Estimated burden of fungal infections in Italy

We read with interest the article by Pegorie and colleagues estimating the burden of fungal infection in United Kingdom.[1]

The burden of fungal diseases has only recently been considered as a health public concern worldwide. The current number of fungal infections occurring each year in Italy is not known.

We have estimated the number of fungal infections for general healthy population and specific at-risk groups in order to define the burden of these diseases in Italy. Demographic data were obtained from the Italian National Statistical Institute (http://www.istat.it/it). Data on the HIV/AIDS population from Istituto Superiore di Sanità (ISS) and recent data estimating adult HIV prevalence in Italy (http://www.iss.it). Tuberculosis statistics were taken from ISS and World Health Organization (WHO) reports (http://www.who.int/en). Chronic obstructive pulmonary disease (COPD) and asthma prevalence were obtained from the Health Examination Survey (http://www.salute.gov.it). Solid organ cancer and haematological diseases cases were taken from Associazione Italiana Oncologia Medica (http://www.aiom.it) and Associazione Italiana dei Registri Tumori reports (http://www.registri-tumori.it). Country's profile, populations and rates required to calculate burden of fungal infections are reported in Table 1.

Italy is a country with an estimated population of 61 million people with approximately 13 million (22%) older than 65 years. COPD prevalence has been estimated in 2.3–5% overall among adult population. The number of HIV-infected patients ranged between 114,000–156,000 people, with approximately 84% of patients receiving antiretroviral therapy (ARV). Solid organ cancer prevalence is 3,037,127 cases, accounting for approximately 5% of overall population. An estimated number of 31.300 new haematological malignancies per year, mainly represented by non-Hodgkin lymphoma and acute leukaemia have been reported in Italian registries. The number of HSCTs is available at the registry of the Gruppo Italiano Trapianto di Midollo Osseo and accounted in 2016 for 4701 transplants (http://www.gitmo.it).

The estimated burden of fungal infections in Italy is reported in Table 2.

The overall prevalence of *tinea pedis* was 22%, ranging from 7% in children up to 29% in the elderly.[2] A total of 16,606,000 cases could be expected considering the prevalence in the different age groups. Regarding *tinea capitis*, the prevalence in child Italian population has shown to be very high with 610,000 cases. Applying data from other countries to Italian population we can expect about 7,929,000 cases of onychomycosis.

An Italian survey, published in 2003 by Corsello et al.[3] on 931 women from eight different hospitals reported a rate of recurrent vulvovaginal candidosis (rVVC) of 8.2% (77/931). We estimated a 6% rVVC rate among adult women, resulting in 1,580,241 affected women.

In HIV infection, oral candidiasis is estimated to occur at least once in 90% of those without ARV, and oesophageal candidiasis in 20% of patients without ARV and 5% of patients on ARV. Using these assumptions, 1763 cases of oral candidiasis and 1413 cases of oesophageal candidiasis are annually expected.

A review of oral fungal infections in patients receiving cancer therapy highlights the prevalence of clinical oral candidosis was 7.5% pre-treatment, 39.1% during treatment, and 32.6% after the end of cancer therapy.[4] Assuming that the majority of cancer patients (90%) receive anticancer treatment, the number of oral candidosis is estimated at 1,066,031 episodes per year.

Recent national surveys show that rate of candidemia ranges from 0.79 to 2.2/1000 per hospital admission.[5,6] We estimate around 13,351 episodes of candidemia; considering one case of intra-abdominal candidiasis (IAC) for every six patients with candidemia a total of 2225 IAC are expected annually in Italy.

A total of 789 new cases of AIDS were diagnosed in Italy in 2015 with a reported incidence of cryptococcosis of 3.4%, we expected 51 cases/year.

