

# The burden of serious fungal diseases in Russia

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## Summary

The incidence and prevalence of fungal infections in Russia is unknown. We estimated the burden of fungal infections in Russia according to the methodology of the LIFE program ([www.LIFE-worldwide.org](http://www.LIFE-worldwide.org)). The total number of patients with serious and chronic mycoses in Russia in 2011 was three million. Most of these patients (2 607 494) had superficial fungal infections (recurrent vulvovaginal candidiasis, oral and oesophageal candidiasis with HIV infection and tinea capitis). Invasive and chronic fungal infections (invasive candidiasis, invasive and chronic aspergillosis, cryptococcal meningitis, mucormycosis and *Pneumocystis pneumonia*) affected 69 331 patients. The total number of adults with allergic bronchopulmonary aspergillosis and severe asthma with fungal sensitisation was 406 082.

**Key words:** aspergillosis, candidiasis, cryptococcal meningitis, fungal infections, mucormycosis, Russia.

## Introduction

Over the past decades fungal diseases have become a serious clinical problem. Worldwide mortality from fungal infections is comparable to mortality from tuberculosis or malaria and is thought to exceed 1 350 000 patients per year.<sup>1,2</sup> The number of mycoses is progressively increasing worldwide and there is generally a lack of population-based epidemiologic data. Some older large population studies have been done, and recent studies of incidence have been completed in candidaemia and cryptococcosis. Several recent studies have been conducted in specific patients groups such as candidaemia in intensive care, invasive aspergillosis (IA) in hospitalised patients with chronic

obstructive pulmonary disease (COPD) or liver failure, to name some examples.

The incidence and prevalence of fungal infections in Russia is unknown. The aim of this research is to estimate the burden of serious and chronic fungal diseases in Russia. To this end, we have used the deterministic scenario modelling proposed by LIFE ([www.LIFE-worldwide.org](http://www.LIFE-worldwide.org)), and previously published.

## Materials and methods

We have based our estimates primarily on national data from 2011. The results of already published epidemiological studies of fungal infections in Russia were analysed. Statistical information about the Russian population structure was obtained from the Federal State Statistics Service ([www.gks.ru](http://www.gks.ru)).

The incidence of scalp mycosis (tinea capitis) was assessed according to the data of the Ministry of Health [3]. The number of patients with recurrent vulvovaginal candidiasis was calculated according to the international epidemiological study data indicative of 9% of women in their fertile years suffering from this problem.<sup>4</sup> We have used a 'discounted' rate of 6% to correct for inaccurate self-diagnosis.

The number of patients with HIV/AIDS in Russia was derived from the data provided by the Ministry of

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Health (<https://www.rosminzdrav.ru/docs/mzsr/stat/46>). Literature data showed that oropharyngeal candidiasis was detected in 90% of those without Antiretroviral drugs (ARVs), and oesophageal candidiasis in 20% of patients without ARVs and 5% of patients on ARVs.<sup>5-7</sup>

According to the results of our previous studies, the incidence of candidaemia and *Candida* peritonitis was 0.37 per 1000 persons hospitalised to in-patient department.<sup>8</sup> The annual number of in-patients in Russian hospitals was obtained from the report about hospital-acquired infections of Federal Service on Consumers' Rights Protection and Human Well-being Surveillance (<http://34.rosпотреbnadzor.ru/documents/ros/80337/>).

The prevalence of haematological diseases was evaluated according to the data of the Ministry of Health [9]. In patients with haematological diseases, the risk of IA development was calculated according to the data of the Register of Patients with IA in St. Petersburg.<sup>10</sup> The information about number of organ and tissue transplantation procedures in 2011 was obtained from Russian Transplantation Society data (<http://www.transpl.ru/>). Among patients who underwent haematopoietic stem cell transplantation (HSCT) the incidence of invasive mycosis was evaluated according to our earlier study results.<sup>11</sup> The total number of patients with IA in solid organ transplantation (SOT) was calculated according to these rates: renal 1%; liver 4%, heart 6% and lung 20% (including tracheobronchitis).

