics for TB cases with positive HIV (+) and negative HIV (-) status. Due to actions undertaken, a significant increase of the percentage of TB cases with known HIV status was reported. Nearly a half of all TB cases were tested for HIV while in WHO African Region (AFR) – even ¾ (6). In the last 20 years, the percentage of persons infected with HIV in TB cases was stable, amounting

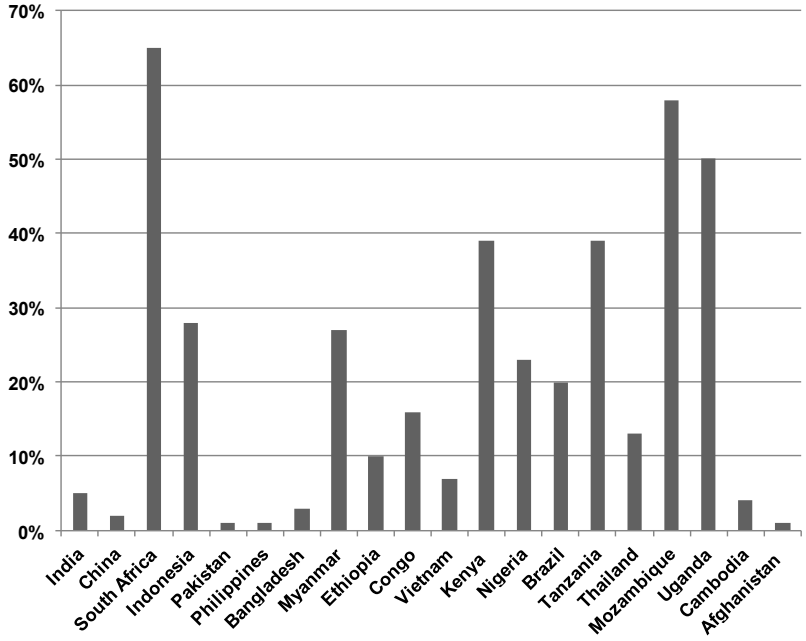

Fig. 2. Percentage of *Mycobacterium tuberculosis* and HIV co-infections in the countries with the poorest epidemiological situation [based on WHO report 2013 (6)].

to 13%. However, in the AFR, 76% of *M.tuberculosis* and HIV co-infections are reported (6). As many as 92% of co-infections with *M.tuberculosis* and HIV were identified in the AFR and WHO South-East Asia Region (SEAR). In the remaining regions, these co-infections account for 1-2% (6). Considerable regional differences in the occurrence of these infections are observed. In Swaziland, 77% of TB cases are concomitantly infected with HIV while in Angola and Ethiopia – only 9.6% (6). Especially high discrepancies are reported in countries with the poorest epidemiological situation (Fig. 2). In a group of new TB cases, only 200, 300 and 500 persons are infected with HIV in Bangladesh, Afghanistan and Philippines, respectively while their numbers amount to 330,000 in the South Africa, 130,000 in India and 83,000 in Mozambique. In a number of European countries, *M.tuberculosis* and HIV co-infection rate does not exceed 0.1/100,000, however, in Russia and Moldova and Ukraine - it is 6.5/100,000 and 10/100,000, respectively (6). HIV infection leads to an increase in the fatality of TB. In this group, it rises up to 29%. There are significant regional differences in the number of fatal TB cases infected with HIV (Fig. 3). Tuberculosis is one of the leading cause of death in AIDS cases. In 2012, only 57% of TB cases infected with HIV were subject to antiretroviral therapy, however, a year earlier, their number did not exceed 50% (6). Thus, it was feasible to reduce TB fatality in persons infected with HIV, however, the pace of this decrease is significantly lower compared to HIV negative persons. Not earlier than in 2003, this situation was improving, which was later compared to HIV non-infected persons (1998). Only the AFR and SEAR succeeded in reducing the number of