The AIDS-defining condition was Pneumocystis jirovecii pneumonia (PCP) in 21.8–24.6% of the Italian cases in the 2 periods, which allow estimating a total number about 300 cases per year. Outside of the HIV-positive population, data about incidence and prevalence of PCP in Italy do not exist. Since in developed countries patients with proven PCP are mainly non-AIDS patients (60%) we estimated that PCP in non-HIV patients are likely to be 450 per year in Italy. Incidence of invasive aspergillosis (IA) in Italy is extremely difficult to estimate due to the lack of a national registry. Regarding the haematological malignancies overall, 31.300 new cases per year have been reported deriving an estimated number of IA of 907 cases per year. A total of approximately 1750 allogeneic HSCT and 3000 autologous HSCT per year have been performed, with an estimated of 120 cases of IA per year in allogeneic HSCT and 15 cases of IA per year in autologous HSCT.[7] An emerging problem is represented by IA among non-neutropenic patients with underlying pulmonary disease, mainly represented by COPD. We have estimated a burden of 1560 cases per year among non-neutropenic patients in Italy.

With respect to asthma, Denning et al. reviewing the published studies on asthma and allergic bronchopulmonar aspergillosis (ABPA) and found a prevalence of 2.5% (range 0.72%–3.5%).[8] Based on these data we estimated a total burden of 106,137 cases of ABPA in our country.

Severe asthma with fungal sensitivization (SAFS) refers to patients with severe asthma and evidence of fungal sensitisation. In Italy there are 3,272,000 people suffering of asthma, assuming a prevalence of SAFS of 6.2% we estimate 107,997 people with SAFS.

Considering that approximately 2.5 millions of Italian people wear contact-lens (http://optoservice.info) we have estimated 375 cases of fungal keratitis per year in this population; moreover, 200 cases among non contact-lens wearers. Overall, approximately 500 cases per year of fungal keratitis are expected in Italy.

DOI of original article: http://dx.doi.org/10.1016/j.jinf.2016.10.005

Table 1 Country's profile, populations and rates required to calculate burden of serious fungal infections.

Demographic data	Total population: 60,656,000 % of children (<14 years): 8.3 millions (13.7%) % population >65 years: 13.4 millions (22%)	Source: ISTAT
Respiratory diseases		
COPD	Prevalence of COPD in adults (all GOLD stages): 3.5–5% in men and 2.3–3.3% in women COPD (GOLD stage I) prevalence in adults: 7.3–12.3% COPD (GOLD stage II) prevalence in adults: 2.2–4.5% COPD (stages III–IV) prevalence in adults: 0.3–0.4%	Sources: Seventh Health Search Report, Health Examination Survey (OEC/HES) 2008–2012
Asthma	Asthma prevalence in adults: 7%	Source: Health Examination Survey (OEC/HES) 2008–2012
Lung cancer	Lung cancer prevalence: 87,641 (0.14%)	Source: Registro tumori 2016
Cancer	Solid cancer prevalence: 3,037,127 (4.9%) AML (incidence/100,000/year): 3.4–4.4 Leukaemia (new cases/year): 9100 Myeloma (new cases/year): 5700 Non-Hodgkin lymphoma (new cases/year): 14,300 Hodgkin lymphoma (new cases/year): 2200	Source: Registro tumori 2016 Source: I Tumori in Italia-rapporto 2016
Transplant	Autologous HSCT (number/year): 3000 Allogeneic HSCT (number/year): 1700 SOT (number/year): 2825 - kidney: 1499 - liver: 995 - heart: 219 - lung: 112	Source: www.GITMO.IT Source: CNT 2009 and 2013
HIV/AIDS	Estimated number of people living with HIV in 2012 in Italy: 114,812–156,910 (0.19–0.26/100) AIDS cases prevalence (2012): 22,941 (0.037/100) Annual new HIV cases (2015): 3444 (incidence 5.7/100,000) Annual new AIDS cases (2015): 789 (incidence 1.4/100,000) Proportion of diagnosed cases on ARVs: 83.9% Number of AIDS-related deaths (2012): 635	Source: ISS, Camoni L. 2015
Tuberculosis	Tuberculosis cases notifications in 2008: 4418 Tuberculosis incidence: 7.66/100,000 Pulmonary: 5–6/100,000 Extra-pulmonary: 2/100,000 Tuberculosis cases in HIV patients notifications (2013): 890	Source: ISS, WHO
ICU patients	Critical care beds nationally: 4650	Source: Ministero della Salute (website: http://www.salute.gov.it/)

COPD: chronic obstructive pulmonary disease; AML: acute myeloid leukaemia; HSCT: haematopoietic stem cell transplantation; SOT: solid organ transplant; ARV: anti-retroviral therapy.