The incidence of mucormycosis in the general population was calculated using data of the Register in St. Petersburg and data of Ministry of Health on acute myeloid leukaemia (AML) prevalence.<sup>9</sup>

The overall notified cases of tuberculosis was obtained from the Ministry of Health [12]. The calculation of cases of chronic pulmonary aspergillosis (CPA) after tuberculosis was as previously described.<sup>13</sup> There are many underlying pulmonary diseases associated with CPA including sarcoidosis,<sup>14</sup> allergic bronchopulmonary aspergillosis (ABPA),<sup>15</sup> prior pneumothorax, non-tuberculous mycobacterial infection, prior pneumothorax and COPD.<sup>16</sup>

The number of patients with asthma was obtained from the Russian Respiratory Society data.<sup>17</sup> The estimated number of patients with ABPA was calculated by formula: 2.5% of patients with asthma + 15% of adult patients with cystic fibrosis.<sup>18</sup> The information about cystic fibrosis (CF) incidence was obtained from the Russian Register of Patients with Cystic Fibrosis ([http://www.cf-ru.ru/content/ru/information\\_for\\_experts.html](http://www.cf-ru.ru/content/ru/information_for_experts.html)).

According to the data of Medical Genetic Research Center of Russian Academy of Science among patients with CF 21% were adults (<http://mukoviscidoz.org/mucrussia.html>). To assess patients with severe asthma with fungal sensitisation (SAFS), it was considered that 10% of patients with asthma have severe course of disease and 33% of them have fungal sensitisation.<sup>19</sup>

The results of research performed in St. Petersburg were used to calculate the incidence of cryptococcal meningitis and *Pneumocystis* pneumonia (PCP). In 2011, cryptococcal meningitis occurred in 0.44% patients with first diagnosed HIV infection,<sup>20</sup> PCP developed in 2.1% of patients with first diagnosed HIV infection.<sup>21</sup>

## Results and discussion

In 2011, the population of Russia was 142.9 million, 85% of which were adults and 15% were children younger than 14 years. Among adults, 54% were women. Table 1 shows the prevalence of different fungal diseases and their incidence or prevalence per 100 000 inhabitants.

### Tinea capitis

The total number of patients with tinea capitis (caused by *Microsporum canis* or *Trichophyton* spp.) was 60 366, 47 092 of which were children.<sup>3</sup> Overall

**Table 1** Fungal diseases in Russian Federation.

Fungal diseases	Rate/100K	Total burden
Newly emerged diseases		
Invasive aspergillosis	2.27	3238
Invasive candidiasis	8, 29	11 840
Cryptococcal meningitis	0.21	296
Mucormycosis	0.16	232
<i>Pneumocystis</i> pneumonia	0.99	1414
Tinea capitis ( <i>Microsporum canis</i> )	40.8	57 871
Tinea capitis ( <i>Trichophyton</i> spp.)	1.8	2495
		77 386
Chronic diseases		
Chronic recurrent	3481	2 487 215
<i>Candida</i> vulvovaginitis		
Recurrent oral candidiasis	33.92	48 469
Recurrent oesophageal candidiasis	8.01	11 444
Chronic pulmonary aspergillosis	126.19	52 311
Allergic bronchopulmonary aspergillosis	122.52	175 082
Severe asthma with fungal sensitisation	161.65	231 000
		3 005 521
Total burden estimated		3 082 907

prevalence of tinea capitis caused by *M. canis* was 40.8/100 000 and 213.1 per 100 000 children. Tinea capitis caused by *Trichophyton* spp. was less frequent – 1.8/100 000 and 6.9 per 100 000 children. These results exceeded the average levels in Europe: in Czech Republic the overall incidence of tinea capitis was 6.06/100 000<sup>22</sup> and in Denmark was 3.3/100 000.<sup>23</sup> A high incidence of this mycosis was documented in Vietnam was 457/100 000,<sup>24</sup> and several African countries.

### Mucosal candidiasis

Recurrent vulvovaginal candidiasis is the most common mycosis in Russia. According to our estimations, 2 487 215 Russian women suffer from this disease (3481/100 000 females). Similar data were obtained in Europe (in Hungary – 2193/100 000)<sup>25</sup> and in other countries (in Iraq – 2664/100 000).<sup>26</sup> These estimates exclude post-menopausal vulvovaginal candidiasis, which is a problem for some women taking hormone replacement therapy.