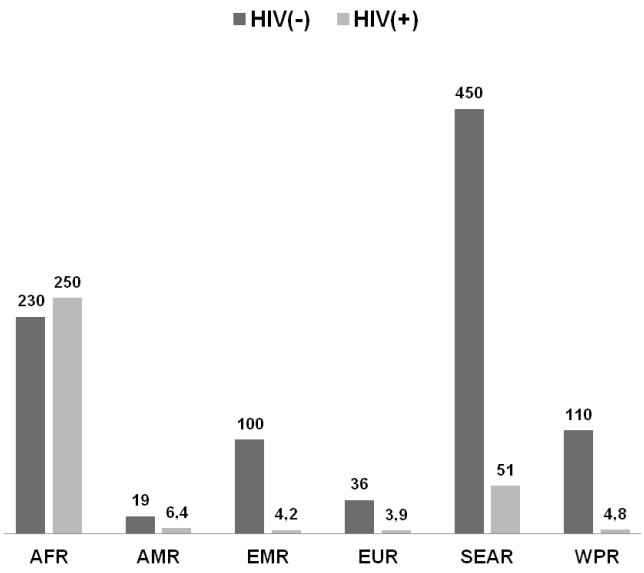

Fig. 3. Number of fatal cases (in thousands) due to tuberculosis in the group of HIV(+) and HIV(-) patients in different WHO regions [based on WHO report 2013 (6)].

TB in HIV cases. In the EUR and WHO Region of the Americas (AMR), an increase in the number of these cases is reported. In Poland, it is a marginal problem. In 2012, tuberculosis was an indicator disease for only 26 persons infected with HIV (12).

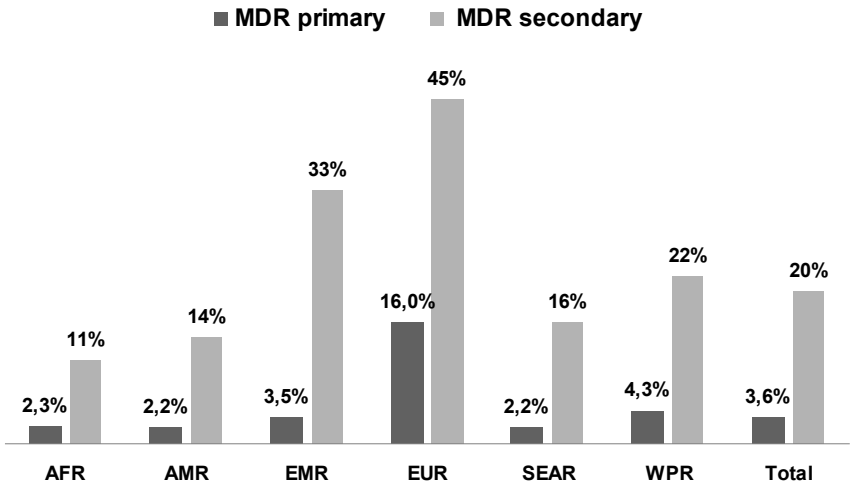

Fig. 4. Percentage of primary and secondary multi-drug-resistant *M.tuberculosis* strains in different WHO regions [based on WHO report 2013 (6)].

MULTI-DRUG-RESISTANT TUBERCULOSIS (MDRTB)

Resistance of *M.tuberculosis* to single drugs does not pose any risk, however, its increasing resistance to isoniazid and rifampicin (MDRTB) becomes a challenge from health and economic perspective as long-term treatment of such forms is very expensive and not always effective. In 2012, 450,000 MDRTB cases were reported worldwide, of whom 170,000 died (6). Fatality in this group amounts to 38% while in case of infections with non-resistant *M.tuberculosis* – only 7% (6).

MDRTB cases account for 3.6% and 20% of all new and previously treated infections, respectively (6). Situation is highly diverse in different regions (Fig. 4). It results from non-compliance with therapeutic recommendations or poor control over infection. From epidemiological perspective, it is more advisable not to treat TB cases than treat them poorly, i.e. not long enough, in an intermittent manner and without the use of several drugs. The majority of MDRTB cases are reported in the Eastern Europe and Central Asia. In several countries, MDRTB cases account for more than 20% and 50% of new and previously treated infections, respectively (6). In Belarus, MDRTB accounts for 35% of new cases and 69% of previously treated cases. In Uzbekistan, it is 23% and 63% while in Russia - 23% and 49%, respectively (6). In countries with very poor epidemiological situation, the frequency of MDRTB does not have to be always high, e.g. in Ethiopia it is reported in only 1.6% of new cases and 12% of relapse cases while in Indonesia – 1.9% and 12% and India – 2.2% and 15% (6). In the EUR, the former USSR countries make an important contribution to the percentage of MDRTB (Fig. 4). Irrespective of very good epidemiological situation in many countries of Western Europe, in which the percentage of MDRTB in new cases does not exceed 1% (e.g. in Ireland – 0.4%, Austria – 0.3%, Denmark and Finland – 0.2% while in Luxembourg, Netherlands and Switzerland – it is below 0.1%), the share of MDRTB in new cases for the whole EUR is 4-fold higher than global average and amounts to 16% (6). In the EUR, similarly poor epidemiological situation is observed with regard to MDRTB in previously treated cases as it accounts for 45% of all such cases. It results from a high percentage of MDRTB in countries with the highest number of infections.