Recent data suggest that chronic rhinosinusitis affects approximately 10.9% of European adult population, with an incidence of 1100 cases per 100,000 patients per year.[9] Based on these data, we estimated a burden of 1,141,000 cases of fungal rhinosinusitis in Italy.

This is the first attempt to estimate the burden of fungal infections in Italy. Overall, about 47.8% of Italians suffer from fungal infections yearly: 25,145,000 (41.2%) with superficial and 4,033,904 (6.6%) with invasive fungal infections, respectively. There are currently no epidemiology papers that have reported on the fungal infection rates in Italy, so every estimate is based on modelling. This approach was already used in several reports from other countries.[1,10,11]

In Italy, there are many superficial mycoses, especially onychomycosis and tinea capitis. Recurrent VVC is clearly a very substantial problem for women with over a 1 million and a half affected annually. Oral candidiasis is an emerging problem, especially in cancer patients. Candidemia is more common than in other European countries and has risen in frequency in the last decade. Serious deep mycoses with a high mortality, such as IA, IAC, PCP and cryptococcosis are not numerous in Italy but affect patients with severe underlying diseases and are linked to poor outcomes.

In summary, using local data and available national and international literature estimates of the incidence or prevalence of fungal infections, almost 29 M of people are affected each year by a fungal infection in Italy, with 6.6% of them that are affected by invasive forms. These estimates are higher than those reported from other European countries. Given these estimates, increased public health efforts are required to document and control this substantial burden of disease.

Table 2 Estimated annual case load of fungal infections in Italy.

Infection	Number of infections per underlying disorder per year						Rate/100K	Total burden
	None	HIV/AIDS	Respiratory	Cancer	ICU	HSCT		
Superficial fungal infections								
Tinea pedis	16,606,000						27,222	16,606,000
Tinea capitis	610,000						1003[b]	610,000
Onychomycosis	7,929,000						12,990	7,929,000
Total superficial	**25,145,000**						**41,221**	**25,145,000**
Invasive fungal infections								
Recurrent vaginal candidiasis (4×/year +)	1,580,241						2590[a]	1,580,241
Oral candidiasis	–	1763		1,066,031			1750	1,067,794
Oesophageal candidiasis		1413					2.3	1413
Candidemia	13,351				2480	20	21.8	13,351
Candida peritonitis	2225				413		3.6	2225
Cryptococcal meningitis		30		21			0.08	51
Pneumocystis pneumonia		300		450			1.2	750
Invasive aspergillosis		97	7295	1154	856	140	15.41	9402
ABPA			106,137				174	106,137
SAFS	–	–	107,997				178	107,997
Chronic pulmonary aspergillosis	–	–	2951	–	–		4.85	2951
Chronic fungal rhinosinusitis	1,141,000						1870	1,141,000
Mucormycosis				12		5	00.2	12
Histoplasmosis	–	–	–	5			0.01	5
Fungal keratitis	575	–	–	–	–		0.94	575
Total invasive fungal infections	**2,737,392**	**3603**	**224,380**	**1,067,673**	**3749**	**165**	**6617**	**4,033,904**
Total fungal burden estimated	**27,882,392**						**47,839**	**29,178,904**

Abbreviations: ABPA, allergic bronchopulmonary aspergillosis; SAFS, severe asthma with fungal sensitization.
[a] Rate in woman population.
[b] Rate in children population.