In 2011 in Russia, the number of patients with first diagnosed HIV infection was 67 317 (47.1/100 000), and 13 463 patients received ARV.<sup>9</sup> Hence, the number of HIV-infected patients with oropharyngeal candidiasis amounted 48 469 persons (33.9/100 000). The estimated number of HIV-infected patients with *Candida* oesophagitis was 11 444 (8.01/100 000). International epidemiological observations are focused on only in HIV-infected patients. The prevalence of *Candida* oesophagitis in Hungary was 1.56/100 000, in UK and Denmark was 0.1/100 000.<sup>23,25,27</sup> In Nigeria, incidence of *Candida* oesophagitis (93.2/100 000) and oropharyngeal candidiasis (163.2/100 000) was high.<sup>28</sup> In addition, oesophageal candidiasis occurs in other ill and immunocompromised patients, as well as in the community in apparently normal individuals, for which we have not attempted to estimate the incidence.

### Invasive candidiasis

In 2011 in Russia, 32 million patients were hospitalised. The total number of patients with invasive candidiasis (IC) was 11 840 per year. Thus, the frequency of IC in the population was estimated 8.29 per 100 000. These data correspond to a high average for Europe (5.0–11.4/100 000), very similar to Spain and Denmark, but higher than the UK and France. In addition, a multicentre study in France showed that 50% of patients in the ICU with IC had *Candida* peritonitis

or intra-abdominal candidiasis.<sup>29</sup> According to the results of our research, candidaemia was noted more often (81%) than *Candida* peritonitis (17%).<sup>7</sup> We have not estimated *Candida* peritonitis complicating chronic ambulatory peritoneal dialysis.

### Pulmonary aspergillosis

According to our register, 88% of patients with IA have haematological diseases and 30% of which is AML. These data correlate with the results of European studies. AML was the underlying disease in 36% of all patients in Italy<sup>30</sup> and 35% in France.<sup>31</sup> According to European average values, the risk of IA in these patients is 10%. Thus, in Russia every year there are 160 new cases of IA in patients with AML. This number is roughly 50% of all non-HSCT haematology patients with IA in Austria<sup>32</sup> and France,<sup>31</sup> so the estimate for this group is 320.

In 2011, about 200 HSCT procedures were carried out in Russia. According to our studies, the incidence of invasive mycosis in HSCT recipients was 19.1% and in recipients of allogeneic HSCT – 23.2%.<sup>12</sup> 82.3% of these mycoses are caused by *Aspergillus* spp. Thus, in Russia the incidence of IA in HSCT recipients varied from 16% to 20%. We used a rate of 20%, so in these patients there were 40 cases of IA following HSCT.

Solid organ transplantation and related immunosuppression are also key risk factors for IA. The results of international studies show that the incidence of IA after SOT varies from 0.3% to 14%.<sup>33,34</sup> In 2011 in Russia, 975 kidney, 204 liver and 106 heart transplantations were performed.<sup>35</sup> For determining the risk of IA we used European average values of 1%, 4% and 6% respectively. Summing up all the parameters, 385 cases of IA had occurred in haematological patients and recipients of SOT.

In 2011 in Russia 219 322 in-patients with COPD were hospitalised. The risk of IA development in these patients is 1.3%. Thus, IA had occurred in 2853 patients with COPD. We did not attempt to estimate risk in other immunosuppressed patients, including HIV patients, thus the annual total incidence of IA in Russia amounts to at least 3238 patients (2.27/100 000). The similar results were in Europe (Czech Republic – 3.27/100 000, Hungary – 1.54/100 000) as well as in Iraq (2.62/100 000).<sup>22,25,26</sup>

