

Burden of serious fungal infections in Ukraine

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Summary

Ukraine has high rates of TB, AIDS and cancer. We estimated the burden of fungal disease from epidemiology papers and specific populations at risk and fungal infection frequencies. HIV/AIDS cases and deaths (2012) and tuberculosis statistics were obtained from the State Service of Ukraine, while chronic obstructive pulmonary disease (COPD) cases were from M. Miravittles et al., *Thorax* **64**, 863–868 (2009). Annual estimates are 893 579 Ukrainian women get recurrent vaginal thrush ($\geq 4\times$ per year), 50 847 cases of oral candidiasis and 13 727 cases of oesophageal candidiasis in HIV, and 101 (1%) of 10 085 new AIDS cases develop cryptococcal meningitis, 6152 cases of *Pneumocystis* pneumonia (13.5 cases per 100 000). Of the 29 265 cases of active respiratory TB in 2012, it is estimated that 2881 new cases of chronic pulmonary aspergillosis (CPA) occurred and that the 5-year period prevalence is 7724 cases with a total CPA burden of 10 054 cases. Assuming adult asthma prevalence is $\sim 2.9\%$, 28 447 patients with allergic bronchopulmonary aspergillosis (ABPA) are likely and 37 491 with severe asthma with fungal sensitisation. We estimate 2278 cases and 376 postsurgical intra-abdominal *Candida* infections. Invasive aspergillosis in immunocompromised patients is estimated at 303 patients annually; 930 cases in COPD patients. Ninety cases of mucormycosis (2 per 1 000 000) are estimated. In total, $\sim 1\,000\,000$ (2.2%) people in Ukraine develop serious fungal infections annually.

Key words: Fungal infections, Ukraine, aspergillosis, candidiasis, cryptococcosis.

Introduction

Fungal infections make a major contribution to human morbidity and mortality, as well as being the predominant pathogens of plants and contributing to more species extinctions than any other microorganism (Fisher et al.¹ cited by Brown et al.²). However,

the impact of these diseases on human health is not widely appreciated.²

Invasive fungal diseases are associated with very high mortality rates. For example, the crude mortality rate of *Candida* bloodstream infections is 47–55%, which is higher than the mortality rate of the most merciless viral or bacterial sepsis.³ Untreated invasive aspergillosis, *Pneumocystis* pneumonia and cryptococcal meningitis are uniformly fatal. Over one million people every year die from fungal infections, and maybe as many as two million, as many or more than those dying from tuberculosis or malaria.²

The current incidence of invasive fungal diseases is a consequence of significant growth of number of immunocompromised patients in recent decades. This is caused by significant burdens of immunosuppressive conditions such as HIV infection, cancer chemotherapy, autoimmune disorders, numerous targeted

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monoclonal antibody therapies affecting immune responses, prolonged stay in ICU and increasing number of transplant patients.⁴⁻⁶

This work aims to estimate serious fungal infection burdens in Ukraine. No estimate of fungal infection burden has been made previously for Ukraine. Such work is crucial to inform healthcare and research funding agencies and to prioritise funds to diagnose and treat fungal infections.

Materials and results

Ukraine is a large country in Eastern Europe with a population of 45.5 million people⁷ and an estimated domestic product of \$3960 per person in 2013.⁸ Of these, 14% of population are children, 54% are women, 12% of women are over 60 years (2.9 million).⁷ The total burden of fungal infection, the rate per 100 000 inhabitants and the numbers of infections categorised with regards to the main risk factors are shown in Table 1. Geographical distribution of serious fungal infections in Ukraine is summarised in Fig. 1.