Conflict of interest

Dr. Bassetti has participated in advisory boards and/or received speaker honoraria from Achaogen, Angelini, Astellas, AstraZeneca, Bayer, Basilea, Gilead, Menarini, MSD, Pfizer, The Medicine Company, Tetraphase and Vifor. Dr Denning and family hold Founder shares in F2G Ltd, a University of Manchester spin-out antifungal discovery company, in Novacyt which markets the Myconostica real-time molecular assays. He acts or has recently acted as a consultant to Astellas, Sigma Tau, Basilea, Scynexis, Cidara, Biosergen, Quintiles, Pulmatrix, Pulmocide and Zambon. In the last 3 years, he has been paid for talks on behalf of Astellas, Dynamiker, Gilead, Merck and Pfizer. He is a longstanding member of the Infectious Disease Society of America Aspergillosis Guidelines group, the European Society for Clinical Microbiology and Infectious Diseases Aspergillosis Guidelines group and the British Society for Medical Mycology Standards of Care committee. The other authors declare no conflict of interest.

References

1. Pegorie M, Denning DW, Welfare W. Estimating the burden of invasive and serious fungal disease in the United Kingdom. *J Infect* 2017 Jan;**74**(1):60–71.
2. Roseeuw D. Achilles foot screening project: preliminary results of patients screened by dermatologists. *J Eur Acad Dermatol Venereol* 1999;**12**(Suppl. 1):S6–9, discussion S17.
3. Corsello S, Spinillo A, Osnengo G, Penna C, Guaschino S, Beltrame A, et al. An epidemiological survey of vulvovaginal candidiasis in Italy. *Eur J Obstet Gynecol Reprod Biol* 2003; **110**(1):66–72.
4. Lalla RV, Latortue MC, Hong CH, Ariyawardana A, D'Amato-Palumbo S, Fischer DJ, et al. A systematic review of oral fungal infections in patients receiving cancer therapy. *Support Care Cancer* 2010;**18**(8):985–92. doi:10.1007/s00520-010-0892-z.
5. Tortorano AM, Prigitano A, Esposto MC, Arsic Arsenijevic V, Kolarovic J, Ivanovic D, et al. A 1-year prospective survey of candidemia in Italy and changing epidemiology over one decade. *Infection* 2013;**41**(3):655–62. doi:10.1007/s15010-013-0455-6.
6. Bassetti M, Merelli M, Ansaldi F, de Florentiis D, Sartor A, Scarparo C, et al. Clinical and therapeutic aspects of candidemia: a five year single centre study. *PLoS One* 2015;**10**(5), e0127534. doi:10.1371/journal.pone.0127534.
7. Girmenia C, Raiola AM, Piciocchi A, Algarotti A, Stanzani M, Cudillo L, et al. Incidence and outcome of invasive fungal diseases after allogeneic stem cell transplantation: a prospective study of the Gruppo Italiano Trapianto Midollo Osseo (GITMO). *Biol Blood Marrow Transpl* 2014 Jun;**20**(6):872–80.
8. Denning DW, Pleuvry A, Cole DC. Global burden of allergic bronchopulmonary aspergillosis with asthma and its complication chronic pulmonary aspergillosis in adults. *Med Mycol* 2013 May; **51**(4):361–70.
9. Bakhshaee M, Fereidouni M, Mohajer MN, Majidi MR, Azad FJ, Moghiman T. The prevalence of allergic fungal rhinosinusitis in sinonasal polyposis. *Eur Arch Otorhinolaryngol* 2013;**270**(12): 3095–8. doi:10.1007/s00405-013-2449-5.
10. Gangneux JP, Bougnoux ME, Hennequin C, Godet C, Chandenier J, Denning DW, et al. An estimation of burden of serious fungal

infections in France. *J Mycol Med* 2016;**26**(4):385–90. doi:10.1016/j.mycmed.2016.11.001.
11. Ruhnke M, Groll AH, Mayser P, Ullmann AJ, Mendling W, Hof H, et al. Estimated burden of fungal infections in Germany. *Mycoses* 2015;**58**(Suppl. 5):22–8. doi:10.1111/myc.12392.