Chronic pulmonary aspergillosis occurs in patients with chronic pulmonary diseases (tuberculosis, sarcoidosis, COPD, CF). The overall incidence of tuberculosis in Russia in 2011 was 104 320 cases (68.1/100 000), which included 94 297 cases of pulmonary

tuberculosis (66.0/100 000). Fibrous-cavernous lung tuberculosis was diagnosed in 1901 patients (1.33 per 100 000 population). 10.3% of patients with tuberculosis were HIV positive. The incidence rate of tuberculosis in association with HIV infection in 2011 was 5.6/100 000. During 5-year period, 13 078 cases of CPA on the background of tuberculosis had occurred. The total number of patients with CPA was 52 311 (126/100 000). These data were consistent with the results in Ukraine – 109/100 000.<sup>36</sup> In other countries this parameter was much lower: in UK – 8.1/100 000, in Czech Republic – 3.48/100 000, in Denmark – 3.05/100 000.<sup>22,23,27</sup>

### Mucormycosis

The calculated incidence of mucormycosis in patients with AML was 3.6%. In 2011 in Russia, 1599 patients with AML were registered. Based on our study results, AML was a risk factor for mucormycosis only in 25% of cases. Thus, the total number of mucormycosis patients was 232 (0.16/100 000). Calculated incidence of mucormycosis in Russia corresponded to the values in European countries. Mucormycosis frequency in Spain was 0.04/100 000, in Czech Republic was 0.12/100 000 and in Hungary was 0.1/100 000 population.<sup>22,25,38</sup>

### *Pneumocystis* pneumonia and cryptococcal meningitis

*Pneumocystis* pneumonia and cryptococcal meningitis are among the major opportunistic infections in patients with HIV. In Russia, the incidence of PCP was 0.99 cases per 100 000 people or 1414 cases per year. In Europe, this parameter was lower: Czech Republic – 0.52/100 000 and Hungary – 0.05/100 000 people.<sup>20,21</sup> The highest incidence of PCP was marked in Nigeria – 48.2/100 000.<sup>26</sup>

The overall incidence of cryptococcal meningoencephalitis in Russia was 296 cases per year (0.21/100 000). In UK the frequency of cryptococcal meningoencephalitis was 0.16/100 000<sup>25</sup> and in Spain was 0.03/100 000.<sup>36</sup> In other European countries the incidence of this opportunistic infection was lower. For example, in Czech Republic were detected less than five cases per year, in Denmark – two cases per year.<sup>20,21</sup>

### Allergic bronchopulmonary diseases

The experts of the Russian Respiratory Society estimated that the number of patients with asthma in Russia is about seven million people. We used the formula

proposed by Denning *et al.* [17,18] for calculation of number of patients with ABPA (175 082), and SAFS (231 000). The incidence of ABPA and SAFS in Russia corresponded the parameters in Denmark (ABPA – 125/100 000; SAFS – 163/100 000).<sup>21</sup> High level of ABPA was in UK (287/100 000) and the lowest was in Iraq (16/100 000).<sup>24,25</sup> In India the highest frequency of ABPA (1.06 million) and SAFS (1.52 million persons) was noted.<sup>37</sup>

Our results showed that mycoses are common diseases in Russia. The major limitations of our estimates are the paucity of data from nationwide prospective studies. Further investigation of the mycoses epidemiology is very important because the results of it are the basis for preventive measures and treatment optimisation of these diseases.

### Conflict of Interest

NK received grants and honoraria from MSD, Pfizer and Astellas. YK, SK, OS, YB, EB, and NV declare no conflict of interest. DWD holds Founder shares in F2G Ltd a University of Manchester spin-out antifungal discovery company, in Novocyt which markets the Mycostatica real-time molecular assays and has current grant support from the National Institute of Allergy and Infectious Diseases, National Institute of Health Research, NorthWest Lung Centre Charity, Medical Research Council, Astellas and the Fungal Infection Trust. He acts as a consultant to T2 Biosystems, GSK, Sigma Tau, Oxon Epidemiology and Pulmicort. In the last 3 years, he has been paid for talks on behalf of Astellas, Dynamiker, Gilead, Merck and Pfizer. He is also a member of the Infectious Disease Society of America Aspergillosis Guidelines and European Society for Clinical Microbiology and Infectious Diseases Aspergillosis Guidelines groups. He is also President of the Global Action Fund for Fungal Infections.

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