In Poland, MDRTB is not of special concern. In 2012, only 31 such cases were reported. It accounted for 0.6% of new cases and 3% of previously treated cases. Only one case in paediatric population was noted (12).

In the recent years, the number of extensively drug-resistant tuberculosis (XDRTB) is on the increase worldwide. Currently, it accounts for 9.6% of MDRTB cases (6). A total of 92 countries have already reported such cases. In Poland, XDRTB was diagnosed in immigrants (35).

EXTRAPULMONARY TUBERCULOSIS

Significant differences are also observed in case of extrapulmonary tuberculosis (Fig. 5). In WHO Western Pacific Region (WPR), extrapulmonary tuberculosis was reported only in 5% of patients while in WHO Eastern Mediterranean Region (EMR) in 22% (6). Except for involving larynx, trachea and bronchi, extrapulmonary TB is not an infectious disease. Therefore, a number of countries do not run a register of such cases which would allow for precise assessment of epidemiological situation. Difficulties arising from specimen collection for testing and low sensitivity of bacteriological methods result in a high percentage of undetected cases. In case of patients infected with HIV, extrapulmonary TB is more frequently reported (36).

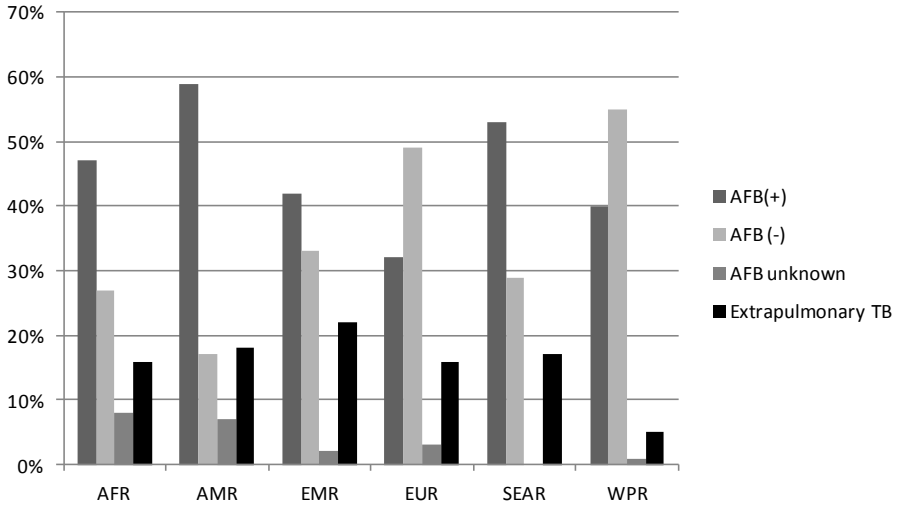

Fig. 5. Percentage of tuberculosis confirmed by bacterioscopy and extrapulmonary tuberculosis in different WHO regions [based on WHO report 2013 (6)].

Probably, the frequency of extrapulmonary TB in the AFR is considerably higher compared to other regions, however, there is no evidence for such assumption. In highly developed countries, a decrease in TB incidence is accompanied by an increase in the percentage of its extrapulmonary localization. In Canada, the percentage of extrapulmonary TB increased from 18% to 25% within 20 years (37). In countries, where co-infection with *M.tuberculosis* and HIV is rarely reported, the percentage of extrapulmonary TB is low. In Finland, Sweden, Great Britain and Netherlands, extrapulmonary TB accounts for more than 1/3 of infections (38,39). In Baltic countries and Hungary, this percentage is several times lower (5-9%) (39).

In Poland, the percentage of extrapulmonary TB is only 6.9% (12). The majority of infections is accompanied by involvement of pleura (36%), lymph nodes, bones and joints and also urinary system (12). Partially, it results from the low frequency of *M.tuberculosis* and HIV co-infections in Poland, low percentage of immigrants and predominance of males at older age in TB cases (40), while young age and female gender favour extrapulmonary localization (41). It may not be excluded, however, that extrapulmonary TB is to some extent underestimated.