Matteo Bassetti*
Alessia Carnelutti
Maddalena Peghin
Infectious Diseases Clinic, Department of Medicine, University of Udine and Azienda Sanitaria Universitaria Integrata, Udine, Italy

Franco Aversa
Department of Clinical and Experimental Medicine, Hematology and BMT Unit, University of Parma, Parma, Italy

Francesco Barchiesi
Dipartimento di Scienze Biomediche e Sanità Pubblica, Clinica Malattie Infettive, Università Politecnica delle Marche, Ancona, Italy

Corrado Girmenia
Dipartimento di Ematologia, Oncologia, Anatomia Patologica e Medicina Rigenerativa, Azienda Policlinico Umberto I, Sapienza University, Rome, Italy

Livio Pagano
Istituto di Ematologia, Università Cattolica S. Cuore, Roma, Italy

Maurizio Sanguinetti
Institute of Microbiology, Università Cattolica del Sacro Cuore, Fondazione Policlinico Universitario Agostino Gemelli, Rome, Italy

Anna Maria Tortorano
Department of Biomedical Sciences for Health, Università degli Studi di Milano, Via Pascal 36, 20133, Milan, Italy

Maria Teresa Montagna
Department of Biomedical Science and Human Oncology – Hygiene Section, University of Bari "Aldo Moro", Bari, Italy

Pierluigi Viale
Infectious Diseases Unit, Department of Medical and Surgical Sciences, Hospital S. Orsola-Malpighi, University of Bologna, Bologna, Italy

Claudio Viscoli
Infectious Diseases Unit, IRCCS AOU San Martino-IST, University of Genoa (DISSAL), Genoa, Italy

David W. Denning
Global Action Fund for Fungal Infections (GAFFI), Rue de l'Ancien-Port 14, Geneva 1, 1211, Geneva, Switzerland

National Aspergillosis Centre, University Hospital of South Manchester, The University of Manchester, Manchester Academic Health Science Centre, Manchester, M23 9LT, UK

* Corresponding author. Clinica Malattie Infettive, Azienda Sanitaria Universitaria Integrata, Presidio Ospedaliero Universitario Santa Maria della Misericordia, Piazzale Santa Maria della Misericordia, 15, 33100, Udine, Italy. Fax +39 0432 559360.
E-mail addresses: matteo.bassetti@uniud.it, mattba@tin.it (M. Bassetti)

Accepted 27 July 2017

https://doi.org/10.1016/j.jinf.2017.07.008

The importation of the phylogenetic-transition state of Zika virus to China in 2014

Dear Editor:

We read with interest about the article published by Sun J. et al. in your journal.[1] They found 19 Zika virus (abbreviated to 'ZIKV') infected cases in Guangdong, China were imported from America (From February 12 to September 16, 2016), and inferred it may increase the risk of ZIKV local transmission. That is an exactly alarming Issue. However, we suspected ZIKV has been introduced into China before this time because the Asian-lineage virus had been reported to cause sporadic outbreaks and low-scaled epidemics in Asia before 2010.[2,3] Here, we report a ZIKV imported case from Bangladesh, a South Asian country. This may be the first recorded ZIKV imported case in China. Our finding may complement the considered transmission profile of ZIKV in China.

Since the first discovery of ZIKV in Uganda,[4] only limited ZIKV circulation had been observed in Africa and South/Southeast Asia (abbreviated to 'SSEA'). It came as a surprise that large-scaled outbreaks of the Asian-lineage viruses had been reported in the French Polynesian islands,[5] and more surprisingly, they had taken place as well in the Americas where it was first detected in Brazil in 2015.[6] Since then, ZIKV had rapidly spread to more than 32 countries and territories[7–9] and has become an emerging global public health problem. Imported infection was one of the main channels for the rapid spread of ZIKV from epidemic areas to other countries, especially to China.[1,7,8] The Asian-lineage virus had been reported to cause sporadic outbreaks and low-scaled epidemics in Asia before 2010,[2,3] while it had been found out that all the recent ZIKV cases reported in Asia were imported from South America or Oceania.[9]

We analyzed 133 ice-stored serum samples with retrospect, as they were collected from travelers coming to Yunnan Province from January 2014 to June 2016, and we discovered that one of them was determined as ZIKV-positive. The carrier of this ZIKV strain, named ZK-YN001, was a 56-year-old male citizen of Bangladesh, arriving to China from Dhaka for a business trip at the Kunming Airport on November 3rd, 2014. Apart from the fever with a recorded axillary temperature of 37.8 °C, the patient had no other obvious symptoms. Although there had never been