Initially we identified all epidemiological papers on serious fungal diseases. Unfortunately, there are no published data on serious fungal diseases burden in

Ukraine. Then by using official sources, we determine population characteristics⁷ and women that are at risk for development of recurrent vulvovaginal candidiasis (rVVC). rVVC is defined as ≥ 4 episodes per year, although a minority of women appear to be continuously affected.⁹ On the basis of the data of the Population Census,⁷ we estimated that there are 14 892 983 women between the ages of 15 and 50, the major risk period for VVC. Assuming a rate of 6%, based on anonymous Internet surveys of women in Europe and the United States, we estimate that 893 579 (1961 per 100 000) women are affected by rVVC in any given year.^{10,11}

We used data^{12,13} provided by the State Service of Ukraine on Countering HIV/AIDS and Other Socially Dangerous Diseases¹⁴ for the number of TB patients as well as HIV/TB coinfection. These data are generated using reports from healthcare and prophylactic institutions for TB. We also used the data from State Service of Ukraine for HIV statistics. The number of HIV-positive patients in 2013 was 161 483 (355 per 100 000). Because of social and financial reasons the proportion of people that receive antiretroviral therapy (ART) is low and comprises 30% (48 445) of all HIV-positive patients. There are no data available on CD4 cell count in HIV/AIDS patients, but UNAIDS estimates

Table 1 Burden of serious fungal infections in Ukraine.

Infection	Number of infections per underlying disorder per year					Rate per 100K	Total burden
	None	HIV/AIDS	Respiratory	Cancer/Tx	ICU		
Oesophageal candidiasis	–	13 727	–	–	–	30.134	13 727
Candidaemia	–	–	–	–	752	5.0	2278
Candida peritonitis	–	–	–	–	376	0.8254	376
Recurrent vaginal candidiasis (4× per year+)	893 579	–	–	–	–	1961.625	893 579
ABPA	–	–	28 447	–	–	62.448	28 447
SAFS	–	–	37 491	–	–	82.3019	37 491
Chronic pulmonary aspergillosis	–	–	10 054	–	–	22.071	10 054
Invasive aspergillosis	–	–	930	303	–	2.7067	1233
Mucormycosis	–	–	–	90	–	0.1975	90
Cryptococcal meningitis	–	101	–	–	–	0.2217	101
<i>Pneumocystis</i> pneumonia	–	6152	–	–	–	13.5052	6152
Total burden estimated	893 579	19 980	76 952	393	752	–	999 152

SAFS, severe asthma with fungal sensitisation.

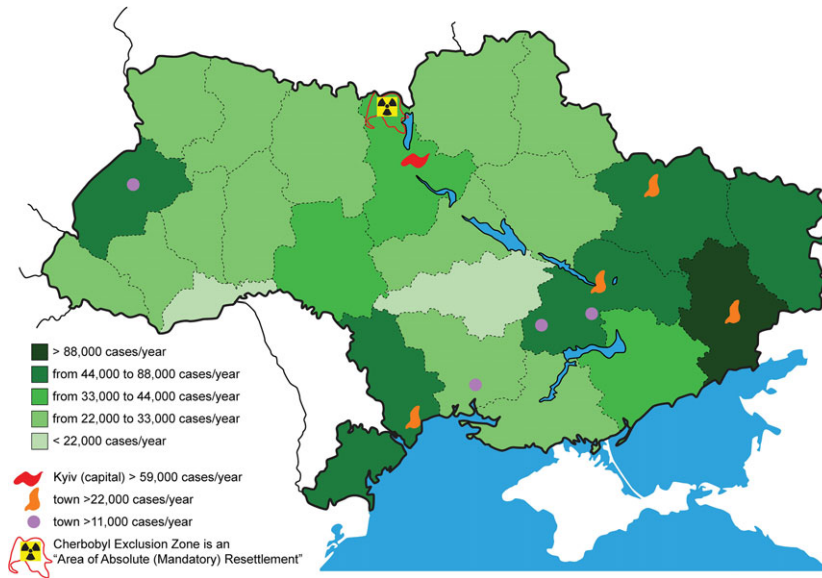


Figure 1 Geographical distribution of serious fungal infections in Ukraine. The figure was generated based on population density and presence of a large health-care centres which were used as a source of immunocompromised patients.⁶²

that 113 053 people with CD4 counts $<350 \mu\text{L}^{-1}$ require antiretrovirals (ARVs) (2010 WHO recommendations). If we assume that 50% of these patients have CD4 counts $<200 \mu\text{L}^{-1}$ and 50% progress to an AIDS-defining illness in any given year, the annual high-risk population for fungal infections is $\sim 56\,500$ people.