TUBERCULOSIS CASES WITH ABUNDANT EXPECTORATION OF *M.TUBERCULOSIS*

Detection of *M.tuberculosis* by direct sputum smear microscopy is indicative of abundant expectoration of this pathogen (at least 10,000 bacilli in 1 ml of sputum). From epidemiological perspective, it is especially dangerous manifestation of disease as long-term contact with such TB cases poses a considerable threat of *M.tuberculosis* transmission to their contacts. WHO strategy of TB prevention is concentrated especially on detection and treatment of TB cases of such manifestation. Identification of acid-fast bacilli (AFB) under microscope does not prejudge a diagnosis of tuberculosis. Thus, it is recommended to perform molecular diagnostic test which allows for differentiating between *M.tuberculosis* and other bacilli (6). The highest number of patients with abundant expectoration of *M.tuberculosis* is reported in the AMR – 59% and SEAR – 53% while the lowest one in the EUR - 32% (Fig. 5). It is difficult to decide whether it results from good epidemiological situation in Western Europe or low level of bacteriological diagnostics in Eastern Europe. Epidemiological situation in the AMR is affected by the situation in the countries of South America which is considerably poorer compared to North America. Undoubtedly, high percentage of patients with abundant expectoration of *M.tuberculosis* in the AFR (47%) is a reflection of poor epidemiological situation there. TB cases confirmed by bacterioscopy predominate in the majority of regions with the exceptions of the EUR and WPR, where more patients have negative test results by this method (Fig.5).

In Poland, significant differences in the percentage of patients with abundant expectoration of *M.tuberculosis* are reported between provinces. In Kujawsko-pomorskie, Wielkopolskie and Zachodniopomorskie provinces, they account for more than 50% of TB cases while in Łódzkie and Lubuskie provinces, the percentages amount to 16% and 27.6%, respectively (Fig. 6). It may not be excluded that these differences are not a real reflection. To some extent, detection of *M.tuberculosis* by direct sputum smear microscopy depends on the quality of laboratory equipment as well as qualifications and experience of personnel. In Kujawsko-pomorskie province, tuberculosis is confirmed by culture in 90% of cases and 56% by bacterioscopy while

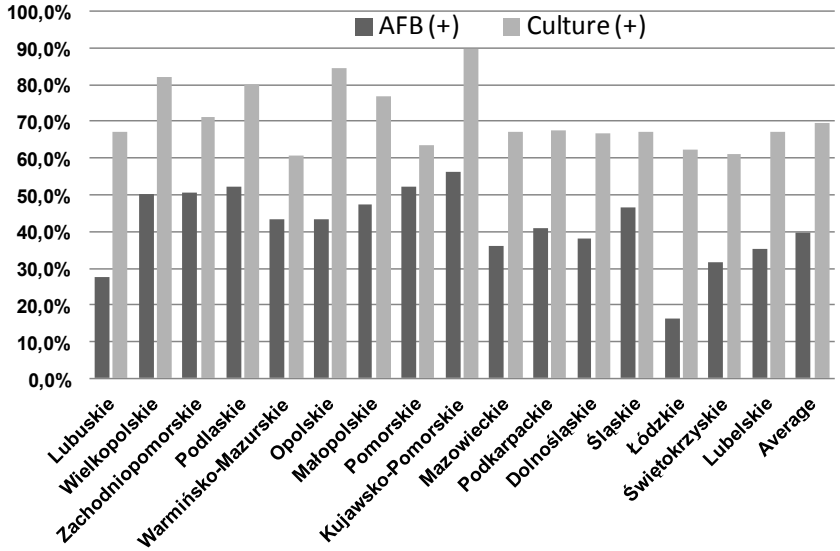

Fig. 6. Percentage of tuberculosis confirmed by bacterioscopy and culture in Poland. Provinces were listed from the lowest to the highest incidence rate [based on the Institute of Tuberculosis and Lung Diseases report 2013 (12)].

in Łódzkie province it is 62% and 16%, respectively (Fig.6). A special attention should be paid to the low percentage of bacteriologically confirmed tuberculosis in provinces with the poorest epidemiological situation and low percentage of bacteriologically confirmed cases in Lubuskie province with the best epidemiological situation. A reason of such situation may be poor quality of bacteriological tests and precipitant diagnosis of TB in some provinces (42).

SUMMARY

There are regional differences in the epidemiological situation of tuberculosis worldwide. Furthermore, it is subject to dynamic changes. It is associated not only with the general health of citizens, but also financial capacity of particular countries, organization of healthcare system, infection control, cultural problems favouring the transmission of HIV infection. Referring to average epidemiological indicators results in underestimation of the problem. Therefore, it is necessary to analyze local epidemiological situation. In the light of epidemiological data presented, the significance of tuberculosis should neither be neglected nor overemphasized. There is a necessity of monitoring epidemiological trends and developing appropriate diagnostic-therapeutic-preventive models.

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