There are total 27 181 AIDS patients living and 10 085 new cases of AIDS annually. In 90% of patients, with CD4 count less than 200 cells per μL , oral candidiasis occurs at least once and oesophageal candidiasis occurs in 20%.^{15–17} We estimated 50 847 (112 per 100 000) cases of oral candidiasis and 13 727 (30.1 per 100 000) cases of oesophageal candidiasis, based on the at-risk population above. The annual incidence of *Pneumocystis pneumonia* in AIDS was estimated ~ 6150 cases per year, based on a 60% rate of new AIDS patients presenting with this infection, a rate of 13.5 cases per 100 000 population,¹⁸ probably an underestimate. In the absence of local data for cryptococcal meningitis, we estimated a low rate of 1%, between the USA a rate of 3% and the French a rate of 0.2%^{17,19} of new AIDS cases (10 085) develop cryptococcal meningitis which is 101 patients per year (0.2 per 100 000).²⁰ Again this is likely to be an underestimate.

The TB epidemic is another serious problem in Ukraine that contributes to a high burden of fungal infections. The total number of patients with TB that were registered at healthcare facilities in 2012 is 420 844 (926 per 100 000); the number of patients with active TB is 61 749 (135 per 100 000). There were 29 265 cases (64.3 per 100 000) of active

respiratory TB in 2012. This problem is complicated by a high level of TB/AIDS coinfection which is 15 251 cases (33.6 per 100 000). In addition there are 4726 (15.8 per 100 000) cases of active TB/AIDS cases in 2012.

After tuberculosis, chronic pulmonary aspergillosis (CPA) may occur, which when advanced may lead to the formation of an aspergilloma or fungal ball in the lung. Studies in the United Kingdom²¹ indicated that 22% of those with a residual cavity after pulmonary tuberculosis develop CPA.

There were 26 679 (58.7 per 100 000) TB patients in 2012 that had lung involvement; 1574 (6%) of them had surgical treatment. We estimated the annual number of new CPA cases to be 2881. Assuming a 15%²¹ annual mortality and 6%¹² resection rate, the 5-year period prevalence is 7724 cases.²¹

Tuberculosis is only one underlying disease for CPA, and other conditions including COPD, non-tuberculous mycobacterial infection, prior pneumothorax, sarcoidosis and other disorders²² are also important. The average prevalence of CPA caused by other underlying conditions was estimated using the data from Spain, UK and Israel.^{23–25} Using these data it was found that the total 5 year prevalence of CPA in Ukraine is 10 054 cases.

Estimates of asthma prevalence in adults vary from 2.77% to 2.9%, a total of $\sim 1\,136\,092$ people affected.²⁶ Severe asthma is thought to affect about 10% of adults and in other countries, 33–70% are sensitised to fungi.²⁷ Assuming 2.5%²⁸ of asthmatics have ABPA we have found that there are 28 447 (62 per

100 000) patients with ABPA and 37 491 (37.5 per 100 000) with severe asthma with fungal sensitisation (SAFS) (using a 33%²⁷ sensitisation rate). There may be some overlap between ABPA and SAFS, estimated at 20%, depending on the severity of asthma in ABPA and the proportion of SAFS patients who are sensitised to *Aspergillus fumigatus* as opposed to other fungi.

The number of critical care beds and abdominal surgery was taken from the Ukrainian Ministry of Health (2012).²⁹ The rate of candidaemia was assumed to be a low European average of 5.0 per 100 000.²³ Therefore, we estimate there to be 2278 cases (5.0 per 100 000) of candidaemia per annum in Ukraine. The actual rate of invasive candidiasis is substantially higher than this because blood cultures are not very sensitive for invasive candidiasis^{30,31} and fluconazole reduces the culture positive rate.³² According to the Ministry of Health data (2012),²⁹ there are ~195 000 abdominal surgeries per year. We used existing French data showing that there is one case of postsurgical candida peritonitis/intra-abdominal candidiasis for every two patients with candidaemia in ICU.³³ If we assume that 33%^{34–38} of cases of candidaemia occur in ICU, then around 376 intra-abdominal candidiasis cases (0.8 per 100 000) occur each year. We have not been able to estimate the number of chronic ambulatory peritoneal dialysis-related cases of fungal peritonitis.

The number of transplant patients in Ukraine is small (15 haematopoietic stem cell transplantation (HSCT), 86 renal transplants in 2011),³⁹ so the contribution of such patients to fungal burden is insignificant. On the other hand, the acute myeloid leukaemia (AML) population frequency is relatively high at 4 per 100 000 and there were a total of 1 052 174 cancer patients in 2012.⁴⁰ Therefore invasive aspergillosis complicating all leukaemias was estimated at 303 patients annually (0.7 per 100 000), as an equal number of invasive aspergillosis cases occur in AML as in all other leukaemias.⁴¹ We found the number of patients with chronic obstructive pulmonary disease (COPD) in 2013 is 516 571 (prevalence is 1134 per 100 000).⁴⁰ Further we estimated that 5%⁴² of these patients were admitted to hospital each year and 3.6% developed invasive aspergillosis.⁴³ This equates to 930 patients per annum (2.0 per 100 000), a total therefore of 1233 patients (2.7 per 100 000) with invasive aspergillosis. This omits those with other underlying diseases, such as solid tumours and those treated with corticosteroids for other reasons.

There are no data on mucormycosis cases, but the general rate⁴⁴ of 2 per 1 million suggests that there are 90 cases annually.

Discussion

The total burden of serious fungal infections in Ukraine is probably higher than other European countries because of the high HIV and tuberculosis burden. However, asthma rates are lower and so probably fungal asthma (ABPA and SAFS) is less frequent. The burden may be underestimated due to the lack of epidemiological surveillance, lack of reporting to authorities, but principally a lack diagnostic capability leading to an incorrect or incomplete diagnosis. The military actions in Ukraine are an additional risk factor for development of serious fungal infections.^{45,46} However, the burden of fungal infections caused by military injuries cannot be assessed due to the absence of data. This is an additional factor that leads to underestimation of fungal infection rates.

There are also differences in fungal infection risk groups between Ukraine and Western Europe. This is caused by difference in factors that contribute to fungal diseases. The first major difference is the number of bone marrow and solid organ transplants done annually. There are almost no transplant patients in Ukraine. Only 86 renal transplants were done since 2011 and the total number of patients that undergo HSCT is only 15 patients per annum, despite the relatively high rate of AML. Given that there is a generally high rate of cancer with over one million cases in Ukraine,⁴⁰ our inability to satisfactorily estimate fungal infections in this group will also contribute to an underestimation of some fungal disease.

Patients with different forms of oncologic diseases make a significant contribution to fungal burden. There are more than one million (~2.2% of population) cancer patients in Ukraine,²⁹ much higher than the European average.⁴⁷ Higher radiation load (due to Chernobyl nuclear plant disaster) compared to the European average had some impact. There is a 2600 km² Exclusion Zone⁴⁸ (radius is approximately 30 km⁴⁹) around the Chernobyl nuclear plant which means that people are not allowed to live there (Fig. 1). On the other hand, people who were exposed to radiation resettled to other areas of Ukraine which in its turn has led to an increase in the average oncology rates in Ukraine. A link between radiation exposure and some oncologic diseases was shown in general population. These diseases are leukaemia and lymphoma in population aged 0–20⁵⁰ and thyroid cancer in children.^{51,52}

For example, we have used a rate of *Candida* bloodstream infection of only five per 100 000, compared with 8.1 in Spain as found by Puig-Arsenio et al.⁵³

and as cited by Rodriguez-Tudela et al.²³ Invasive aspergillosis complicates lung cancer,¹⁹ which is common in Ukraine. However, the quality of cancer patients treatment is not as high as in Western Europe, so many patients do not survive to the stage when they can develop fungal infection.

Ukraine has an especially high rate of HIV patients with few on ARVs. Early diagnosis of HIV is infrequent. Most Ukrainians are poorly educated about the necessity for early HIV diagnosis. In addition, too many clinicians do not consider HIV infection as a differential diagnosis with early signs, so many patients are diagnosed HIV positive only when they develop AIDS or when they are hospitalised.⁵⁴ Another key reason for this is social discrimination of HIV-positive patients⁵⁵; intravenous drug users often ignore their own healthcare, and intravenous drug use can be disclosed to authorities engendering additional social problems. Another major problem is low-quality anti-retroviral drugs and insufficient supply. The governmental strategy is to purchase the lowest cost ARVs some of which are low-quality Indian generics. A large number of AIDS patients refuse to take these drugs because of the multiple side effects. The government does provide drugs at no cost to the patient, but there is a general lack of confidence in their quality, so only patients who can pay from their pocket receive high-quality treatment. As the result, the proportion of patients not receiving ARVs is high (70%). Overall, the number of cases of opportunistic fungal infection complicating HIV in Ukraine is probably very high.

Tuberculosis remains a crucial social and medical problem in Ukraine and it contributes significantly to fungal burden in Ukraine. For social reasons, TB patients do not receive appropriate treatment and many of them refuse treatment completely, so TB epidemic is poorly controlled in Ukraine.^{56,57} This probably contributes to many cases of CPA.

International guidelines for rational antimicrobial use are not implemented in Ukraine. Stewardship for rational use of antibiotics has been implemented only in some regions of the country. Such polypharmacy with broad spectrum antimicrobials in ICUs is another predisposing factor for high fungal burden.^{58–60}

The COPD prevalence in 2013 is estimated as 516 571 cases (1134 per 100 000)⁴⁰; additionally, a large part of the population is involved in coal mining or the metallurgical industry. Smoking is common: 57% of Ukrainian men and 10% of Ukrainian women are smokers; 21% of Ukrainian men and 7% of Ukrainian women are ex-smokers.⁶¹ Based on this it is

highly likely that COPD prevalence is underestimated in Ukraine. High COPD prevalence, in its turn, is another major factor contributing to a high pulmonary fungal infection burden, notably CPA and invasive aspergillosis.

Despite the size and urgency of the problem of fungal disease in Ukraine, there is no reference laboratory for medical mycology and there are no courses that can provide training in this discipline. Diagnosis is based primarily on culture, which is insensitive. Hence, fungal infections are underdiagnosed in the Ukrainian healthcare system. The field of the medical mycology needs to be developed in Ukraine. There are three main components of addressing this deficiency.²⁴ The first component is to estimate fungal burden with local epidemiological studies and provide ongoing epidemiological surveillance. The problem should be highlighted at the national level and requires funding. The second is providing diagnostic facilities and establishing reference laboratories in large healthcare and academic centres. The third is ensuring availability of antifungal medication. Flucytosine is registered in Ukraine, but this drug is not on sale and is required for cryptococcal meningitis. There is no lipid form of amphotericin B available on the market, whereas these are routinely used throughout Europe.

In summary, fungal infections are almost certainly a significant healthcare problem in Ukraine. Given the all-pervasive nature of fungi, the problem will not go away spontaneously.

Conflicts of interest

Dr Osmanov reports no conflicts of interest. Dr Denning holds Founder shares in F2G Ltd, a University of Manchester spin-out antifungal discovery company, in Novocyt which markets the Myconostica real-time molecular assays and has current grant support from the National Institute of Allergy and Infectious Diseases, National Institute of Health Research, North-West Lung Centre Charity, the National Institute of Health Research, Medical Research Council, Astellas and the Fungal Infection Trust. He acts as a consultant to Trinity group, T2 Biosystems, GSK, Sigma Tau, Oxon Epidemiology and Pulmicort. In the last 3 years, he has been paid for talks on behalf of Astellas, Gilead, Merck and Pfizer. He is also a member of the Infectious Disease Society of America Aspergillosis Guidelines Committee and European Society for Clinical Microbiology and Infectious Diseases Aspergillosis Guidelines groups.

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